

Short-Term Intensive Insulin Therapy in Newly Diagnosed Type 2 Diabetes

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OBJECTIVE — Type 2 diabetes is associated with defects in insulin secretion and insulin action. Hyperglycemia may aggravate these defects, a feature known as glucose toxicity. Previous studies have shown that acute correction of hyperglycemia in subjects with long-standing type 2 diabetes gives only short-term improvement in glycemic control after discontinuation of insulin. The current study attempts to identify any characteristics of patients with newly diagnosed type 2 diabetes (fasting glucose >11.0 mmol/l) who would have a long-term benefit, in terms of glycemic control, from a brief course of insulin therapy.

RESEARCH DESIGN AND METHODS — A total of 16 subjects (52 ± 2 years old [range 36–64], BMI 30.8 ± 1.9 kg/m²) with newly diagnosed type 2 diabetes had a 2–3 week course of intensive insulin therapy that was then discontinued.

RESULTS — Fasting glucose fell from 13.3 ± 0.7 to 7.0 ± 0.4 mmol/l, and this improvement was maintained at the 1-year follow-up (6.7 ± 0.3 mmol/l). The insulin area under the curve for the posttreatment oral glucose tolerance test also improved ($8,251 \pm 1,880$ before therapy, $18,404 \pm 4,040$ directly after insulin therapy, and $42,368 \pm 8,517$ pmol · min at the 1-year follow-up). At 1 year, seven of the subjects maintained good glycemic control on diet therapy alone, eight required oral hypoglycemic agent (OHA) therapy, and one required insulin therapy. The distinguishing features of those who did not require OHA or insulin therapy were that they required less insulin during the active insulin therapy phase (0.37 ± 0.05 vs. 0.73 ± 0.07 units · kg⁻¹ · day⁻¹) and were able to attain a lower fasting serum glucose at the end of the period of insulin therapy (5.9 ± 0.3 vs. 7.7 ± 0.4 mmol/l).

CONCLUSIONS — These results demonstrate that in newly diagnosed type 2 diabetes with elevated fasting glucose levels, a 2- to 3-week course of intensive insulin therapy can successfully lay a foundation for prolonged good glycemic control. The ease with which normoglycemia is achieved on insulin may predict those patients who can later succeed in controlling glucose levels with attention to diet alone.

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Glucose toxicity likely explains the clinical adage that it is easier to maintain than attain glycemic control. Glucose toxicity may be defined as impaired insulin release and/or action as a consequence of exposure to hyperglycemia. Hyperglycemia itself induces insulin resistance and/or impairs β -cell function.

Correction of the hyperglycemia improves insulin sensitivity and insulin secretion (1). When a patient presents with new-onset type 2 diabetes and severe hyperglycemia, there are defects in insulin secretion and action that may in part be mediated by glucose toxicity (2,3). Correction of the hyperglycemia may im-

prove these defects such that euglycemia might be maintained for a variable duration of time.

For patients with type 2 diabetes whose glucose control has deteriorated when on oral hypoglycemic agents (OHAs) (secondary failures), if treated with intensive insulin therapy, they gain marked improvement of glycemia associated with improved insulin secretion and action (1). Rarely, however, has a prolonged benefit been demonstrated, with virtually all patients becoming hyperglycemic again after a few weeks (4,5). It is unknown if such an outcome pertains to new-onset type 2 diabetes, although patients who have failed diet therapy may show a good response to a short period of intensive insulin therapy (6).

The caregiver faced with a patient with newly diagnosed type 2 diabetes can try diet counseling, OHAs, or insulin, but an alternative strategy is to briefly but aggressively render the patient euglycemic and then see if euglycemia can be maintained for a prolonged period of time (7). This pilot study was designed to assess what readily available parameters would predict which patients will achieve long-term success with either diet alone or OHAs after correction of the glucose toxicity with a short period of intensive insulin therapy.

RESEARCH DESIGN AND METHODS

— A total of 16 subjects (6 men and 10 women) with newly diagnosed type 2 diabetes completed the study. Five others entered the study: one of these developed congestive cardiac failure during the intensive insulin therapy, one subject became pregnant and one developed cancer during the year follow-up, one was lost to follow-up, and one declined OHA therapy when it was indicated. All 16 subjects presented with a fasting serum glucose value that was >11.0 mmol/l at the time of initial diagnosis, and none required acute hospitalization. The mean age was 52 ± 2 years (range 36–64) and the BMI 30.8 ± 1.9 kg/m². Subjects remained untreated, with only dietary advice to reduce consumption of sweetened beverages, until entry

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Abbreviations: AUC, area under the curve; OGTT, oral glucose tolerance test; OHA, oral hypoglycemic agent.

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Table 1—Measures of glycemia and insulin secretion, lipids, and body weight before insulin therapy, directly after insulin therapy, and at 1-year follow-up

	Before insulin treatment	After insulin treatment	1 Year
Fasting serum glucose (mmol/l)	13.3 ± 0.7	7.0 ± 0.4*	6.7 ± 0.3†
HbA _{1c} (%)	11.8 ± 0.3	—	6.6 ± 0.3†
Fructosamine (μmol/l)	428 ± 38	286 ± 15*	288 ± 11†
AUC _g (mmol · min)	1,176 ± 66	1,184 ± 65	916 ± 53††
Fasting serum insulin (pmol/l)	84.7 ± 10.8	97.6 ± 12.2	108.3 ± 15.1
Fasting C-peptide (μg/l)	1.04 ± 0.36	1.27 ± 0.29	—
AUC _i (pmol · min)	8,251 ± 1,880	18,404 ± 4,040	42,368 ± 8,517††
Total cholesterol (mmol/l)	6.16 ± 0.42	—	4.72 ± 0.28†
Triglycerides (mmol/l)	3.90 ± 0.72	—	2.08 ± 0.39†
Free fatty acids (mmol/l)	1.1 ± 0.10	0.76 ± 0.10	0.64 ± 0.08§
BMI (kg/m ²)	30.8 ± 1.9	30.9 ± 1.9	30.3 ± 1.8§

Data are means ± SE. * $P < 0.01$ significant difference of before versus after insulin treatment; † $P < 0.01$ significant difference of before versus after 1 year; ‡ $P < 0.01$ significant difference of after insulin treatment versus 1 year; and § $P < 0.05$ significant difference after insulin treatment versus 1 year.

into the study, which occurred within 4 days of the diagnosis of diabetes. All patients were fully briefed on the study, and all gave written informed consent. The protocol was approved by the research ethics board of the University of Alberta.

Study design

Subjects underwent a 75-g oral glucose tolerance test (OGTT) upon study entry. An intravenous line was started after an overnight fast. At -15 min, baseline blood samples were drawn for HbA_{1c}, cholesterol, triglyceride, fructosamine, C-peptide, free fatty acids, glucose, and insulin. At 0 min, a second baseline blood sample was drawn for glucose and insulin. Then, 75 g glucose Trutol syrup (Custom Laboratories, Baltimore, MD) was administered and consumed over 5 min. Blood samples for glucose and insulin were drawn at 15, 30, 60, 90, 120, and 180 min. After the OGTT, subjects were instructed about a diabetic diet and home capillary glucose monitoring. The techniques for insulin injection were taught, as was the management of hypoglycemia. Subjects were then followed as outpatients and were in daily contact by phone with a study physician for insulin adjustment. Visits to the clinic were made twice a week for dietary review and a glucose meter check. At the end of the insulin therapy period, the OGTT was repeated, and patients were then followed monthly until normoglycemia was confirmed and bimonthly thereafter until 1 year after the initial diagnosis. The blood work and OGTT were repeated at 1 year.

Intensive insulin therapy

Subjects were taught to inject short-acting insulin before each meal and intermediate-acting insulin at bedtime. Insulin was started at a dose of 5 units of regular insulin before meals and 10–15 units NPH at 10:00 P.M. Capillary glucose levels were measured before breakfast and 2 h postprandially. Targeted glucose levels were <6 mmol/l before breakfast and <7 mmol/l 2 h after meals, and the insulin dose was increased by 2–5 additional units each injection time every day to attain these levels. If, after 2 weeks on insulin, these targets had not been achieved, insulin therapy was extended for a 3rd week. The bedtime intermediate-acting insulin injection was omitted the evening before the post-insulin treatment OGTT.

Analytical methods

Serum glucose concentrations were determined by the glucose oxidation method (glucose analyzer; Beckman, Irvine, CA). Serum insulin levels were assayed using the enzyme-immunological test on a Boehringer Mannheim ES300 instrument (Mannheim, Germany). An Immulite automated analyzer (Diagnostic Products, Los Angeles, CA) measured C-peptide levels using an enzyme immunoassay method. Free fatty acid levels were determined enzymatically using a Wako NEFA C test kit (Wako Chemicals, Dallas, TX). Serum fructosamine values were measured using a colorimetric method on a Hitachi 717 chemistry analyzer (Boehringer Mannheim). HbA_{1c}, total cholesterol, and triglyceride levels were assayed

with a Hitachi 917 assay system (Boehringer Mannheim).

Statistics

Group mean data were compared by Student's two-tailed paired *t* test or repeated-measures ANOVA as appropriate, and significance was taken at $P < 0.05$. All group values are expressed as the means ± SE. All statistics were performed using Sigma Stat from Jandel Scientific (San Rafael, CA). The area under the curve (AUC) and the incremental AUC for glucose and insulin (AUC_g and AUC_i, respectively) represent the area under the curve above baseline (mean of sample at -15 and 0 min) over the 180 min after glucose ingestion.

RESULTS— All 16 subjects tolerated the intensive insulin treatment well. No hypoglycemic reactions were recorded. Symptoms of diabetes (frequent urination, excessive thirst, and fatigue) resolved shortly after insulin therapy was instituted.

Table 1 shows the changes in biochemical measurements over the course of the study, and the glucose and insulin excursions at each OGTT are illustrated in Fig. 1. Fasting serum glucose levels decreased from 13.3 ± 0.7 mmol/l before insulin therapy to 7.0 ± 0.4 mmol/l after insulin therapy ($P < 0.01$), and they remained improved at 1 year (6.7 ± 0.3 mmol/l). AUC_g (above baseline) remained unchanged from before to after insulin therapy but was decreased significantly at 1 year (Table 1). Basal insulin levels rose slightly over the study period, but this change was not statistically significant. AUC_i increased at the post-insulin therapy OGTT and was dramatically higher than study entry values by year end. At the year end, the AUC_i in the diet-alone group (37,362 ± 10,332 pmol · min) was not different from the OHA-treated group (47,376 ± 14,107 pmol · min, $P = 0.577$). Overall blood glucose control, as measured by HbA_{1c} and fructosamine levels, improved significantly over the course of the study, with fructosamine showing immediate improvement with insulin therapy. Fasting C-peptide values were unchanged with insulin therapy, whereas free fatty acid levels declined after insulin therapy and remained lower at 1 year. Lipid values improved significantly by year end. BMI remained unchanged during insulin therapy (30.8 ±

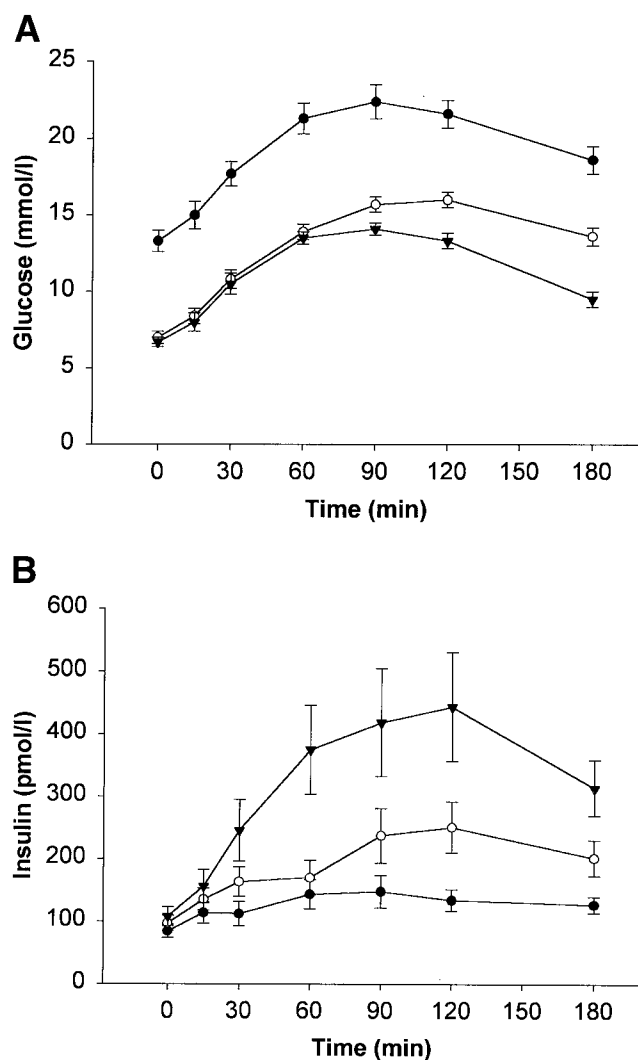


Figure 1—Means \pm SE for serum glucose (A) and insulin (B) concentrations during OGTT before insulin therapy (\bullet , $n = 16$) immediately after insulin therapy (\circ , $n = 16$) and at 1-year follow-up (\blacktriangledown , $n = 14$). Both the AUC_g ($\text{mmol} \cdot \text{min}$) and the AUC_i ($\text{pmol} \cdot \text{min}$) at 1 year were significantly different from the values before and directly after insulin therapy ($P < 0.01$).

1.9 vs. $30.9 \pm 1.9 \text{ kg/m}^2$ before vs. after insulin therapy) but decreased significantly by 6 months to $29.0 \pm 1.7 \text{ kg/m}^2$ ($P < 0.01$). However, by 1 year body weight rose to near study entry levels, with a final mean BMI of $30.3 \pm 1.8 \text{ kg/m}^2$, significantly less than after insulin therapy ($P < 0.05$).

At 1 year, all subjects had reasonable glycemic control, with a mean HbA_{1c} of $6.6 \pm 0.3\%$. Seven subjects remained off medication, six were on glyburide alone, two were on a combination of glyburide and metformin, and one was on insulin. Characteristics of the subjects at study entry, as well as response to insulin therapy, were examined in an attempt to identify parameters that might predict the long-

term success of this short-term insulin therapy regimen. Table 2 shows the clinical and biochemical parameters at study entry and at the completion of the acute insulin therapy of the group who remained normoglycemic at 1 year without medication (diet only) versus those who required OHAs or insulin (OHA/insulin).

The pre-insulin therapy HbA_{1c} , fasting serum glucose, insulin, C-peptide, free fatty acids, AUC_g , AUC_i , waist-to-hip ratio, and BMI values were not different between the two groups at baseline (Table 2). However, the diet-only group required significantly less insulin per day to achieve normoglycemia (0.37 ± 0.05 vs. $0.73 \pm 0.07 \text{ units} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in the OHA/insulin group, $P < 0.01$). Blood

glucose control was achieved within 2 weeks in all seven diet-only subjects. This is in contrast to the OHA/insulin group, in which four patients did not achieve normoglycemia after 2 weeks on insulin, and two subjects were still hyperglycemic after 3 weeks on insulin. After insulin therapy, the fasting serum glucose values (Fig. 2) were significantly lower in the diet-only versus the OHA/insulin group (5.9 ± 0.3 vs. $7.7 \pm 0.4 \text{ mmol/l}$, $P < 0.01$), with similar respective changes seen in the post-insulin therapy fructosamine levels (277 ± 15 vs. $293 \pm 25 \mu\text{mol/l}$, $P = 0.6$).

Basal insulin-to-glucose ratios were similar in the diet-only and OHA/insulin groups before insulin treatment. With the post-insulin therapy OGTT, the fasting insulin-to-glucose ratio was lower in the diet success group (11.3 ± 1.3 vs. 16.7 ± 3.0 in the diet failure group), but this difference was not statistically significant. The ratios at the 30-min point in both the pre- and postinsulin OGTT were not different between the diet success and diet failure groups. There was no change in BMI throughout the insulin treatment in either group. In the diet-only group, the BMI was significantly lower at 6 months (26.5 ± 1.7 vs. $29.0 \pm 2.1 \text{ kg/m}^2$ at study entry, $P < 0.01$) and marginally lower at year end ($27.5 \pm 1.8 \text{ kg/m}^2$, $P = 0.07$). In the OHA/insulin group, there were no significant changes in BMI at 6 months or at 1 year (31.0 ± 2.6 vs. $32.8 \pm 2.8 \text{ kg/m}^2$, respectively). The BMI values of each group at 1 year were not significantly different from each other ($P = 0.15$).

CONCLUSIONS— Our results show that we were successful in rapidly correcting the serum glucose levels in most of these subjects with newly diagnosed diabetes. The mean fasting glucose decreased by $>5 \text{ mmol/l}$, and the fructosamine level declined, as did the free fatty acids. The AUC_g did not change immediately after insulin therapy, but this only reflects the incremental change above baseline. We saw an immediate increase of the AUC_i , suggesting that we did improve insulin secretion by our intervention. The more impressive rise in AUC_i at study end was irrespective of the need for OHAs and indicates a remarkable recovery of β -cell function. It is of note that directly after the insulin therapy, the AUC_i was not maximal, as shown by the subsequent improvement over time. The acute insulin

Table 2—Clinical and biochemical characteristics at baseline or at the end of the initial insulin therapy of the group maintained on diet alone versus those requiring OHA or insulin on long-term follow-up

	Diet only	OHA/insulin
<i>n</i>	7	9
BMI (kg/m ²) before insulin therapy	29.0 ± 2.1	32.2 ± 2.9
Waist-to-hip ratio before insulin therapy	0.98 ± 0.02	1.01 ± 0.02
Fasting serum glucose before insulin therapy (mmol/l)	13.2 ± 0.8	13.3 ± 1.1
Fasting serum glucose after insulin therapy (mmol/l)	5.9 ± 0.3	7.7 ± 0.4*
HbA _{1c} before insulin (%)	12.3 ± 0.5	11.5 ± 0.5
Fasting insulin before insulin therapy (pmol/l)	82.4 ± 16.5	86.7 ± 14.9
Fasting C-peptide before insulin therapy (μg/l)	0.96 ± 0.31	1.10 ± 0.62
Free fatty acids before insulin therapy (mmol/l)	0.94 ± 0.18	1.18 ± 0.11
AUC _i before insulin therapy (pmol · min)	7,937 ± 3,983	8,498 ± 1,576
AUC _i after insulin therapy (pmol · min)	17,870 ± 6,175	18,821 ± 5,661
Insulin dose required during intensive therapy (unit · kg ⁻¹ · day ⁻¹)	0.37 ± 0.05	0.73 ± 0.07*

Data are means ± SE. *Significant difference of group maintained on diet only versus those requiring OHA or insulin ($P < 0.01$).

therapy did not affect body weight. These changes then resulted in 7 of 16 subjects being able to maintain good glycemic control on diet alone for a year, and the changes in glycemia were mirrored in an improvement of the lipid profiles.

Glucose toxicity has been demonstrated clinically and has been investigated extensively in the laboratory. Animal studies have demonstrated specific gene alterations in the β -cell after exposure to hyperglycemia (3). Human islets exposed to very high glucose levels in culture have alterations in interleukin-1 β (8). Defects in insulin secretion have also been documented and are directly related to hyperglycemia (9). Insulin action is also defective after exposure to hyperglycemia and is correctable with the establishment of euglycemia (1). Although we do not have detailed measures of insulin secretion or action, our results do support the concept that rapid correction of hyperglycemia can improve insulin secretion. Ilkova et al. (6) also used intensive insulin therapy for a short period in subjects who had failed 3–6 weeks of diet therapy. They also found that a significant proportion of subjects showed a good long-term response to 2 weeks of insulin pump therapy, although some required repeat courses of insulin therapy.

Our 1-year success rate of nearly 50% is in marked contrast to what happens in secondary failure, where usually the glucose levels rise within a few weeks of the period of euglycemia (4,5). This differ-

ence likely represents the earlier stage of the disease in these newly diagnosed patients. Our original hypothesis assumed that many patients would require insulin therapy within the year of follow-up, given the initial high fasting glucose, but this was not found to be the case. When we examined the results to assess what differences were apparent in those who could be maintained on diet alone in the long term versus those who required OHA or insulin, none of the baseline measures were helpful. The only predictors were the ease with which glycemic con-

trol could be attained in the subjects. Those who did well on diet alone at the longer-term follow-up were the subjects who needed half the dose of insulin (0.37 ± 0.05 vs. 0.73 ± 0.07 units · kg⁻¹ · day⁻¹) to attain good glucose control, achieved it readily in the 2-week window of therapy, and attained a lower fasting glucose level with the insulin therapy (5.9 ± 0.3 vs. 7.7 ± 0.4 mmol/l) (Fig. 2).

It is recognized that if the fasting glucose is >6.4 mmol/l, then the first-phase insulin secretion is lost (10), so that it may be that the group with persisting higher glucose values never truly eliminated their glucose toxicity, hence the less-than-optimal outcome. Rather, we suspect that their inherent defects were more severe and prevented the ready normalization of glucose, hence the poorer outcome in the long term. Those who responded better to the intensive insulin therapy were ipso facto more sensitive to insulin, and this may be an underlying contributor to their longer-term success. In addition, our patients were newly diagnosed, which is not synonymous with new onset of diabetes. Thus, the subjects in whom it was more difficult to achieve euglycemia may have had diabetes for longer. Garvey et al. (1) found in subjects with type 2 diabetes who were predominantly secondary treatment failures that those with a longer duration of diabetes responded less well to intensive insulin therapy. Finally, the BMI in those who succeeded on diet alone did fall more at 6 months, but at 1 year it was

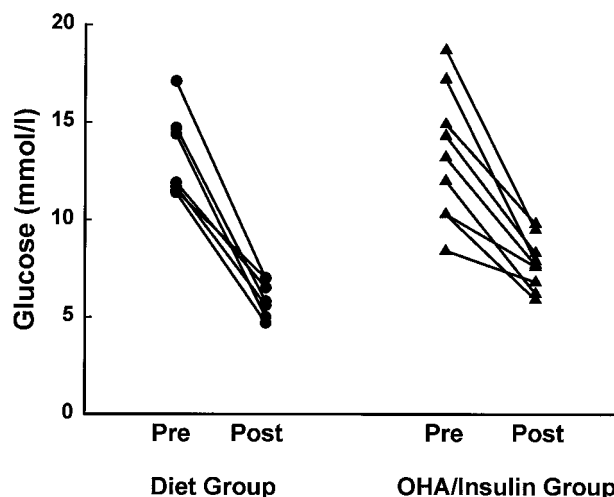


Figure 2—Fasting serum glucose levels before and after the brief course of insulin therapy in the group who remained in good glycemic control on diet alone and the group who needed either OHA or insulin therapy on follow-up. The mean glucose values after insulin therapy in the two groups were significantly different from each other (see text).

not significantly different from that of the OHA/insulin group and thus does not likely explain the findings.

It is clear that we do not have a control group, and this is the important next step. The design was directed to elucidate what predicts success in achieving glycemic control. Further studies will be required to compare intensive dietary therapy and aggressive therapy with insulin or OHAs used to achieve the same ends. A short course of insulin therapy that readily rendered the patient normoglycemic was associated with an excellent long-term outlook. It is of interest that the results in patients with secondary failure of OHAs who have been given a short course of intensive insulin therapy are quite different in that they usually can maintain glycemic control on diet alone for a very short period. The natural history of type 2 diabetes is one of declining function over a number of years, and it is likely that our newly diagnosed patients have more reserve of function and 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. Patients who remain hyperglycemic on oral agents are much further along in the course of their disease and hence do not have as favorable an outcome with the short course of insulin.

In conclusion, we have demonstrated that in severe newly diagnosed type 2 di-

abetes, a short course of intensive insulin therapy can successfully lay a foundation for long-term good glycemic control. The ease with which normoglycemia is achieved on insulin may predict those patients who can later succeed in controlling glucose levels with attention to diet. However, the numbers in this study were small, and the results need confirmation with larger studies before being considered as a routine clinical option.

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