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Short Term Intensive Insulin Therapy Improves Insulin Secretion Significantly in Type 2 Diabetic Patients

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Abstract To investigate the effects of short-term (1 week) intensive insulin therapy, on glycemic control, insulin secretion, and insulin sensitivity in type 2 diabetic patients, an open prospective study was conducted in sixteen type 2 diabetic patients receiving diet therapy alone or treatment with oral hypoglycemic agents. Of the study subjects, 8 patients were treated with insulin, the remaining 8 patients served as the control group. The metabolic parameters were evaluated once before treatment and once during one of the following treatments: glycemic control as measured by 1,5-anhydro-D-glucitol (1,5-AG) and area under curve of glucose (AUC_{glucose}), insulin secretion as measured by area under curve of daily serum insulin (AUC_{insulin}), and insulin sensitivity as measured by the K index of the insulin tolerance test (K_{ITT}).

Post-treatment plasma glucose (AUC_{glucose}) and 1,5-AG levels in patients who had received intensive insulin therapy were comparable to those of the control group. A statistically significant increase in AUC_{insulin} occurred after intensive insulin therapy for just 1 week, while no change occurred in the control group. Insulin sensitivity (K_{ITT}) did not improve significantly in patients treated with insulin or patients from the control group.

These results indicate that intensive insulin therapy for 1 week improves insulin secretion remarkably but has little effect on insulin sensitivity in type 2 diabetic patients. Clinically, this suggests that intensive insulin therapy for one week might be one of the initial treatments of choice for such patients.

Key words: intensive insulin therapy, glucose toxicity, type 2 diabetes, insulin secretion, insulin sensitivity

Introduction

Glucose toxicity may be defined as impaired insulin release and/or a consequence of exposure to hyperglycemia. Thus, when a patient presents with type 2

diabetes and severe hyperglycemia, there is a deficient insulin secretion that may in part be mediated by glucose toxicity¹⁾²⁾. Correction of the hyperglycemia improves insulin sensitivity and insulin secretion³⁾. Patients with type 2 diabetes, whose glucose control has deteriorated while on oral hypoglycemic agents (OHA) or after an adjustment of diet only, who have been treated with intensive insulin therapy, gained a marked improvement of their glycemia that was associated

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with improved insulin secretion and sensitivity³⁾. The question arises if the beneficial effects of the correction of hyperglycemia are related to the duration of intensive insulin therapy. Many documents argue in this connection^{4)~8)}. Recently, Ryan et al.⁹⁾ showed the 2-to-3 weeks course of intensive insulin therapy successfully laid a foundation for prolonged good glycemic control in newly diagnosed type 2 diabetic patients. Li et al.¹⁰⁾ reported that intensive insulin therapy with continuous subcutaneous insulin infusion for 2 weeks improved long-term glycemic control in newly diagnosed type 2 diabetic patients¹⁰⁾. Against this background, we examined insulin secretion and sensitivity after one week of intensified insulin regimens with three or four daily injections in type 2 diabetes patients who were no longer adequately controlled by diet and OHA medication. If this short term intensive insulin therapy is beneficial, this treatment can lead to a shorter stay in hospital.

Patients and Methods

Sixteen type 2 diabetic patients gave informed consent to participate in this study. The study protocol was approved by the institutional review board of the National Hospital Organization Kyushu Medical Center. Patients were admitted to the National Hospital Organization Kyushu Medical Center because their diabetes could be controlled poorly. They had no severe disease of the liver or endocrine system or displayed any severe diabetic complication. They received either diet therapy alone or treatment with oral hypoglycemic agents including gliclazide, glibenclamide, nateglinide, acarbose and metformin.

Of the 16 patients, 8 patients were treated with short-acting insulin before each meal

and intermediate-acting insulin at bedtime if necessary without using any oral hypoglycemic agents. In concrete insulin was started at a dose of 4 units of regular insulin (Novolin R FlexPen, Novo Nordisk, Denmark) before meals and 4-8 units NPH (Novolin N FlexPen, Novo Nordisk, Denmark) at 10:00 PM if necessary. Capillary glucose levels were measured before meals and 2h post prandially once on 2 days. Targeted glucose levels were <8 mmol/l before breakfast and <15 mmol/l 2h after a meal, and the insulin dose was increased by 4-8 additional units with each injection to attain these levels. The other 8 patients received diet therapy alone or treatment with oral hypoglycemic agents which they used before hospitalization continuously and served as control subjects. These patients were divided in these two groups at random.

The demographic characteristics of the patients are shown in Table 1. The age, BMI, diabetic therapy, and duration of the illness of the patients who received insulin therapy were comparable to the control patients. Other parameters, HbA1c, total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol were also comparable in both groups.

Daily glycemic excursions, insulin secretion, and insulin sensitivity were measured before patients entered the study and 1 week after commencement of study treatment. Insulin therapy was terminated on the day before the study day to avoid that exogenous insulin would be included in the circulating insulin levels and make interpretation about insulin secretion impossible. Blood samples were taken at 07:00, 10:00, 11:30, 14:00, 17:30, 20:00, and 22:00 hours to determine plasma glucose and serum insulin levels. HbA1c and 1,5-anhy-

Table 1 Clinical characteristics of type 2 diabetic patients

	Insulin-treated	Control
n (M/F)	8 (8/0)	8 (7/1)
Age (yers)	59.1±8.6	63.5±11.6
BMI (kg/m ²)	23.8±3.0	24.2±2.5
Treatment (diet/SU)	4/4	2/6
Duration of illness	12.1±8.7	15.9±6.2
HbA1c (%)	11.5±2.3	10.3±1.3
TC (mg/dl)	195.6±49.2	201.3±34.5
TG (mg/dl)	163.3±122.7	185.3±99.1
HDL (mg/dl)	40.3±7.0	40.0±9.8
LDL (mg/dl)	122.8±36.9	127.1±40.0

Data are means±SD

TC: total cholesterol TG: triglyceride HDL: HDL-cholesterol LDL: LDL-cholesterol

dro-D-glucitol (1,5-AG) were measured in blood samples obtained at 07:00. Glycemic control was assessed by area under the curve of glucose (AUC_{glucose}), and insulin secretion was assessed by area under the curve of insulin (AUC_{insulin}). AUC_{glucose} and AUC_{insulin} were calculated by the trapezoidal method¹¹⁾. Insulin sensitivity was assessed by the K index of the short insulin tolerance test (K_{ITT}) according to the method of Borona et al.¹²⁾. Briefly, a baseline blood sample was obtained 3 min before insulin infusion in the morning before breakfast. A bolus of regular insulin (0.1 U/Kg) was infused, and blood sample were then obtained 3, 6, 9, 12, and 15 min after insulin infusion. K_{ITT} was calculated from the formula $K_{\text{ITT}} = 0.693/t_{1/2}$. Plasma glucose $t_{1/2}$ was calculated from the slope of least-squares analysis of plasma glucose concentrations from 3 to 15 min after the bolus injection of insulin.

Plasma glucose was measured with an automatic analyzer by the glucose oxidase method (Kyoto-Daiichi Kagaku, Kyoto, Japan). Immunoreactive insulin was measured by a commercial radioimmunoassay kit (Shionogi, Osaka, Japan). HbA1c was measured by the high-performance liquid

chromatography method (Kyoto-Daiichi Kagaku, Kyoto, Japan). Serum 1,5-AG was measured by enzymatic methods (Nippon Kayaku, Tokyo, Japan).

Statistical analysis

Statistical analysis was conducted with the two-tailed Student's t test for paired and unpaired data. Data were presented as means ± SE or SD. Differences were considered statistically significant at $P < 0.05$.

Results

The baseline values of AUC_{glucose} of patients on intensive insulin therapy were not significantly different from control patients (Table 2). As shown in Fig 1 A and B the daily profiles of plasma glucose in the two groups of the patients before study treatment were also comparable. Significant decreases in 1,5AG and AUC_{glucose} were observed in both groups, and the levels were almost comparable between the two groups. Therefore, both groups of patients reached similar levels of glycemic control after study treatment (Table 2).

Insulin secretion before study treatment in patients receiving intensive insulin therapy was comparable to that of control

patients, as assessed by $AUC_{insulin}$ or the graphed daily profiles of serum insulin (Table 2, Fig 1C and D). A statistically significant increase in $AUC_{insulin}$ was observed in patients on insulin after treatment. In contrast, $AUC_{insulin}$ did not change in control patients after treatment. After patients were treated with insulin, a remarkable increase after meals in the graphed serum insulin was observed (Fig 1C). In contrast, the graphed serum insulin level did not change in control patients (Fig 1D). K_{ITT} , an index of insulin sensitivity, did not change after study treatment in patients receiving insulin and control patients (Table 2). Therefore, the insulin sensitivity did not improve in both groups after 1 week.

Even though we have changed the method of treatment to OHA medication or diet cure only after 1 week intensive insulin treatment, the blood sugar level control did not worsen at least for 7–10 days beyond the testing until the patients discharged. (data was not shown).

Discussion

Prolonged hyperglycemia per se was shown to cause β -cell secretory defects¹³⁾¹⁴⁾ and resistance to insulin action¹⁵⁾¹⁶⁾. Several studies have shown that induction of normoglycemia in type 2 diabetes resulted in an improved β -cell function and improved insulin action. Although results

have been variable, there seems to be a consensus that a period of normal blood glucose levels improves insulin secretion and reduces insulin resistance^{17)~19)}.

The question arises whether beneficial effects of correction of hyperglycaemia are related or not to the duration of β -cell rest. If beneficial effects were to increase with duration, then a prolonged period of intensive insulin treatment should precede other less demanding treatments. It has been reported that intensive insulin treatment for 2–3 months can produce lasting results⁷⁾⁸⁾. Recently several results indicated that a 2-to-3 week’s course of intensive insulin therapy can successfully lay a foundation for prolonged good glycemic control in newly diagnosed type 2 diabetic patients⁹⁾¹⁰⁾. However the possible advantage of long versus short period of intensive insulin treatment for improving insulin secretion in diabetes patients who were not adequately controlled by diet and OHA medication for a long term has not been specifically tested. Here we demonstrated the effect of intensive insulin therapy during one week on insulin secretion and insulin action in diabetes patients whose duration of the known illness were more than ten years.

Our results showed that plasma glucose ($AUC_{glucose}$) and 1, 5-AG in patients who had received intensive insulin therapy were comparable to patients in the control group.

Table 2 Glycemic control, insulin secretion and insulin sensitivity in type 2 diabetic patients before and after the study treatment

	Insulin-treated			Control			P value
	Before	After	after/before%	Before	After	after/before%	
AUC glucose (mmol)	252.99±24.29	180.25±12.65	75.75±8.20	192.99±18.37	150.45±16.23	78.65±4.05	0.7559
1,5 AG	1.70±0.25	3.51±0.89	259±57	2.9±0.68	4.58±0.86	170±10	0.0551
AUC insulin (pmol)	1500.22±360.11	2371.88±481.74	167.01±14.80	1779.74±232.20	1522.05±214.20	83.85±4.89	0.0001
Kitt (%/min)	1.90±0.30	1.54±0.20	85±8	1.97±0.31	1.83±0.24	104±21	0.3894

after/before % means the ratio that divided the each values of AUC glucose, 1,5 AG, AUC insulin and Kitt before the study treatment by the values after the treatment, respectively.
Data are mean±SE. P value showed the difference of the values of after/before %.

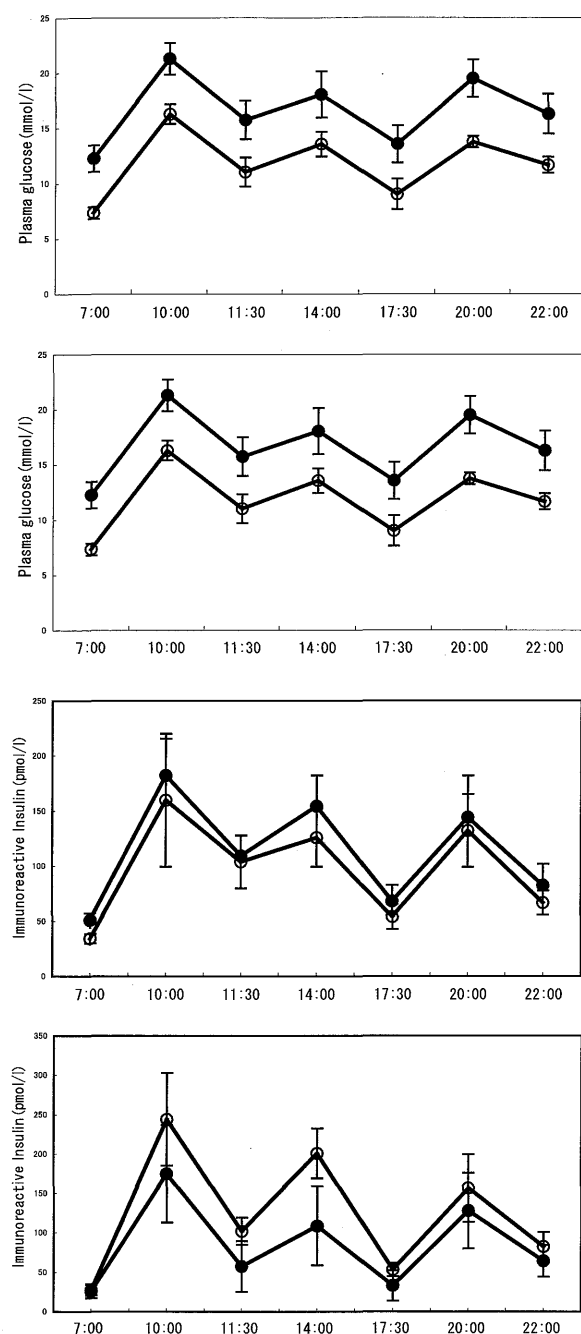


Fig. 1 Changes in daily plasma glucose and serum insulin levels before (●) and after (○) treatment. Data are presented as mean $\pm$ SE. A: Plasma glucose levels in patients treated with insulin. B: Plasma glucose levels in control patients receiving diet therapy alone or treated with an oral hypoglycemic agent. C: Serum insulin levels in patients treated with insulin. D: Serum insulin levels in control patients receiving diet therapy alone or treated with an oral hypoglycemic agent.

However, a statistically significant increase in AUC_{insulin} occurred after short term intensive insulin therapy, but no change occurred in the control group. Insulin sensitivity (K_{ITT}) did not improved to a statistically significant level in patients treated with insulin and patients in the control group. These results indicate that intensive insulin therapy for only one week improved insulin secretion remarkably but had little effect on insulin sensitivity despite a improved control in type 2 diabetic patients. Although we do not have detailed measures of insulin secretion or action, our study supports recent work suggesting that rapid correction of hyperglycemia can improve insulin secretion²⁰). We assumed that intensive insulin therapy could improve insulin secretion at first, the recovery of insulin action gradually appeared in diet-unresponsive type 2 diabetic patients. According to standard practice, when controlling diabetes by diet fails, oral agents and/or insulin are added in increasing doses as needed to control hyperglycemia. Here, we demonstrated that intensive short term insulin therapy is beneficial method, long term insulin therapy is not necessarily required. Furthermore, even though we changed the treatment method to diet cure or medication of oral agents after insulin therapy, the blood glucose level control did not worsen at least until the patients discharged.

A primary effect of glucotoxicity is reduced insulin secretion, which occurs via hyperglycaemic activation of the UCP2 gene in the β -cell and insulin secretion may be further reduced by hyperglycemic induced apoptosis of β -cell²¹⁾²²⁾. It is possible, but not proven, that the remaining β -cell mass could influence the time dependency of the effect of blood glucose normalization on β -cell function. However the

question arises why insulin levels increased in the insulin treatment group only while glycemic control improved almost equally in both groups. If the improvement in insulin secretion was due to reduced glucose toxicity only, the improvement should have occurred in both groups. It is unclear but we supposed the possibility that exogenous insulin therapy have other mechanisms for improvement in insulin secretion from β cell. Unfortunately we do not have the means which can prove this speculation.

It is still unclear how long the period of intensive insulin treatment should be for reestablishment of diet responsiveness significantly in patients for up to several years. It should be noted that our results pertain to type 2 diabetic patients whose durations of the illness are more than ten years. It is well-known that the ability for insulin secretion decreases with duration of diabetic state¹⁴⁾²³⁾. This makes it probable that patients with secondary drug failure are able to enhance their β -cell function to a lesser extent than newly diagnosed patients during intensive insulin treatment. In other words the natural history of type 2 diabetes is one of declining function over a number of years, and it is likely that the patients in the present study still have some function left and thus can be rescued. Such a recovery in insulin release raises the possibility that the natural history in type 2 diabetes of a relentless decline in insulin secretion may be altered by intervention. Thus, we think that it is proper to take an identical one week intensive insulin treatment again if the blood sugar control worsens in the future.

In summary, β -cell function is rapidly reversible after one week of intensive insulin treatment in subjects with type 2 diabetes. Clinically, this study suggests

that one week intensive insulin therapy, which was well tolerated and safe, might be the initial treatment of choice for such patients. We show clearly that improved β -cell function drives this recovery, but that insulin resistance remains present despite the improved control. The long term prognosis for these subjects is uncertain and these conclusions are not final but represent a fractional indication as to the advantage of short term intensive insulin therapy.

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(和文抄録)

2 型糖尿病患者において短期インスリン 強化療法にてインスリン分泌能は著明に改善する

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2 型糖尿病患者において, 1 週間の短期インスリン強化療法による血糖コントロール, インスリン分泌能およびインスリン感受性の効果をみるため, 16 名のインスリンを使用していない 2 型糖尿病患者を研究に供した. このうち 8 名には実際に 1 週間の短期インスリン強化療法を施行し, 残りの 8 名はインスリンを導入せず外来治療をそのまま入院中継続した. 血糖コントロールの指標には 1,5-アンヒドログルシトール (1,5-AG) と AUC_{glucose} を, インスリン分泌能の指標には AUC_{insulin} , インスリン感受性の指標には K_{ITT} を用いた. 治療後の

AUC_{glucose} と 1,5-AG は短期インスリン強化療法導入群と非導入群の間に有意差を認めなかったが, AUC_{insulin} については, 短期インスリン強化療法群は非導入群と比較して著明に増加していた. K_{ITT} は両者の間に有意差は認めなかった. 以上の結果から 1 週間の短期インスリン強化療法でインスリン分泌能は著明に改善することが判明した. このことから臨床的に 1 週間の短期インスリン強化療法は血糖コントロールのために選択されるべき一つの治療法であると考えられた.