Natural Course of Insulin Sensitivity and Insulin Reserve in Early Insulin-Dependent Diabetes Mellitus

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Preservation of endogenous insulin in insulin-dependent diabetes mellitus (IDDM) may prevent the occurrence of diabetes-related complications. Therefore, it is important to know about insulin reserve and insulin sensitivity at clinical manifestation. Twenty-four patients (aged 23 ± 6 years) were evaluated for 2 years starting at the day of clinical manifestation. Insulin secretion was stimulated by glucagon, arginine, and glucose on separate days. Insulin sensitivity was evaluated by hyperinsulinemic-euglycemic clamp. Two control groups were established, one consisting of age-, weight-, and sex-matched healthy individuals, the other of patients with diabetes of long duration (6 to 13 years). Sensitivity improved from 30% of normal at baseline to 84% after only 2 weeks in the newly manifested patients. Subsequently, insulin released by nonglucose stimuli increased by 75%. Glucose-induced first-phase insulin secretion did not recover. After 2 years, sensitivity was 20% less than normal and glucagon-stimulated C-peptide (GSCP) was 0.64 ± 0.20 nmol/L (0.41 ± 0.19 at baseline, $P < .002$). Insulin sensitivities in euglycemic and hyperglycemic conditions were closely correlated. In conclusion, improvement of insulin sensitivity precedes and is possibly a prerequisite for the recovery of residual insulin in early IDDM.

CLINICAL STUDIES have suggested that early insulin treatment in insulin-dependent diabetes mellitus (IDDM) results in a temporal remission of insulin dependency.[1-3] A negative relationship between preserved β-cell function and progression of diabetes complications such as retinopathy and nephropathy was reported.[4-6] Forty percent to 50% of patients developed temporary remission of the disease ("honeymoon") and were able to reduce the daily insulin markedly or even discontinue it.[7] The remission period is associated with a recovery of residual insulin and therewith resembles the prediabetic state. One of the earliest defects in the pathogenesis of IDDM is impaired glucose-stimulated insulin release. On the other hand, nonglucose stimuli can mobilize insulin better than glucose itself.[8] In consequence, we wanted to answer the question whether, during remission, glucose-induced insulin could be restored, or alternatively, if endogenous insulin was only available in the presence of nonglucose stimuli such as arginine or glucagon.

Insulin action is reduced in newly diagnosed hyperglycemia and in long-standing diabetes.[9] It is restored by insulin therapy. The question has been raised of whether improvement of insulin sensitivity contributes to the development of partial remission together with the recovery of insulin secretory capacity. Conversely, the need for higher doses of insulin may result from the reappearance of insulin resistance, a reduction in residual β-cell function, or both. While most studies have focused on residual insulin, there is less information on insulin resistance after clinical manifestation of IDDM. This study was therefore undertaken to address the following questions: (1) Can insulin therapy normalize insulin resistance?; (2) To what extent do insulin sensitivity and insulin reserve contribute to clinical remission?; and (3) Is there a chronologic sequence of improvement of insulin sensitivity and insulin reserve? Compared with childhood diabetes, adult-onset diabetes is characterized by a longer period before diagnosis and better preservation of residual β-cell function.[10] Therefore, we chose adult patients to provide an expanded profile of the interrelations of insulin reserve and insulin action. Insulin sensitivity was estimated by insulin-mediated glucose uptake during a euglycemic insulin clamp at defined time intervals after the beginning of therapy. We found that initial insulin resistance returned to normal only 2 weeks after starting insulin therapy. Normalization of insulin sensitivity was followed by an increase of residual insulin with a maximum at 6 months. Residual insulin only responded to nonglucose stimuli, and glucose never became an effective stimulant for insulin release again.

SUBJECTS AND METHODS

Subjects

Twenty-four patients with IDDM were evaluated for 2 years after clinical manifestation. IDDM was defined on the basis of insulin dependency according to World Health Organization recommendations.[11] Mean weight loss before diagnosis was 5.7 ± 2.9 kg, and duration of symptoms was 7.2 ± 2.1 weeks. Patients were either nonsmokers or gave up smoking. They were hospitalized in the beginning for 2 weeks. During this time, they passed a 1-week diabetes education program including training for self-monitoring of blood glucose. They were started on a twice-daily dose of intermediate-acting insulin, and regular insulin was added if postprandial capillary glucose levels exceeded 11 mmol/L.

Once a year, patients were examined for retinopathy and albuminuria. By the end of the follow-up period, none of the patients had developed these complications.

Two control groups were selected: (1) patients with long-standing IDDM with a mean duration of 9 ± 3 years (range, 6 to 13) (n = 6) and (2) age-, sex-, and weight-matched healthy persons. Volunteers gave informed written consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the Hospital Ethics Committee. Clinical characteristics of the patients are listed in Table 1.

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Table 1. Baseline Demographic Characteristics of the Three Groups: Subjects With Newly Manifested Diabetes, Subjects With Long-standing Diabetes, and Healthy Controls

Variable	Healthy Controls (n = 24)	Diabetics	
		Newly Manifested (n = 24)	Long-standing (n = 6)
Age (yr)	24 ± 6	23 ± 6	22.9 ± 8
BMI (kg/m²)	22.5 ± 5	20.2 ± 6	24.5 ± 3
Sex (F/M)	14/10	14/10	3/3
FPG (mmol/L)	4.9 ± 1.2	9.2 ± 3.2	7.4 ± 2.5
HbA_{1c} (%)	5.0 ± 0.2	12.4 ± 1.1	7.6 ± 1.1
Insulin*	—	0.92 ± 0.23	0.58 ± 0.26
ICA	—	19	1

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose.
*$U \cdot kg^{-1} \cdot d^{-1}$.

Protocol

Patients were studied first before initiation of insulin treatment (baseline), at 2 and 6 weeks, and thereafter every 3 months during the first year and every 6 months during the second year. The following tests were performed: glucagon (1 mg)-stimulated C-peptide (GSCP), hyperglycemic clamp combined with arginine bolus, and euglycemic-hyperinsulinemic clamp. Tests were performed at least 3 days apart and only when patients presented with blood glucose values in the target range for the week preceding tests and on the morning of the tests. No detectable hypoglycemia had occurred during the 24 hours preceding the tests. Subcutaneous insulin administration was stopped 12 to 14 hours before.

GSCP

Plasma C-peptide level was measured before and after stimulation by 1 mg intravenous (IV) glucagon. Venous blood samples were collected in EDTA-coated tubes before and 6 minutes after glucagon challenge. Plasma samples were kept at ice-cold temperature and then centrifuged at 4°C. Samples were kept at −20°C until assay and thawed only once.

Analytic Procedures

A glucose analyzer measured plasma glucose levels (Beckman, Fullerton, CA). Hemoglobin A_{1c} (HbA_{1c}) level was measured using a Diamat (Biorad, Munich, Germany). Islet-cell antibodies (ICAs) were determined according to the recommendations of the Fourth International Serum Exchange Workshop on islet cell antibodies.[12] They were considered positive at ≥20 JDF (Juvenile Diabetes Foundation).

Plasma C-peptide was determined by a double-antibody liquid-phase radioimmunoassay kit with intraassay variation of 5.3% and interassay variation of 8.8% (Biermann, Bad Nauheim, Germany). Cross-reactivity to proinsulin was 18%. Free immunoreactive insulin was assessed by a radioimmunoassay kit (Pharmacia, Heidelberg, Germany) after precipitation with polyethyleneglycol according to the method reported by Nagakawa et al.[13]

Hyperglycemic Clamp and Arginine Bolus

The hyperglycemic clamp was performed in normal subjects and in newly manifested diabetics. After a 12-hour fast (8 to 9 AM), a hand vein was cannulated retrogradely (20 g braunula) and maintained wrapped in a heating pad to obtain arterialized plasma samples. At the same time, an antecubital vein was cannulated for infusion of glucose or arginine on the contralateral side. Patency of these lines was maintained by slow infusion of saline. After collection of two baseline specimens over 30 minutes, 5 g L-arginine hydrochloride solution (10%) was injected over 30 seconds. Following arginine administration, blood was withdrawn every 2 minutes for the first 10 minutes, then at 15, 20, and 30 minutes, and immediately placed on ice. A bolus of 0.2 g/kg glucose over 1 minute was injected, and samples were taken at 2.5, 5, 7.5, 10, 12.5, 15, and 20 minutes after glucose injection. Then a variable infusion of 20% glucose was started to maintain arterialized venous plasma glucose concentration at 10 mmol/L for the next 180 minutes. Blood samples were taken every 20 minutes. Blood glucose was determined every 5 minutes, and glucose infusion rates were adapted depending on blood glucose measurements. Another arginine bolus was administered during hyperglycemia at time point 180 minutes. Total blood withdrawal was less than 150 mL, and maximal total fluid infusion was less than 2,000 mL.

In patients with diabetes of long duration, the arginine bolus was applied under basal conditions only.

Euglycemic-Hyperinsulinemic Clamp

The euglycemic clamp was initiated in the postabsorptive state at 8 AM. Rapid euglycemia was achieved by priming boluses of IV insulin (80 to 120 $mU \cdot m^{-2} \cdot min^{-1} \cdot h$) over 15 minutes. Thereafter, insulin (Insulin H; Höchst, Germany) was infused at a constant rate of 40 $mU \cdot m^{-2}$ body surface $\cdot min^{-1}$ for 180 minutes. Blood glucose concentration was determined every 5 minutes with a glucose-oxidase method and manually maintained close to 5 mmol/L by variation of the infusion rate of a 20% glucose solution. Every 20 minutes blood was drawn. At the end of the test, the IV glucose infusion was maintained for another 60 minutes, its rate was progressively decreased, and blood glucose was frequently monitored.

Calculations and Statistical Analysis

Values are the mean ± SE for results and statistical treatment. ANOVA tested for differences between groups. As noted, we studied three groups: newly manifested diabetics, long-standing diabetics, and metabolically normal persons. With parametric values, we also performed a univariate repeated-measures analysis with time as the repeated measure and all the patients of one of the three groups. The tests were performed with the SPSS statistical software system (SPSS, Heidelberg, Germany).

The insulin area under the curve (AUCIns) for the arginine and glucose bolus was calculated according to the trapezoidal rule from 0 to 10 minutes. $AUCIns_{10\,min}$ was considered to represent first-phase insulin secretion. The slope of glucose potentiation of the arginine-stimulated insulin impulse was used as an indirect measure of insulin responsiveness to the potentiating effects of glucose, as proposed by Ward et al.[14] The slope of potentiation was calculated as Δacute insulin response after arginine bolus ($AUCIns_{10\,min}$ at clamped glucose [10 mmol/L] minus $AUCIns_{10\,min}$ at fasting glucose) divided by Δplasma glucose level. It was assumed that a steady state of glucose and insulin turnover was reached after 120 minutes during the hyperglycemic clamp. The steady-state insulin (I) level during hyperglycemia (10 mmol/L) was the mean insulin concentration measured between 120 and 180 minutes during the hyperglycemic clamp.

Insulin sensitivity was calculated as M/I from euglycemic-hyperinsulinemic clamp data and hyperglycemic clamp data, respectively. Glucose disposal (M) was estimated from the average glucose infusion rate ($\mu mol \cdot kg^{-1} \cdot min^{-1}$) during the last hour of each individual clamp, and was divided by I (picomolar) at the corresponding point of time.

RESULTS

Clinical Course and Islet β-Cell Challenge by Glucagon

Fasting plasma glucose in newly manifested patients declined continuously, reaching the normal range at 3 months (6.4 ± 1.3 *v* 9.2 ± 3.2 mmol/L at baseline, $P < .001$). The insulin dose was not reduced unless hypoglycemia occurred. The mean daily insulin dose was 0.92 ± 0.23 U · $kg^{-1} \cdot d^{-1}$ at baseline and 0.37 ± 0.05 ($P < .01$) after 1 year. HbA_{1c} decreased from 12.4% ± 1.1% before the first insulin injection to 6.3% ± 0.8% 1 year later ($P < .001$) (Fig 1).

HbA_{1c} levels were 7.6% ± 1.1% in long-standing well-controlled diabetic subjects, and they did not change significantly during the 2-year follow-up period.

GSCP concentrations at baseline were lower in recent-onset patients as compared with healthy controls (Fig 2). Six months after diagnosis, the improvement in glycemic control was associated with a 67% increase in insulin secretory function as assessed by stimulated C-peptide levels (0.43 *v* 0.72 nmol/L, $P < .05$; Fig 2A). By the end of the 2-year treatment, GSCP in newly manifestated patients was 51% of levels in healthy controls (Fig 2B).

β-Cell Challenge by Glucose (hyperglycemic clamp)

Fasting serum insulin levels were 67 ± 3 pmol/L in healthy controls. Figure 3A shows acute insulin release during the 10 minutes after a glucose bolus. Glucose-induced acute insulin release was less than 5% of normal. No significant improvement of insulin secretion was found during the course of the study. By contrast, steady-state insulin (I) as a parameter for the late phase of insulin response to glucose reached a maximum after 6 months ($P < .05$; Fig 3B) and declined again.

β-Cell Challenge by Arginine

The acute insulin response to IV arginine was measured before and during a hyperglycemic clamp because arginine-induced insulin release is dependent on blood glucose concentration.[15] Arginine-induced insulin secretion before starting the hyperglycemic clamp had increased by 80% ($P < .05$) after 9 months and remained at that level throughout the follow-up period of 24 months. Arginine bolus injection was repeated while glucose was clamped. Clamp glucose concentrations were nearly identical at the different time points (Table 2). The integrated increment of serum free immunoreactive insulin levels at 10 mmol/L glucose 0 to 10 minutes after a single bolus of arginine more than doubled, with a peak at 9 months (Table 2; 221 ± 209 pmol/L · min at 0 months *v* 975 ± 289 at 9 months, $P < .01$). The 9-month peak insulin area was only 15% less than in healthy individuals. After 2 years, arginine-induced insulin release during hyperglycemic clamp was still greater than double the baseline value ($P < .01$).

The potentiation of arginine-stimulated insulin release by glucose also increased during follow-up evaluation, reaching a supranormal maximum at 9 months (Table 2; dl/dG, 209 ± 102 *v* 174 ± 36 pmol/L · min · $mmol/L^{-1}$, $P < .05$).

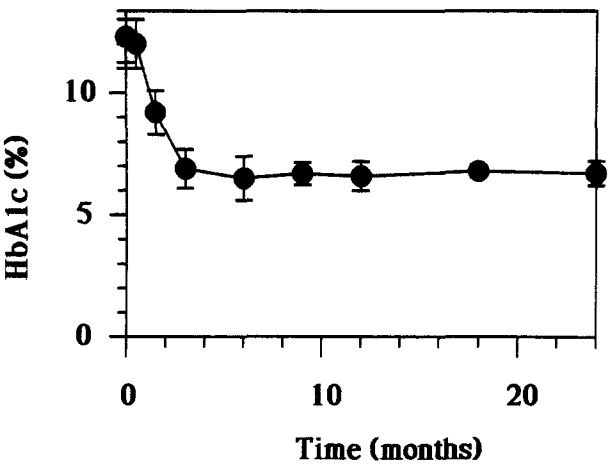

Fig 1. Time course of HbA_{1c} levels (mean ± SEM) during the course of study in patients with IDDM of recent onset.

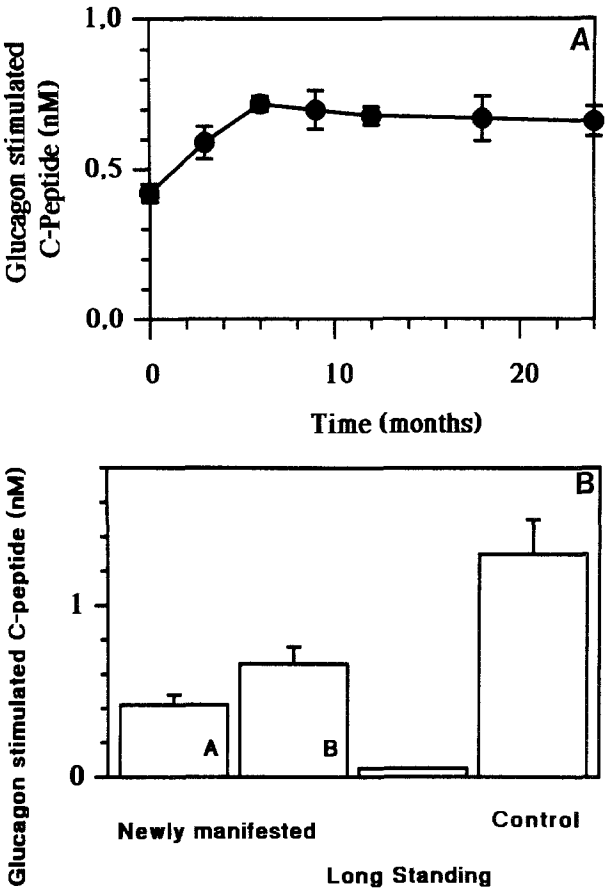

Fig 2. (A) Mean plasma C-peptide levels (nmol/L) of new IDDM patients stimulated by 1 mg IV glucagon (GSCP). After 2 years, GSCP was significantly higher than at baseline ($P < .01$). (B) GSCP in newly manifested patients, long-standing diabetics, and healthy control. All data are the mean ± SEM. (A) Beginning; (B) end of 2 years.

Insulin Sensitivity

During euglycemic clamp studies, plasma glucose levels were 5 mmol/L with a coefficient of variation of 7% ± 1%.

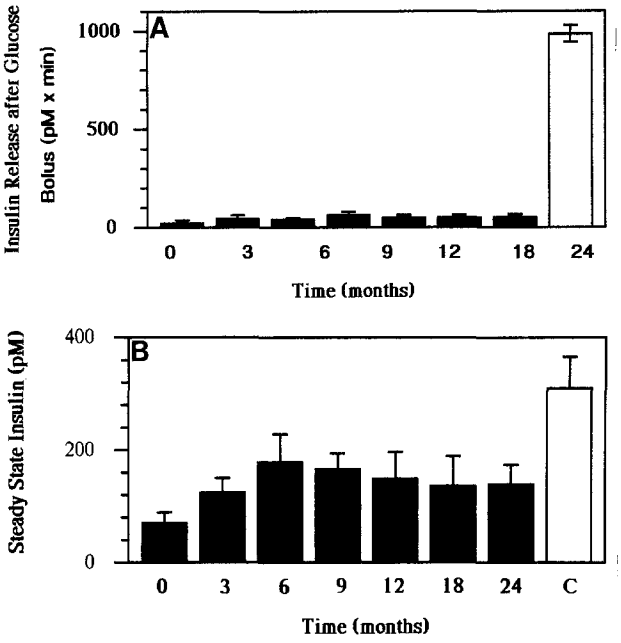

Fig 3. (A) Insulin release after a bolus of 0.2 g/kg glucose IV. Values are the mean $AUC_{10\ min}$ pmol/L · min. (□) Normal controls. (B) Insulin levels during hyperglycemic clamp after attaining steady state (120 to 180 minutes). After 6 months, steady-state insulin was significantly ($P < .05$) higher than baseline. C, normal control. All data are the mean ± SEM.

The time required to reach normoglycemia was 34 ± 4 minutes at baseline and 5 ± 3 at 9 months for newly manifested patients ($P < .001$). Mean steady-state serum free-insulin levels were 510 pmol/L with a coefficient of variation of 11% ± 3%.

At clinical diagnosis of IDDM, insulin sensitivity as judged from M/I during hyperinsulinemic-euglygemic clamp was only 34% of the level for healthy controls (Fig 4B). Thereafter, M/I normalized, and at 24 months after diagnosis it had declined, but still remained at a near-normal level (Fig 4A and B). Directly after beginning insulin therapy (1.5 months), M/I values were 115% of controls, implicating transient hypersensitivity to insulin of the periphery. At the end of the observation period, M/I in the euglycemic condition was still 85% of normal values. A strong correlation was found between M/Is calculated from euglycemic and hyperglycemic clamps, respectively. Reduced insulin sensitivity was measured in all patients who had had diabetes for 6 to 13 years (0.068 ± 0.013 v healthy control 0.0952 ± 0.0143 $\mu mol \cdot kg^{-1} \cdot min^{-1} \cdot pmol/L^{-1}$, $P < .02$).

In metabolically normal subjects, decreases in insulin sensitivity are compensated by an increase in insulin response so glucose tolerance may be conserved. As a result, the product of insulin sensitivity and first-phase insulin release is constant.[15] Figure 5 depicts the reciprocal correlation between M/I and first-phase insulin response to glucose ($AUCIns_{10\ min}$). For every patient finishing the study at 24 months, the individual product was calculated. No healthy person had a constant less than 70, which is represented by the hyperbola in Fig 5. All values for

Table 2. Insulin Stimulation by a 5-g Bolus of Arginine in Newly Manifested Patients, Persons With Long-standing Diabetes, and Healthy Controls

	Time (months)							
	0	0.5	1.5	3	6	9	12	24
Newly manifested diabetics								
Fasting								
Glucose (mmol/L)	9.2 ± 3.2	7.0 ± 1.9	6.8 ± 1.0	6.4 ± 1.3	6.3 ± 0.6	6.4 ± 1.5	5.9 ± 1.8	6.4 ± 2.1
Insulin (pmol/L · min)	127 ± 41	124 ± 56	136 ± 74	148 ± 56	209 ± 78*	214 ± 145*	245 ± 195*	252 ± 195*
Clamp								
Glucose (mmol/L)	10.0 ± 1.5	10.0 ± 1.5	9.9 ± 1.1	10.1 ± 1.0	9.9 ± 1.2	10.2 ± 1.1	10.0 ± 1.3	10.1 ± 1.5
Insulin (pmol/L · min)	221 ± 209	411 ± 256	433 ± 247	514 ± 289	759 ± 229*	975 ± 289*	925 ± 198*	851 ± 289*
Slope dI/dG	105 ± 43	113 ± 64	110 ± 45	122 ± 49	161 ± 53	209 ± 102*	171 ± 111*	163 ± 101*
Long-standing diabetics								
Fasting								
Glucose (mmol/L)	12.1 ± 3.6							
Insulin (pmol/L · min)	0							
Healthy controls								
Fasting								
Glucose (mmol/L)	5.1 ± 1.2							
Insulin (pmol/L · min)	262 ± 89							
Clamp								
Glucose (mmol/L)	10.2 ± 0.9							
Insulin (pmol/L · min)	1,150 ± 127							
Slope dI/dG	174 ± 36							

NOTE. Values are the mean ± SEM. Arginine was injected at two different glucose concentrations: fasting glucose (range, 5.0 to 12.2 mmol/L) or clamped glucose (9.9 to 10.2). Insulin response to arginine was calculated as $AUCIns_{10\ min}$. dI/dG is the potentiation slope of arginine-stimulted insulin release by different levels of glycemia, and is given as pmol/L · min · $mmol/L^{-1}$.

*$P < .01$ baseline.

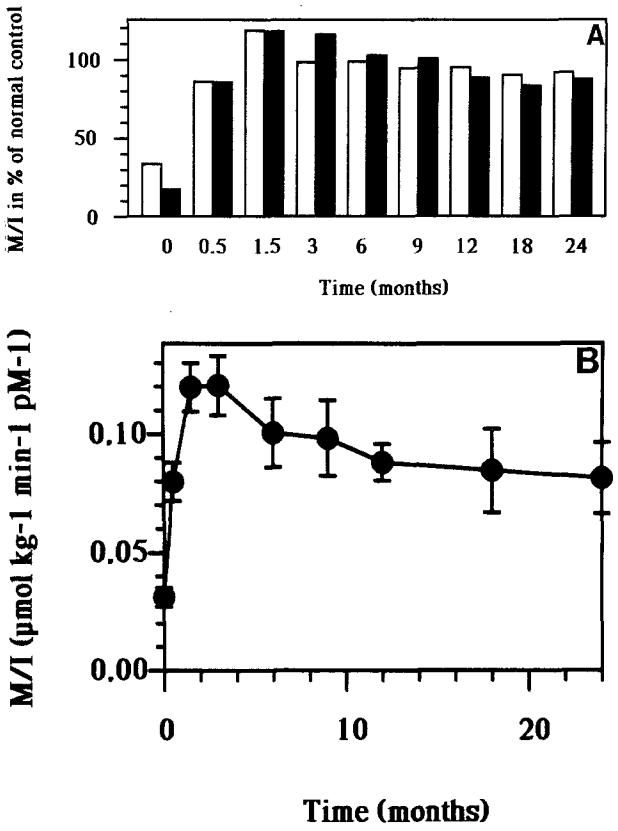

Fig 4. (A) Time course of M/I derived from the euglycemic-hyperinsulinemic clamp. Values are the mean ± SEM. All data points are significantly higher than baseline ($P < .05$). M/Is at 1.5 and 3 months are greater than values measured in healthy controls (not shown). (B) Time course of M/Is (mean values) derived from euglycemic clamps (□) and hyperglycemic clamps (■).

nondiabetic controls are therefore on the right and upper side of the curve, and points for diabetic patients are on the left of the line. None of the patients had a significant glucose-dependent insulin release, but many had normal sensitivity. ICA-negative patients tended to have higher M/I values as compared with ICA-positive patients, and subjects with a long duration of the disease had M/Is in the lower range.

A linear regression line was constructed between potentiation slope dI/dG of arginine-stimulated insulin and M/I values (Fig 6). dI/dG was low at baseline and increased to 80% of normal after 2 years. An individual patient with an M/I in the normal range had a higher dI/dG value than a patient with low M/I. This relationship is depicted in the figure ($r = .95$, $P < .001$). Likewise, GSCP and insulin sensitivity were correlated ($r = .86$, $P < .001$).

Intensive insulin therapy is always accompanied by weight gain in IDDM subjects. There was a significant negative correlation ($r = -.70$, $P = .048$) between M/I and weight gain. Increasing weight more than 10 kg after beginning insulin therapy was associated with a greater than 50% decline of M/I from the individual maximum.

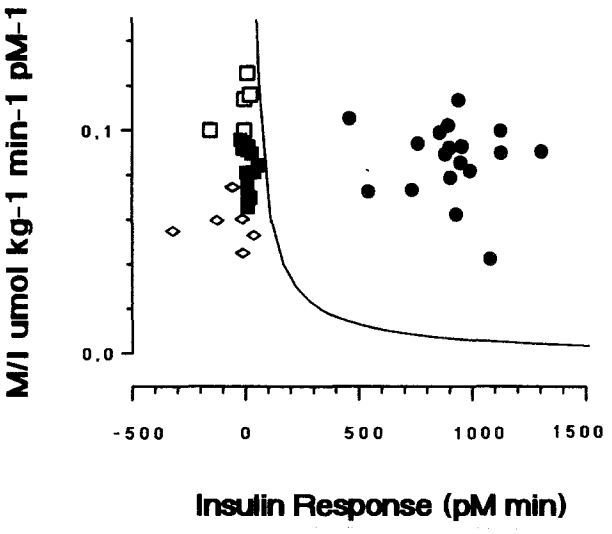

Fig 5. Inverse relationship between M/I derived from the euglycemic clamp and first-phase insulin secretory response to glucose ($AUCIns_{10\ min}$) in glucose-tolerant persons. The hyperbola is the graphic representation of M/I × $AUCIns_{10\ min}$ = 70. None of the healthy controls had an individual constant below this threshold value. The patient values were calculated from clamp tests at the end of the 2-year follow-up. (●) Healthy controls; (◇) long-standing diabetes; (■) newly manifested ICA-positive patients; (□) newly manifested ICA-negative patients. Symbols represent data from single patients.

DISCUSSION

It is well documented that abnormalities in IV glucose–stimulated insulin release occur before the onset of overt diabetes.[16-18] Despite an essentially absent first-phase IV glucose–stimulated insulin secretion, some response to IV glucagon, tolbutamide, and arginine is usually preserved.[8] We used three different intravenously applied stimuli (glucagon, glucose, and arginine) to evaluate insulin release and to obtain objective parameters for insulin reserve. We

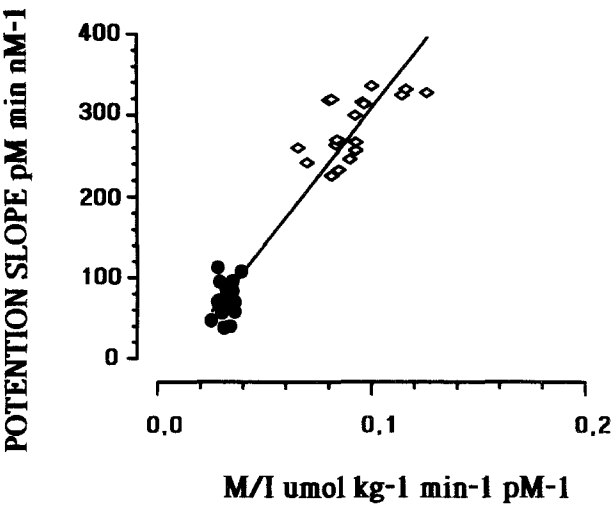

Fig 6. Linear regression between potentiation slope (of arginine-stimulated insulin release) M/I. $R^2 = .90$, $P < .001$. (●) Potentiation slopes at baseline; (◇) at the end of the study.

could demonstrate a significant and sustained recovery of GSCP and arginine-induced insulin release after 6 and 9 months of insulin therapy, respectively. By contrast, glucose-induced acute insulin release did not improve. We have no evidence that arginine-induced insulin output was stimulated by increased glucose sensitivity of the islets of Langerhans. Glucose-dependent insulin secretion seems to be irreversibly damaged at the onset of clinical IDDM. This phenomenon may be explained by the progressive nature of insulin loss in the prediabetic state, beginning with glucose as a stimulus for insulin release, followed by nonglucose stimuli.

Better preservation of insulin sensitivity was related to higher values for the potentiation slope (dI/dG) and higher GSCP levels. The longitudinal design of this study showed that improvement of insulin sensitivity was succeeded by recovery of insulin reserve. Without optimal treatment of insulin resistance, no substantial increase in C-peptide level occurred in a given patient. We hypothesize that there is an interrelationship between insulin action in peripheral tissues and non–glucose-dependent insulin release of the β cell.

In newly manifested patients, insulin therapy was not completely interrupted, but was reduced when hypoglycemic symptoms occurred. We never observed severe hypoglycemia in newly manifested patients during the 2-year study. By contrast, three patients with diabetes of long duration had at least one episode of severe hypoglycemia during the follow-up period.

Clinical studies as early as the 1970s already suggested that intensive insulin treatment resulted in a longer period of good metabolic control and prolonged remissions.[1-3,19,20] Unfortunately, there is no consensus on the definition of clinical remission. Immune intervention trials used the rate of remissions—usually 30% to 50% of patients in the different treatment groups—to evaluate a given therapy. During remission, insulin was discontinued, so that a substantial number of participating patients did not receive insulin treatment for several months. There is reason to assume that reducing the exogenous insulin dose to the lowest level compatible with a normal premeal glucose level may exhaust the remaining β cells found in an individual with recent-onset IDDM. In our study, insulin treatment was continued with the maximal tolerable amount that did not cause recurrent hypoglycemia and normalize blood glucose levels. The mean daily insulin dose was 0.38 ± 0.05 $U \cdot kg^{-1} \cdot d^{-1}$ at 6 months from baseline for all patients with recently manifested disease.

The reported frequency of remissions was difficult to ascertain because of the application of different criteria.[21-23] In studies using stimulated C-peptide as a criterion of remission, patients with the highest stimulated C-peptide at entry were the most likely to have a remission.[23,24] Patients with less weight loss and no ketoacidosis at diagnosis were also more likely to go into remission. Conflicting results on the influence of ICAs and the duration of preceding symptoms were reported.[23-25] Increasing age was identified as one of the strongest parameters for facilitating the so-called honeymoon by most studies. We found that excessive weight gain after insulin therapy was associated with reduced insulin sensitivity and hence lower C-peptide levels. Patient education, diet, and exercise might prove to be additional factors in achieving remission.

It was possible to maintain GSCP on a level superior to the one at diagnosis for a period of 2 years. We attribute this success to several characteristics of the design of this study. Normalization of insulin sensitivity by tight glucose control was an important prerequisite for the recovery of C-peptide levels. All IDDM volunteers practiced glucose control, and they were instructed on the potential importance of residual insulin for the prevention of diabetic complications in the diabetes education program. No children were included because previous studies had shown a rapid loss of C-peptide as compared with adult-onset IDDM.

Previous studies have demonstrated a state of insulin resistance in recent-onset IDDM and its improvement under insulin therapy.[26-28] We also found a large decrease in insulin sensitivity at the onset of diabetes, followed by an impressive restoration to near-normal M/I values within 2 week's time. This is consistent with a recent report on hypersensitivity to insulin as measured by the euglycemic-hyperinsulinemic clamp during remission in cyclosporin-treated patients.[29] Recovery of insulin action clearly preceded and possibly was a prerequisite for the improvement of insulin release. Individually calculated M/I in newly manifested patients showed overlaps with M/I in long-standing diabetics and metabolically healthy persons; however, mean M/I values in the newly manifested group remained in the near-normal range throughout the second year of the study.

In conclusion, M/I increased during insulin therapy after near-normal blood glucose levels were reached. Subsequently, C-peptide and insulin responses to non-nutrient secretagogues were improved and linearly correlated with the degree of insulin sensitivity.

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