High-Dose Intravenous Insulin Infusion Versus Intensive Insulin Treatment in Newly Diagnosed IDDM

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High-dose intravenous insulin infusion at the onset of IDDM has been suggested to improve β-cell function during the 1st year of insulin treatment. To test this hypothesis, we randomly assigned newly diagnosed IDDM patients to receive either an experimental 2-week high-dose intravenous insulin infusion (n = 9; age, 25 ± 7 years; HbA_{1c}, 10.5 ± 2.0%) or an intensive insulin therapy of four injections per day (n = 10; age, 28 ± 7 years; HbA_{1c}, 12.3 ± 3.0%). The experimental-therapy group received three times more insulin (1.2 ± 0.4 U · kg^{-1} · day^{-1}) than the intensive-therapy group (0.4 ± 0.1 U · kg^{-1} · day^{-1}, $P < 0.0005$). By week 3, both groups were treated similarly with intensive insulin therapy and were followed for 1 year. β-cell function was evaluated with fasting plasma C-peptide and glucagon-stimulated and mixed meal–stimulated C-peptide concentrations. In both groups, insulin doses were comparable, and HbA_{1c} levels were near normal during follow-up. At diagnosis of IDDM, fasting C-peptide was 0.40 ± 0.13 nmol/l in the experimental-therapy group and 0.39 ± 0.23 nmol/l in the intensive-therapy group. Irrespective of treatment, a slight decline of fasting C-peptide was observed in sequential measurements up to 12 months in both groups (Δ, –0.13 and –0.08 nmol/l, respectively; NS). Glucagon-stimulated C-peptide concentrations decreased from 0.54 ± 0.18 and 0.70 ± 0.39 nmol/l at month 0 to 0.41 ± 0.20 and 0.61 ± 0.52 nmol/l, respectively, at month 12. In the experimental-therapy group, mixed meal–stimulated C-peptide concentrations (area under the curve over 2 h) increased from 82.10 ± 43.72 to 101.20 ± 32.53 nmol/l and in the intensive-therapy group, from 75.05 ± 46.01 to 107.20 ± 102.51 nmol/l. Changes in stimulated C-peptide concentrations between month 0 and 12 were not significant in both groups. During follow-up, fasting and stimulated C-peptide concentrations were not significantly different between the experimental-therapy group and the intensive-therapy group. We conclude that as initial treatments of newly diagnosed IDDM, high-dose intravenous insulin infusion and intensive insulin therapy equally preserve β-cell function during the 1st year of insulin therapy. *Diabetes* 46:1607–1611, 1997

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AUC, area under the curve; GADA, GAD antibodies; IA-2A, tyrosine phosphatase IA-2 antibody; IAA, insulin autoantibody; ICA, islet cell antibody.

The progressive autoimmune destruction of insulin-producing pancreatic β-cells results in IDDM (1). After the clinical onset of IDDM, a clinical remission or "honeymoon period" induced by transient improvement of β-cell function precedes subsequent gradual loss of insulin secretory capacity (2,3). Several studies have attempted to preserve β-cell function by applying experimental insulin therapies to newly diagnosed IDDM patients, but the data obtained are limited due to the short observation period (4) and relatively insufficient metabolic control during follow-up (5). Furthermore, the assessment of β-cell function was not optimized in the two studies, which compared continuous subcutaneous insulin infusion and multiple subcutaneous injections per day with a conventional therapy of two daily insulin injections (4,6). Glycohemoglobin levels of patients were not reported in a study that used an external artificial pancreas for normalization of blood glucose levels for 5 days at the onset of IDDM (7).

In 1989, Shah et al. (8) reported that intensive intravenous insulin therapy during the first 2 weeks after diagnosis of IDDM had the potential to preserve β-cell function for 1 year, compared with conventional treatment. In this study, glycosylated hemoglobin levels of IDDM patients not having obtained initial intravenous insulin treatment significantly deteriorated at months 9 and 12, despite identical conventional insulin therapy and comparable insulin doses during follow-up (8). These results of a prolonged preservation of β-cell function have not yet been confirmed, and high-dose intravenous insulin treatment after diagnosis of IDDM has not been investigated in direct comparison to an intensive insulin treatment of four daily insulin injections.

The present study, therefore, was designed to evaluate the effect of a 2-week high-dose intravenous insulin therapy in newly diagnosed IDDM patients on integrated parameters of metabolic control (fasting and stimulated C-peptide concentrations and glycosylated hemoglobin levels) and to compare the results with those in patients on intensive insulin therapy.

RESEARCH DESIGN AND METHODS

Patients. The study protocol was approved by the local ethics committee. Newly diagnosed IDDM patients admitted to the Third Medical Department of the Academic Hospital München-Schwabing from June 1994 to June 1995 were included in the study. Informed consent was obtained from the patients or, in case of patients <18 years of age, the parents. After the correction of hyperglycemia, the patients were randomly assigned within 48 h after hospitalization to receive either an experimental 2-week intravenous high-dose insulin therapy (n = 9) or intensive insulin therapy (n = 10) (Table 1).

TABLE 1
Clinical characteristics of the study groups

Characteristic	Experimental-therapy group	Intensive-therapy group
n	9	10
Age (year)	25.1 ± 7.2	27.6 ± 7.0
Sex (M/F)	6/3	8/2
Body mass index (kg/m^2)	20.5 ± 3.0	21.7 ± 2.6
HbA_{1c} (%)	10.5 ± 2.0	12.3 ± 3.0
Ketonuria	9	10
Cholesterol (mmol/l)	5.01 ± 0.87	5.01 ± 1.39
Microalbuminuria (n)	0	0
Retinopathy	0	0
HLA tissue type		
DR3/3	2	2
DR4/4	4	5
DR3/4	2	2
DRX/X	1	1

Data are *n* or means ± SD.

At diagnosis of IDDM, none of the patients exhibited ketoacidosis. Criteria for entry into the study included age at onset between 16 and 35 years, history of hyperglycemia with insulin requirement at the time of diagnosis, and a BMI <25 kg/m^2. All patients were typed for HLA-DR antigens (9). Patients with any concurrent disease were excluded from the study. Patients were kept on a diet appropriate to their age and BMI.

Experimental insulin therapy. After the correction of the initial metabolic disturbances, the patients were started on a 2-week continuous intravenous insulin infusion using a portable external pump (Perfusor, B. Braun Melsungen AG, Melsungen, Germany). The disposable 50-ml syringe of the portable external pump contained 50 IU of insulin (H-Insulin Hoechst, Hoechst AG, Frankfurt am Main, Germany) diluted in 49 ml of a 0.9% sodium chloride solution. The syringe was regularly exchanged after the application of a 48-ml insulin-containing sodium chloride solution. Insulin was infused via a peripheral venous catheter (B. Braun Melsungen AG) into the antecubital vein. The insulin infusion was started at 3 ml/h, and the dosage was adjusted to keep preprandial glucose levels between 3.3 and 4.4 mmol/l and postprandial glucose levels <5.8 mmol/l. In addition, 50–100 ml of 5% glucose per hour was infused *1*) to relatively increase the amount of intravenously applied insulin and 2) to prevent hypoglycemia. Higher doses of 5% glucose were not applied to avoid the necessity of having to insert a central venous catheter.

During the 2nd week of experimental therapy, patients were enrolled in a 5-day structured IDDM education program at the Third Medical Department of the Academic Hospital München-Schwabing. After 2 weeks of intravenous insulin administration, patients were switched to intensive insulin therapy, which included goals of therapy as described below.

Intensive insulin therapy. Intensive insulin therapy consisted of subcutaneous administration of insulin four times daily: rapid-acting insulin before meals (H-Insulin Hoechst, Germany) and long-acting insulin at 10:00 P.M. (Basal-H-Insulin Hoechst, Germany). Insulin dosage was adjusted to maintain preprandial blood glucose concentrations between 3.9 and 6.7 mmol/l and postprandial concentrations at <10 mmol/l, similar to the criteria of the Diabetes Control and Complications Trial (10). The patients were also enrolled in the 5-day structured IDDM education program.

β-cell function. Two different C-peptide stimulation tests were performed for the evaluation of β-cell function. Plasma C-peptide concentrations were measured *1*) 0 and 6 min after intravenous injection of 1 mg glucagon (Novo Nordisk, Denmark) and *2*) 0, 30, 60, 90, and 120 min after mixed-meal stimulation with 300 ml Sustacal (Mead Johnson, Evansville, IL). The area under the curve (AUC) was calculated from C-peptide concentrations obtained after mixed-meal stimulation. Both stimulation tests were conducted after an overnight fast and commenced at 9:00 A.M. in patients having injected the previous insulin dose at 10:00 P.M. on the day before. Stimulation tests were performed in the absence of hypoglycemia 48 h before the investigation and at fasting blood glucose levels between 4.4 and 5.8 mmol/l. Glucagon-stimulated β-cell function was assessed at 0, 3, 7, and 12 months. Mixed-meal C-peptide stimulation was performed at 0, 5, 9, and 12 months. At month 0 and 12, both stimulation tests were performed within subsequent days.

To illustrate urinary C-peptide excretion, urine was collected for 24 h in three patients at day 7 of the experimental insulin therapy and in one patient at day 7 of intensive insulin therapy. The rate of excretion of C-peptide was calculated in nanomoles per liter.

Fasting C-peptide, stimulated C-peptide, and urinary excretion of C-peptide were determined by radioimmunoassay using a commercially available kit (DPC Biermann GmbH, Germany).

Measurement of ICAs, IAAs, GADAs, and IA-2As. Islet cell antibodies (ICAs), insulin autoantibodies (IAAs), GAD antibodies (GADAs), and the tyrosine phosphatase IA-2 antibodies (IA-2As) were determined as previously described (11). The threshold of ICA detection was 5–10 Juvenile Diabetes Foundation units. The results of the assay in the 9th ICA proficiency test were 100% specificity and 67% sensitivity. IAAs were expressed in nanounits per milliliter of insulin precipitated. The IAA assay achieved 100% specificity and 100% sensitivity in the 4th IAA proficiency test. GADAs and IA-2As were assessed using quantitative immunoprecipitation radioligand assays. Radioactivity was expressed relative to an antibody-positive serum, arbitrarily assigned a value of 100 U (GADA and IA-2A). The upper limit of the normal range for GADAs was 13 U and for IA-2A 5 U, defined by the 99th percentile of antibodies in nondiabetic control subjects. The results of the GADA assay in the 2nd GAD proficiency test were 100% specificity and 94% sensitivity. The assay of IA-2As achieved in the 1st IA-2A proficiency test 100% specificity and 100% sensitivity.

Follow-up. During follow-up, both groups received intensive insulin therapy. Management of diabetes was conducted by the same team (B.E. and O.S.). Patients were seen every 2 weeks during the first 2 months and at months 3, 5, 7, 9, and 12 thereafter. They were instructed to aim at the same therapy goals of blood glucose as during hospitalization and to perform home monitoring of blood glucose 4–6 times daily. No attempt was made to minimize insulin requirements. β-cell function was evaluated as above. Glycosylated hemoglobin levels (HbA_{1c}) as assessed by chromatography (normal range, <6.5%) daily insulin doses and BMI were determined at months 1, 2, 3, 5, 7, 9, and 12.

Statistical analysis. Results were expressed as means ± SD. Differences between the groups were compared using the Mann-Whitney *U* test. For the intragroup analysis, Wilcoxon's signed-rank test was performed. Fasting and stimulated C-peptide concentrations were also assessed with repeated measures of multiple analysis of variance. A P value <0.05 was considered significant.

RESULTS

During the first 2 weeks, the experimental-therapy group received three times more insulin than the intensive-therapy group (1.2 ± 0.4 vs. 0.4 ± 0.1 U · kg^{-1} · day^{-1}, respectively; P < 0.0005). Except for month 1, where daily insulin doses were lower in the experimental-therapy group than in the intensive-therapy group (0.3 ± 0.1 vs. 0.4 ± 0.1 U · kg^{-1} · day^{-1}, respectively; P < 0.05), daily insulin doses were comparable between the groups during follow-up (Fig. 1).

At month 3, glycohemoglobin levels (Fig. 2) returned to normal values in both the experimental-therapy group and the intensive-therapy group (5.6 ± 0.4 vs. 6.2 ± 0.8%, respectively). They remained within normal range during follow-up (5.5 ± 0.6 vs. 6.4 ± 1.5% at month 12) and were not significantly different between the groups.

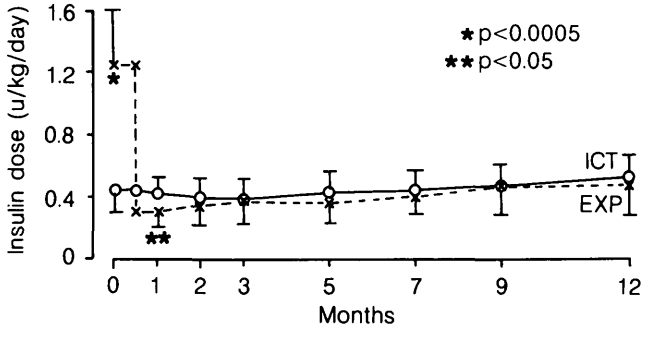

FIG. 1. Insulin doses (x ± SD) during the 1st year of treatment. EXP, experimental-therapy group (*n* = 9); ICT, intensive-therapy group (*n* = 10).

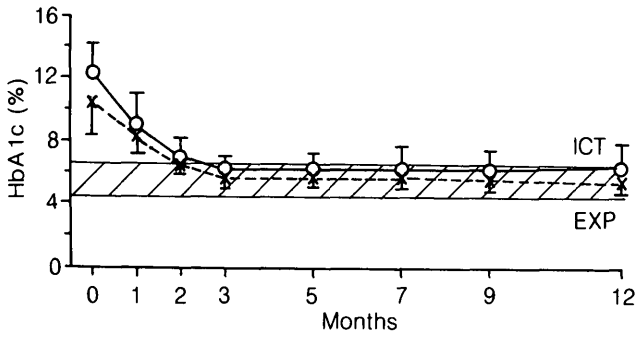

FIG. 2. HbA_{1c} (x ± SD) during the 1st year of insulin treatment. EXP, experimental-therapy group (n = 9); ICT, intensive-therapy group (n = 10). Hatched lines represent the normal range.

In the experimental-therapy group, there were no hypoglycemic episodes in which assistance was required. One hypoglycemic episode necessitating assistance occurred in the intensive-therapy group at month 5.

Comparing the fasting C-peptide concentrations of the experimental-therapy group with the intensive-therapy group demonstrated no significant differences during the 1st year of insulin treatment (Fig. 3*A*). Also, glucagon-stimulated C-peptide concentrations and the AUC over 2 h of the mixed meal–stimulated C-peptide concentrations did not indicate significant differences between the two groups (Figs. 3*B* and *C*).

At diagnosis, fasting C-peptide concentrations were 0.40 ± 0.13 nmol/l in the experimental-therapy group and 0.39 ± 0.23 nmol/l in the intensive-therapy group. It decreased to 0.27 ± 0.15 and 0.31 ± 0.21 nmol/l, respectively, at 12 months, but changes were not significantly different (Fig. 3*A*). In the experimental-therapy group, the decrease in fasting C-peptide concentration at 12 months was significant, when compared with that at 3 months (0.46 ± 0.14 nmol/l, P = 0.01).

In the experimental-therapy group, glucagon-stimulated C-peptide increased from 0.54 ± 0.18 nmol/l at month 0 to 0.78 ± 0.26 nmol/l at month 7 (P < 0.05) and decreased to 0.41 ± 0.20 nmol/l at month 12 (P < 0.05 vs. month 7) (Fig. 3*B*). In the intensive-therapy group, glucagon-stimulated C-peptide concentrations demonstrated only minor changes and were 0.70 ± 0.39 nmol/l at month 0, 0.62 ± 0.29 nmol/l at month 7, and 0.61 ± 0.52 nmol/l at month 12 (Fig. 3*B*).

In both the experimental-therapy and the intensive-therapy group, the AUC of mixed meal–stimulated C-peptide increased from 82.10 ± 43.72 and 75.05 ± 46.01 nmol/l, respectively, at month 0 to 114.38 ± 43.07 and 118.16 ± 85.44 nmol/l, respectively, at month 5 and was 101.20 ± 32.53 and 107.20 ± 102.51 nmol/l, respectively, at month 12. The increase of mixed meal–stimulated C-peptide in the two groups was not statistically significant (Fig. 3*C*).

At month 0, C-peptide concentrations 60 min after mixed meal–stimulation were 0.65 ± 0.33 nmol/l in the experimental-therapy group and 0.70 ± 0.48 nmol/l in the intensive-therapy group. In the experimental-therapy group, it increased significantly to 1.04 ± 0.37 nmol/l at month 12 (P < 0.05). The increase of C-peptide 60 min after mixed meal–stimulation in the intensive-therapy group to 1.08 ± 1.10 nmol/l at month 12 was not statistically significant.

Lack of differences in fasting and stimulated C-peptide concentrations between the two groups were confirmed by applying multiple analyses of variance.

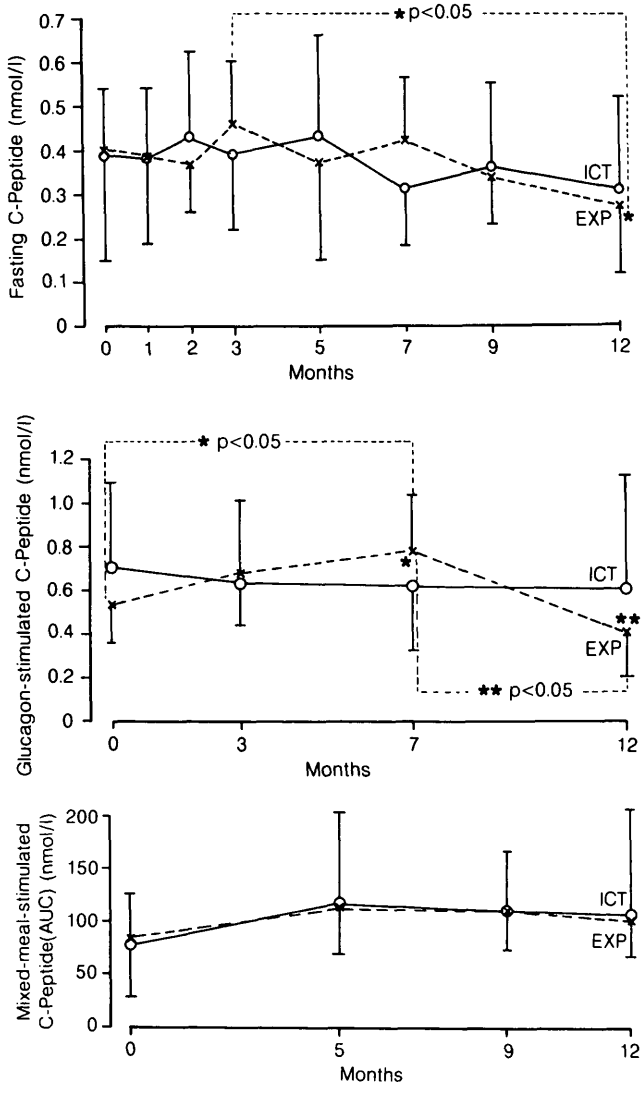

FIG. 3. Fasting C-peptide (*A*), glucagon-stimulated C-peptide at 6 min (*B*), and mixed meal–stimulated C-peptide (AUC over 2 h) (*C*) during the 1st year of insulin treatment (x ± SD). EXP, experimental-therapy group (n = 9); ICT, intensive-therapy group (n = 10).

Urinary C-peptide concentrations as assessed in three patients on experimental insulin therapy and in one patient on intensive insulin therapy were 0.33 ± 0.12 and 4.75 nmol/l, respectively.

In the experimental-therapy group and the intensive-therapy group, ICA-positivity was observed in 4 and 5 patients, respectively, at month 0 and in 4 and 6 patients, respectively, at month 12. Figure 4*A–C* displays titers of IAAs, GADAs, and IA-2As during the 1st year of insulin treatment for both groups.

At month 12, BMI increased by 2.1 ± 0.2 kg/m^2 in the experimental-therapy group and 2.5 ± 0.2 kg/m^2 in the intensive-therapy group.

DISCUSSION

The study provides evidence that in the 1st year of insulin treatment of newly diagnosed IDDM patients both a 2-week high-dose intravenous insulin infusion and intensive insulin therapy are equal in preserving β-cell function, as assessed by fasting and stimulated C-peptide concentrations. Intravenous appli-

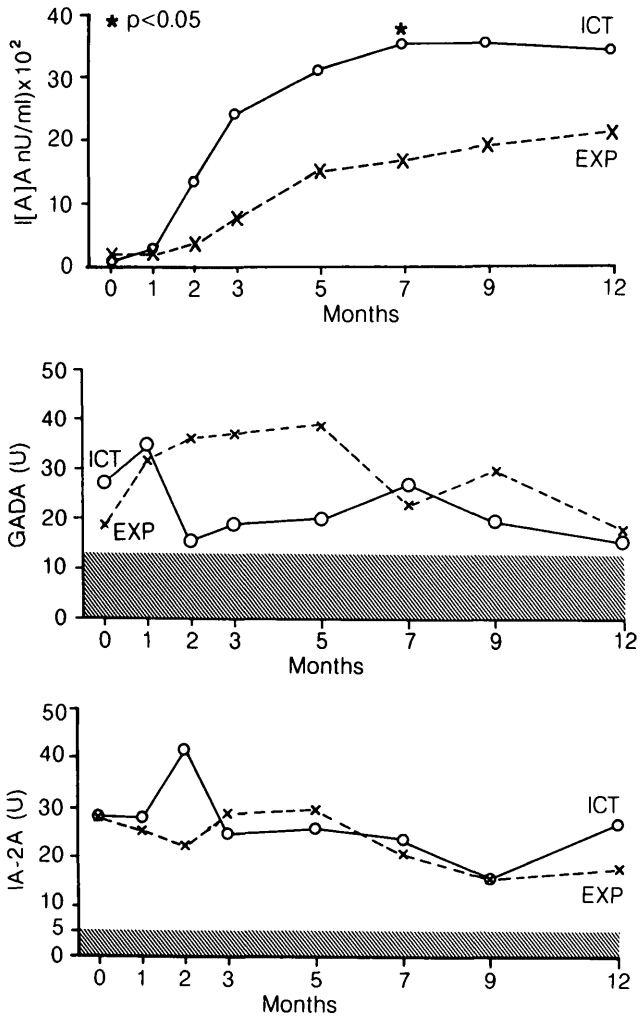

FIG. 4. Mean titers of IAAs (*A*), GADAs (*B*), and IA2-As (*C*) during the 1st year of insulin treatment. EXP, experimental-therapy group (*n* = 9); ICT, intensive-therapy group (*n* = 10). Hatched lines represent the upper limit of the normal range (99th percentile).

cation of a threefold higher amount of insulin, compared with intensive insulin therapy, did not result in a reduction of exogenous insulin requirements for maintaining mean glycohemoglobin levels in the nondiabetic range during follow-up.

In 1989, Shah et al. (8) reported that an intravenous 2-week high-dose insulin treatment at diagnosis of IDDM improves β-cell function during the 1st year of insulin therapy. The suppression of β-cell activity was hypothesized to be the mechanism behind improved β-cell function after insulin administration at high doses in the early stages of IDDM, and the results of the study support this argument (8). In animal models, insulin treatment has been shown to potentially place β-cells at rest (12). Furthermore, it has been demonstrated that resting β-cells are less immunogenic and/or more resistant to autoimmune damage than more active insulin-producing cells (13). Subcutaneous insulin has been found to be effective in preventing diabetes in NOD mice, the NOD-scid/scid adoptive transfer model, and BB rats (14–16). Insulin as a prophylactic in the prediabetic stages of human IDDM has been successfully employed for the first time at the Joslin Diabetes Center in the U.S. (17). It has been suggested that immunologic and metabolic factors contribute to the beneficial effects of prophylactic insulin therapy (15,18).

The results of our study indicate that residual endogenous insulin secretion can be maintained for as long as 1 year by the experimental and the intensive insulin therapy. Both intravenous high-dose insulin treatment and intensive insulin therapy in the initial treatment, together with intensive insulin treatment during follow-up of newly-diagnosed IDDM, prevented a significant reduction in fasting C-peptide concentrations up to 1 year after diagnosis. Compared with the evaluation at diagnosis of IDDM, we observed at 1 year an increase of 1-h mixed meal–stimulated C-peptide of 0.39 nmol/l in the experimental-therapy group and 0.38 nmol/l in the intensive-therapy group, indicating an improvement in β-cell function. Shah et al. (8) reported an increase of 0.29 nmol/l in the experimental-therapy group but only 0.08 nmol/l in the control group (8). Even though the sample size of this study and the study by Shah et al. (8) are small, the nearly superimposable results of our study suggest that a type II error (i.e., inadequate sample size to detect clinically significant differences) is unlikely.

The main difference between the study by Shah et al. (8) and ours is that the control group of Shah et al. (8) received a conventional insulin therapy of two insulin injections and that normal HbA_{1c} levels were not maintained. This may explain the limited increase of 1-h mixed meal–stimulated C-peptide concentrations in this group after 1 year of follow-up (8). In addition, our patients, compared with the patients of Shah et al., exhibited a threefold higher baseline stimulated C-peptide at entry, indicating an earlier diagnosis, and were older, suggesting a slower rate of β-cell destruction (8). During experimental insulin therapy, we administered a threefold higher insulin dose than with intensive insulin therapy, and Shah et al. applied a fourfold higher insulin dose than with conventional insulin therapy (8). In our study, we achieved a marked reduction of urinary C-peptide excretion in the experimental but not in the intensive-therapy group, indicating effective β-cell rest.

Unlike Shah et al., who investigated newly diagnosed adolescent IDDM patients (8), we included adult IDDM patients to avoid the deterioration of metabolic control associated with puberty (19). Euglycemic insulin-clamp studies showed insulin resistance in both normal children and children with diabetes during puberty (20). Hypothetically, this contributed to the higher insulin dosage and smaller amount of intravenously applied glucose in both groups studied by Shah et al. (8).

The absence of a significant improvement in β-cell function after high-dose intravenous insulin treatment is suggested to be a consequence of a too advanced loss of β-cell mass at the diagnosis of IDDM, resulting in the impossibility of exogenous insulin to preserve β-cell function longer.

Immunosuppression with cyclosporin A has been reported to improve β-cell function transiently (21,22). In the Canadian-European Trial, an increase of glucagon-stimulated C-peptide of 0.13 nmol/l in cyclosporin-treated patients, who were comparable in age with our patients, after the 1st year of diagnosis of IDDM was associated with a 25% reduction of creatinine clearance (22). In this study, the dosage of insulin was minimized with target control of blood glucose levels ≤7.8 mmol/l before meals (22). A nonsignificant rise in creatinine was noted in a pilot study on cyclosporin A in asymptomatic IDDM, in which insulin dependency could not be delayed (23). Due to potential toxicity, the improvement of C-peptide

concentrations and diabetic control did not appear sufficient to qualify cyclosporin A as an adjunct therapy in juvenile IDDM (24). Also, nicotinamide has been suggested for secondary prevention of IDDM (25), as it has been demonstrated to prevent the toxic effect of nitric oxide on islets (26) and to partially reverse the interleukin-1b inhibition of islet insulin release (27). A 1-year application of nicotinamide to newly diagnosed IDDM patients <15 years of age, however, could not prevent glucagon-stimulated C-peptide from being reduced by >0.20 nmol/l (25). In six patients who were >15 years of age, glucagon-stimulated C-peptide concentrations were minimally increased from 0.60 to 0.63 nmol/l at 1 year (25). In this study, the patients received three to four injections daily, and insulin dosage during follow-up was comparable with the dosage applied in our study (25). Considering the results together, it seems reasonable to conclude that the administration of both experimental and intensive insulin therapy during the 1st year of IDDM is at least equal in preserving β-cell function to nicotinamide and the potentially toxic cyclosporin A.

The comparable presence of autoantibodies to β-cell antigens in both the experimental-therapy group and the intensive-therapy group during the 1st year of insulin treatment suggests that autoimmune mechanisms targeted at β-cells are neither suppressed nor promoted more by one or the other therapy. The higher frequency of insulin antibodies in the intensive-therapy group, compared with the experimental-therapy group, was surprising. It may indicate that the application of high doses of insulin has indeed some suppressive effect on the immune response to insulin but without beneficial effect on β-cell function at this late stage of the disease.

In summary, we have demonstrated that intravenous high-dose insulin infusion at the onset of diabetes is as effective as intensive insulin therapy with regard to β-cell preservation. Therefore, our results do not support the argument for intravenous high-dose insulin administration in newly-diagnosed IDDM. Whether intensive insulin therapy at the onset of diabetes is superior to conventional therapy in preserving β-cell function during the 1st year of insulin treatment requires further investigation.

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