Intensive Therapy in Adult Insulin-Dependent Diabetes Mellitus Is Associated With Improved Insulin Sensitivity and Reserve: A Randomized, Controlled, Prospective Study Over 5 Years in Newly Diagnosed Patients

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Optimal blood glucose levels and normal insulin sensitivity are aims in the treatment of insulin-dependent diabetes mellitus (IDDM). Insulin sensitivity and insulin reserve are closely interrelated. It is essential to know more about both of these parameters at clinical diagnosis, because their preservation may delay the occurrence of diabetes-related complications. B-cell function is likely to be retained for a longer period in patients with adult onset of the disease compared with children. In this study, intensive insulin treatment was initiated in newly diagnosed adult patients to determine if it preserved endogenous insulin secretion longer than conventional therapy. Forty-nine patients with newly diagnosed diabetes were carefully categorized as having IDDM according to clinical and serological criteria. They were randomized to an intensive (I group) or conventional (C group) insulin therapy and evaluated for 5 years. Every 6 months, a check-up included glucagon-stimulated C-peptide (GSCP), hyperglycemic glucose clamp with arginine bolus, euglycemic-hyperinsulinemic clamp, and screening for microalbuminuria, retinopathy, and neuropathy. At the end of the study, hemoglobin A_{1c} (HbA_{1c}) was 6.3% ± 1.9% in the I patients and 8.1% ± 2.1% in the C patients ($P \leq .001$). Blood glucose concentrations less than 3.5 mmol/L were more frequent in the I group than in the C group ($P < .05$). Insulin sensitivity (M/I) and GSCP were higher in intensively treated patients after 5 years (M/I, I group 40 ± 10 nmol · kg^{-1} · min^{-1} · pmol/L^1 *v* C group 21 ± 11, $P < .005$; GSCP, I group 0.6 ± 0.2 nmol/L *v* C group 0.19 ± 0.11, $P < .005$). The prevalence of peripheral neuropathy was significantly lower in the I group at the end of the study. In conclusion, intensive therapy is more effective in the preservation of insulin action and reserve. In our patients, no case of severe hypoglycemia was observed, indicating that intensive therapy was safe in these patients.

INSULIN-DEPENDENT diabetes mellitus (IDDM) is mediated by an autoimmune process that destroys the insulin-producing B cells of the endocrine pancreas. The sequence of events leading to this destruction is known through animal models. However, epidemiological observations suggest that IDDM is a heterogenous disease depending on factors like sex, age at onset, diet, virus infections, and other environmental influences.[1] Efforts to preserve residual insulin in children with newly diagnosed diabetes have largely been unsuccessful. Preservation of endogeneous insulin release was attempted through the use of either intensive insulin therapy during the first 2 or 4 weeks[2,3] or immunosuppressive treatment.[4] However, improvement of B-cell function did not last beyond 3 months, as evidenced by C-peptide secretion. We and others have found that adult-onset patients have a longer period of residual insulin secretion than children.[5-7]

After initiation of therapy, newly diagnosed IDDM is usually characterized by near-normal glycemia and a decreased need for exogenous insulin,[8,9] a state referred to as the remission period. Insulin action is reduced in newly diagnosed diabetes, but it may be restored by the introduction of insulin therapy.[2,10] Despite reliable methods to evaluate residual insulin secretion and insulin sensitivity, no long-term prospective studies are available to assess the interaction of both parameters under conditions of different insulin regimens. There is conclusive evidence in the literature that lower blood glucose concentrations delay the onset of diabetic complications.[11,12] It is in this context also important to know whether prevention of diabetic complications is possible when both insulin reserve and insulin action are preserved. In the present study, we have focused on the effect of intensive insulin therapy on these parameters using a prospective randomized design.

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SUBJECTS AND METHODS

Subjects and Study Design

The protocol was reviewed and approved by the local ethics committee. It was explained to successive patients with newly diagnosed IDDM admitted to our clinic starting in 1988. After informed consent had been obtained from the patients, randomization was performed with the use of computer-selected random numbers. A total of 49 patients were randomized for intensive (I) or conventional (C) insulin therapy, and they were evaluated for 5 years after clinical diagnosis. IDDM was defined on the basis of insulin dependency according to World Health Organization recommendations.[13] The subjects were hospitalized in the beginning for 2 weeks. During this time, they completed a 1-week diabetes education program including training for self-monitoring of blood glucose and hypoglycemic symptoms. Most patients were given a blood glucose meter (Accutrend; Boehringer, Mannheim, Germany) that was able to store data on blood glucose values, insulin dosages, and the occurrence of hypoglycemic symptoms (when the patient pressed a special button on the meter display). Data were subsequently analyzed by a computer program to calculate the mean blood glucose concentration, mean insulin dosage, and incidence of hypoglycemic events (blood glucose < 3.5 mmol/L) with or without symptoms.

Glucagon-stimulated C-peptide (GSCP) arginine-stimulated insulin secretion, and insulin sensitivity were determined every 6 months, with at least 3 days between tests. These tests were preceded by a 1-week optimization of blood glucose control with frequent self-monitoring and daily visits to correct for the influence of glycemia in both groups.

For the determination of GSCP, blood was drawn 6 minutes

after intravenous (IV) injection of 1 mg glucagon after an overnight fast. Screening for neuropathy, retinopathy, and microalbuminuria was performed regularly once per year.

Intensive therapy included administration of insulin at least three times daily by injection. The dosage was adjusted by the patients or by health care professionals according to the results of self-monitoring of blood glucose, dietary intake, and anticipated exercise. The mean frequency of glucose determinations was 4.2 ± 2.8 per patient per day. Target blood glucose in the I group was defined as self-determined capillary glucose less than 6.8 mmol/L before meals and less than 10 mmol/L postprandially. Capillary blood glucose testing was validated with laboratory values at entry and every half-year thereafter. The goals of intensive therapy also included glycosylated hemoglobin in the normal range (HbA_{1c} < 6.5%). The I group contacted the diabetes educator by visit or telephone once per month to review and adjust the regimens.

Conventional therapy consisted of one or two daily injections of insulin, including mixed intermediate and rapid-acting insulins and variable self-monitoring of blood glucose. Patients contacted the study center quarterly, and the mean for glucose measurements was 2.3 ± 1.9 per patient and day. Conventional therapy did not always include daily adjustments in the insulin dosage. The goals of conventional therapy included the absence of symptoms attributable to glucosuria or hyperglycemia, and freedom from severe or frequent hypoglycemia. In both groups, I and C, a small amount of exogeneous insulin was maintained even when C-peptide secretion recovered significantly.

Hyperglycemic Clamp and Arginine Bolus

The hyperglycemic clamp was performed after a 14-hour fast with 6 to 12 U regular insulin at midnight (mean fasting blood glucose, I group 6.7 ± 1.3 mmol/L *v* C group 6.6 ± 1.9, NS). A hand vein was cannulated retrogradely, and the hand was kept wrapped in a heat 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 two baseline specimens, 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 and then at 15, 20, and 30 minutes, and immediately placed on ice. A bolus of glucose 0.2 g/kg over 1 minute was injected. Then, a variable infusion of 20% glucose was started to maintain an arterialized venous plasma glucose concentration of 10 mmol/L for the next 210 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 given during hyperglycemia at time point 180 minutes. The total amount of blood drawn was less than 80 mL, and the maximal total fluid infusion was not greater than 1,400 mL.

Euglycemic-Hyperinsulinemic Clamp

The euglycemic clamp was initiated in the postabsorptive state at 8:00 AM after 12 hours of optimization of blood glucose control with IV insulin infusion. During the euglycemic clamp, insulin (Insulin H; Hoechst, Germany) was infused at a constant rate of 40 mU/min/m^2 body surface for 3 hours. Blood glucose concentrations were determined every 5 minutes and maintained manually close to 5 mmol/L by variation of the infusion rate of a 20% glucose solution. Every 20 minutes, arterialized blood was drawn. After 180 minutes, insulin infusion was stopped, and IV glucose infusion was maintained for another 60 minutes with a progressively decreasing infusion rate.

Calculations and Statistical Analysis

Insulin sensitivity was calculated as the M/I ratio from the euglycemic clamp. Glucose disposal was estimated from the mean glucose infusion rate, M (μmol/kg/min), during the last hour and was divided by insulin, I (picomoles), during the corresponding period. 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. The slope of potentiation (dI/dG) was calculated as the area under the curve of the insulin response over 10 minutes after the arginine bolus at clamped glucose (10 mmol/L) minus the insulin response at fasting glucose (dI). dI was then divided by the difference for clamped and fasting glucose concentrations (dG). It was assumed that a steady-state glucose and insulin turnover was reached after 2 hours during the hyperglycemic clamp. The steady-state insulin level during hyperglycemia (10 mmol/L) was the mean plasma insulin concentration measured between 120 and 180 minutes of the hyperglycemic clamp. Results are presented as the mean ± SD. ANOVA and χ^2 tests were used to test for differences between groups. With parametric values, we also performed a univariate repeated-measures analysis, with time as the repeated measure and all patients of one of the two groups. Logistic regression analyses were performed to evaluate associations between BMI, GSCP, and M/I. The tests were performed with the SPSS statistical software system (SPSS, Heidelberg, Germany).

Analytic Procedures

Microalbuminuria was measured by immunodiffusion (VLC Partigen Albumintest; Behring, Marburg, Germany). HbA_{1c} was determined by Diamat (Biorad, Munich, Germany). Peripheral sensory neuropathy was diagnosed when at least three of the following categories were positive: clinical symptoms, signs, quantitative sensory testing, and peroneal motor nerve conduction velocity (following the San Antonio Consensus Statement).[14] Patients were screened for retinopathy by the same ophthalmologist once per year according to the recommendations of the Early Treatment Diabetic Retinopathy Study Group and the St. Vincent Declaration.[15,16]

Subjects were typed for HLA-DR and HLA-DQ locus by a standard microlymphocytotoxicity technique.[17] Islet cell antibodies were determined according to the method of the International Workshop on islet cell antibodies.[18] They were considered positive at greater than 19 Juvenile Diabetes Foundation units. Insulin autoantibody levels were measured by radioimmunoelectrophoresis.[19] Antibodies against the 64-kd antigen were determined as previously described.[20]

Plasma C-peptide was determined by double-antibody liquid-phase radioimmunoassay with an 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 radioimmunoassay (Pharmacia, Heidelberg, Germany) after precipitation with polyethyleneglycol according to the method of Nagakawa et al.[21]

RESULTS

Study Course

The diagnosis of IDDM was supported by results for islet cell antibodies, insulin autoantibodies, or antibodies against the 64-kd polypeptide (Table 1). Patients were positive for one of these antibodies at least. In the C group, 12 had DR3 and/or DR4, and seven had other haplotypes; 10 were $DQ8^+$ and two $DQ2^+$ in this group. In the I group, 10 had DR3 and/or DR4, 11 were $DQ8^+$, and four were $DQ2^+$.

Table 1. Baseline Characteristics of Patients With Newly Manifested IDDM Treated With Either C or I Insulin Therapy

Variable	Group I	Group C	P
No. of subjects	23	19	
Weight loss (kg)	5.7 ± 5.2	5.5 ± 5.9	NS
Duration of symptoms (d)	7.2 ± 5.2	7.6 ± 5.6	NS
HbA_{1c} (%)	12.4 ± 5.5	13.1 ± 6.2	NS
ICA > 19 JDF	18 (78)	14 (74)	NS
IAA	6 (26)	5 (26)	
Anti–64-kd	17 (74)	12 (63)	NS
DQ8;DQ2	11;4	10;2	
DR3;DR3/DR4	10;4	12;4	
Sex (F/M)	10/13	9/10	
Age (yr)	27 ± 8	29 ± 8	NS

NOTE. Data are presented as absolute numbers of patients (with %) or as the mean ± SD.

Forty-two of 49 randomized patients completed the 5 years, and only their data were included. After an initial peak in the insulin requirement at diagnosis, the mean daily insulin dosage decreased in both groups, with a nadir at 6 months, only to increase steadily thereafter. There were no differences between the two treatment groups over the 5-year period (Fig 1). In both groups, insulin therapy was accompanied by weight gain, with a tendency for higher body mass index in the I group not reaching statistical significance.

At diagnosis, values for HbA_{1c} were greater than 12% in both groups and not significantly different. During the first 2 weeks of insulin therapy, mean blood glucose levels decreased from 9.1 ± 2.7 to 6.9 ± 4.2 mmol/L ($P < .001$) in the C patients, and from 9.4 ± 5.6 to 6.4 ± 4.5 mmol/L ($P < .005$) in the I patients. Figure 2 shows that intensive insulin therapy was more effective in decreasing HbA_{1c} values, especially at the end of the 5-year observation period, compared with conventional insulin therapy. A statistically significant difference in the mean HbA_{1c} was maintained after 3 years of insulin therapy ($P < .01$). The relative number of hypoglycemic events (< 3.5 mmol/L glucose) over the entire 5-year follow-up period was

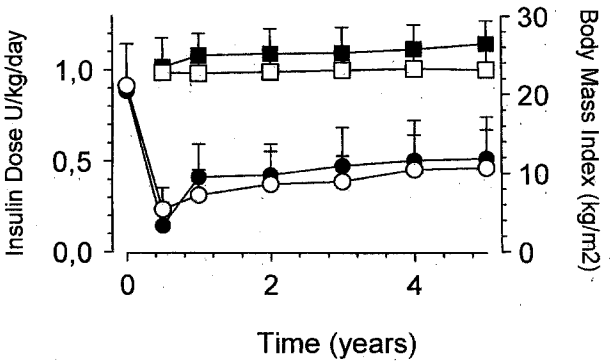

Fig 1. Total insulin dose (U/kg/d) for C (○) or I (●) patients and body mass index (kg/m²) for C (□) or I (■) patients during the 5-year follow-up period. Data are the mean ± SD.

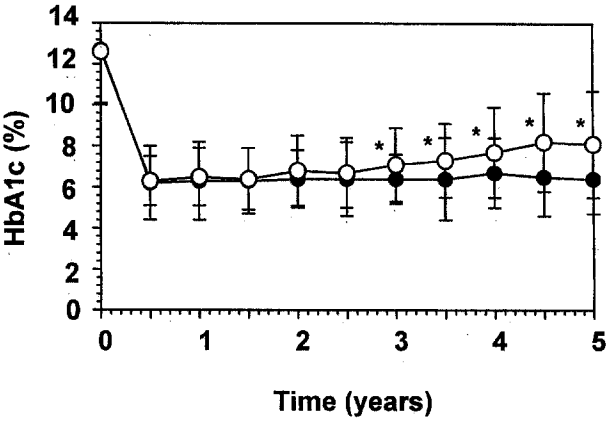

Fig 2. HbA_{1c} values (Mean ± SD) in IDDM patients with C (○) or I (●) insulin therapy. *$P < .001$.

2.2% ± 0.5% in the C group and 3.9% ± 0.7% in the I group ($P < .05$).

Insulin Sensitivity

At diagnosis, insulin sensitivity as judged from the M/I ratio during the euglycemic clamp was at the lowest level (Fig 3). Six months after beginning insulin therapy, insulin sensitivity had increased significantly ($P < .001$) in both groups, but declined thereafter. Except for baseline, all M/I values in the I group were significantly higher compared with the C group. At 5 years, mean insulin sensitivity for the C group was 20.9 ± 12.3 and for the I group 39.7 ± 11.4 nmol · kg^{-1} · min^{-1} · $pmol/L^{-1}$ ($P < .005$). Weight gain expressed as an increase in body mass index from baseline was inversely correlated with insulin sensitivity ($R^2 = .83$, $P < .001$) in both groups.

Insulin Secretory Capacity

At baseline, GSCP was 0.42 ± 0.13 nmol/L in the C group and 0.39 ± 0.19 nmol/L in the I group (NS). GSCP peaked at 6 months after the introduction of insulin therapy

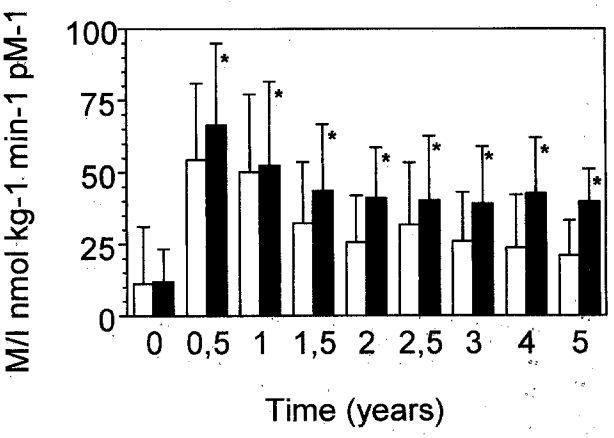

Fig 3. Insulin sensitivity (M/I) (mean ± SD) in IDDM patients with C (□) or I (■) insulin therapy. At all time points except baseline, M/I was lower in the C group. *$P < .02$.

(Fig 4), with an increase of more than 50% in both groups. From 3 years onward, GSCP was significantly higher in the I group compared with the C group. At 5 years, GSCP in the I patients was still more than 30% higher than at the time of diabetes diagnosis (C 0.2 ± 0.1 *v* 0.6 ± 0.2 nmol/L, $P < .005$). A linear regression line was constructed between maximum GSCP concentrations and maximum insulin sensitivity values in the I group ($R^2 = .62$, $P < .001$) indicating that both parameters were correlated.

The acute insulin response to IV arginine was measured before and during a hyperglycemic clamp, and the potentiation slope of arginine-stimulated insulin release by glucose was calculated (Table 2). In C patients, the slope dI/dG reached a maximum after 3 years, and in the I group, after 2 years (C 289 ± 169 *v* I 341 ± 156 pmol/L · min · mmol/L^{-1}, $P < .05$). After 5 years, I patients had a higher mean potentiation slope than those in the C group ($P < .05$). When the potentiation slope was plotted against insulin sensitivity, I patients had higher insulin sensitivity and higher slope values in the end (Fig 5).

Complications

After 5 years, two of 19 C patients and no I patients had developed retinopathy. The difference was not significant. Six patients of the C group and one patient of the I group developed peripheral neuropathy ($P < .05$). Urinary albumin excretion was modestly higher in the C group at the end of the follow-up period (19.4 ± 10 *v* 11.2 ± 10 mg/24 h, $P < .05$). Creatinine clearance was 124 ± 45 mL/min for C patients and 128 ± 51 mL/min for I patients (NS).

DISCUSSION

Insulin Reserve and Remission

Clinical reports as early as the 1970s suggested that intensive insulin treatment resulted in a longer period of good metabolic control and prolonged remissions.[2,7-9] However, these studies had obvious disadvantages: first, patients were evaluated for only 1 year; second, insulin sensitivity was not evaluated; and third, those studies lacked a prospective design. We tried to overcome these drawbacks by choosing a much longer observation period, and we found that the difference in endogenous insulin reserve between I therapy compared with C therapy only began to increase with time after a 3-year follow-up period. Subjects with intensive treatment still had a significant insulin reserve after 5 years, but those with conventional therapy did not.

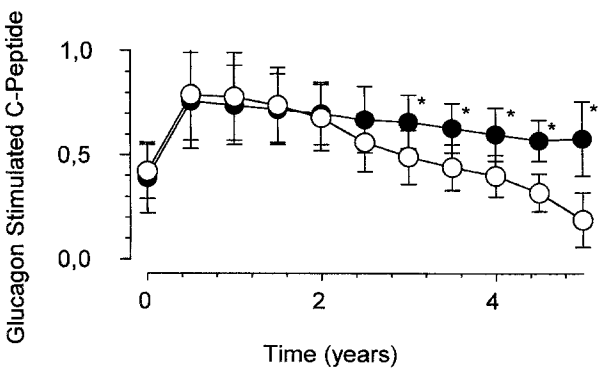

Fig 4. GSCP (mean ± SD) in patients with C (○) or I (●) insulin therapy. *$P < .005$.

A remission or "honeymoon" is thought to be caused by the recovery of endogenous insulin, and it is defined by freedom from the need for exogenous insulin. This is a difficult situation, because exogenous insulin is needed for the remission to develop. Therefore, in our study design, a lack of insulin requirement was not a therapeutic goal. In both treatment groups, insulin was continued with the maximal tolerable amount that did not cause recurrent hypoglycemia and normalize blood glucose levels.

Although remission is known to occur in newly manifested diabetes, it is a rare phenomenon, and there is still no clarity as to what mechanisms contribute to insulin independence. On the basis of our study, the recovery of insulin sensitivity of peripheral tissues may be an important factor.

Characteristics of Adult-Onset IDDM Patients

It has been estimated that among all patients with IDDM, close to 60% develop it as adults.[22] These individuals have low C-peptide levels, are thin, may have islet cell antibodies, and usually require insulin for metabolic control. They are often classified as non–insulin-dependent patients. It is estimated that annually 1% to 2% of people with non–insulin-dependent diabetes become insulin-deficient. About one third of the subjects initially diagnosed with non–insulin-dependent diabetes mellitus have low C-peptide, and 75% of these have latent autoimmune diabetes as indicated by antibodies.

The decreasing frequency of insulin autoantibodies, islet cell antibodies, and high-risk genotype with age at onset of IDDM stress the need to exclude an increasing admixture of non–insulin-dependent diabetic cases, mistakenly classified as IDDM, in the older age groups. Therefore, all of our patients were recruited according to the same clinical criteria.[23] All subjects were positive for at least one type of autoantibody or one susceptibility genotype associated with IDDM. The incidence of DR and DQ genotypes was comparable to that noted in previous mid-European studies in white adult-onset patients.[24,25]

Prevention of diabetes in normoglycemic subjects at risk for developing IDDM with insulin treatment has been reported.[26] Continuous IV insulin therapy for 15 days from the clinical onset of diabetes improved endogenous insulin secretion during the initial 12 months of the disease.[3] Our results extend these clinical reports to an observational period of 5 years in adult-onset patients, and our findings are consistent with theirs.

Frequency of Hypoglycemic Events

Compared with studies in long-standing diabetes reporting a greater than threefold higher risk of serious hypoglycemia accompanying intensive therapy,[11,12] we found a less

Table 2. Time Course of Insulin Secretion and of Parameters for Diabetic Complications

Variable	Years					
	0	1	2	3	4	5
C group						
Insulin (pmol/L) at 10 mmol/L glucose	84 ± 36	116 ± 41	109 ± 89	102 ± 66	85 ± 48	13 ± 26
Slope dI/dG	105 ± 53	213 ± 102	273 ± 156	289 ± 169	251 ± 104	236 ± 61
Urinary albumin (mg/d)	4.1 ± 5.7	5.3 ± 6.9	6.6 ± 5.7	12.6 ± 10.3	15.9 ± 9.2*	19.4 ± 10.0*
Neuropathy	0	0	0	1	2	6*
Retinopathy	0	0	0	0	0	2
I group						
Insulin (pmol/L) at 10 mmol/L glucose	89 ± 61	123 ± 98	156 ± 77*	144 ± 87*	121 ± 53*	105 ± 25†
Slope dI/dG	102 ± 49	256 ± 57	341 ± 156*	330 ± 112*	319 ± 127*	306 ± 142*
Urinary albumin (mg/d)	9.2 ± 11.2	4.3 ± 8.3	6.1 ± 7.3	7.9 ± 7.2	12.9 ± 9.9	11.2 ± 9.6
Neuropathy	0	0	0	0	0	1
Retinopathy	0	0	0	0	0	0

NOTE. Steady-state insulin at 120 to 180 minutes of hyperglycemic (10 mmol/L) clamp and potentiation slope (dI/dG) of arginine-stimulated insulin secretion represent the residual insulin capacity during the 5-year follow-up period. Urinary albumin was used as a screening test for diabetic nephropathy. No case of microalbuminuria (30 to 300 mg/d) was detected in either group, but urinary albumin was higher in the C group after 4 years of insulin therapy. Patients diagnosed for neuropathy or retinopathy are also shown for both groups. Data are either the absolute number of patients with neuropathy/retinopathy or the mean ± SD.

*$P < .05$.

†$P < .001$.

than twofold increase of mild hypoglycemia and no severe hypoglycemic events. This finding is consistent with the observation that patients with residual insulin experience hypoglycemia less frequently than IDDM patients with long-standing diabetes and no C-peptide. Several reasons may be discussed. The risk of severe hypoglycemia during intensive therapy significantly increases in IDDM subjects with defective counterregulation.[27] Such individuals experience low blood glucose symptoms at significantly lower blood glucose levels than those with adequate counterregulation.[28] Severe hypoglycemia was associated with lower stimulated C-peptide values, a larger insulin dose per kilogram of weight, and younger age at onset of diabetes.[29] Our patients had significant C-peptide levels and thus were less prone to iatrogenic insulin excess, because their insulin requirement was lower than in patients with no residual C-peptide. Insulin excess is known to be one of the most prominent sources of recurrent hypoglycemia. Moreover, no hypoglycemia unawareness was observed in our patients.

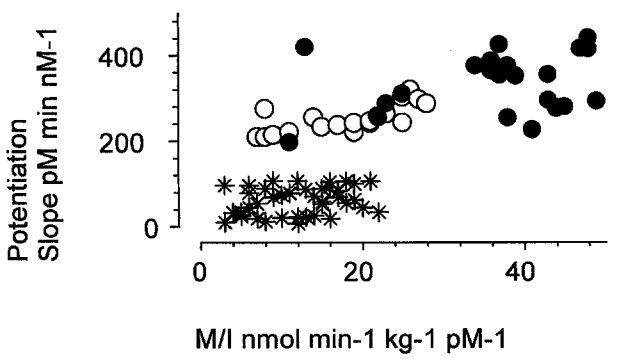

Fig 5. Association of insulin sensitivity (M/I) and potentiation slope (dI/dG) in IDDM patients at clinical diagnosis (*) and after 5 years of continuous C (○) or I (●) insulin treatment.

Mean plasma glucose levels to elicit symptom responses to hypoglycemia were not different between the two treatment groups.

Role of Insulin Sensitivity

Previous studies have demonstrated a state of insulin resistance in recent-onset diabetes that improved under insulin therapy.[30,31] In this study, we found a maximum increase of insulin sensitivity ½ year after beginning the insulin therapy. During the 5-year observation period, intensive insulin therapy was accompanied by higher insulin sensitivity as compared with conventional insulin therapy. Two important factors influencing insulin sensitivity were blood glucose level and body weight. Decreasing hyperglycemia is one of the prerequisites for the reduction of initial insulin resistance. There appears to be a detrimental influence of only modest postprandial hyperglycemia (8.5 to 9.5 mmol/L) on insulin sensitivity. Avoiding excessive weight gain was one of the therapeutic aims with the I group, since intensive insulin therapy is accompanied by significant weight increases.[11]

Role of Insulin Reserve in Relation to Insulin Sensitivity

Better preservation of insulin sensitivity in a given patient was related to higher values for the potentiation slope and GSCP. In both treatment groups, recovery of insulin sensitivity preceded the improvement of insulin reserve. This finding is consistent with previous reports on the interrelationship between insulin action and non–glucose-dependent insulin release of the B cell in newly diagnosed diabetes.[6,32] Other potential reasons for the sustained preservation of endogenous C-peptide secretion in this study could be the continuous insulin treatment despite significant improvement of C-peptide and the achievement of tight metabolic control in the I group.

Conclusions

As expected, intensive therapy favorably altered the incidence of peripheral neuropathy and slowed the progression of microalbuminuria in our experimental group. We conclude that intensive insulin therapy is safe in adult-onset patients and serves to sustain both insulin sensitivity and insulin secretory capacity. A cost-effective, possibly computer-assisted method of intervention to achieve similar results would be helpful in extending these benefits to all patients.

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REFERENCES

1. Nyström L, Dahlquist G, Östman J: Risk of developing insulin dependent diabetes mellitus (IDDM) before 35 years of age: Indications of climatological determinants for age at onset. Int J Epidemiol 21:352-358, 1992

2. Perlman K, Ehrlich RM, Filler RM, et al: Sustained normoglycemia in newly diagnosed type-1 diabetic subjects: Short-term effect and one year follow-up. Diabetes 33:995-1001, 1984

3. Shah SC, Malone JI, Simpson NE: A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 320:550-554, 1989

4. Stiller CR, Dupre G, Gent M, et al: Effects of cyclosporine immunosuppression in insulin dependent diabetes mellitus of recent onset. Science 223:1362-1367, 1984

5. Karjalainen J, Salmela P, Ilonen J, et al: A comparison of childhood and adult type-1 diabetes mellitus. N Engl J Med 320:881-886, 1989

6. Linn T, Ebener K, Laube H: A one-year study of newly manifested type 1 diabetes mellitus under tight glucose control. Med Welt 45:57-61, 1994

7. Schiffrin A, Suissa S, Weitzner G, et al: Factors predicting course of B-cell function in IDDM. Diabetes Care 15:997-1001, 1992

8. Mirouze J, Selam JL, Pham TC, et al: Sustained insulin induced remissions of juvenile diabetes by means of an external artificial pancreas. Diabetologia 14:223-227, 1978

9. Madsbad S, Krarup T, Faber OK, et al: The transient effect of strict glycemic control on B-cell function in newly diagnosed type-1 (insulin-dependent) diabetic patients. Diabetologia 22:16-20, 1982

10. Yki-Järvinen H, Koivisto VA: Insulin sensitivity in newly-diagnosed type-1 diabetics after ketoacidosis and after three months of insulin therapy. J Clin Endocrinol Metab 59:371-378, 1984

11. Reichard P, Pihl M: Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. Diabetes 43:313-317, 1994

12. Diabetes Control and Complications Trial Study Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977-986, 1993

13. World Health Organization Study Group: Diabetes mellitus. WHO Tech Rep Ser 727:17-19, 1985

14. Consensus Statement: Report and recommendations of the San Antonio Conference on Diabetic Neuropathy. Diabetes 37: 1000-1004, 1988

15. Diabetes Care and Research in Europe: The Saint Vincent Declaration. Diabetic Med 7:360-363, 1990

16. Kohner EM, Porta M (eds): Screening for Diabetic Retinopathy in Europe: A Field Guide Book. Geneva, Switzerland, International Diabetes Federation/World Health Organization, 1992

17. Pagano G, Cavallo-Perin P, Cavalot F, et al: Genetic, immunologic, and environmental heterogeneity of IDDM. Incidence and 12-mo follow-up of an Italian population. Diabetes 36:859-863, 1987

18. Lernmark A: The Fourth International Serum Exchange Workshop to Standardize Cytoplasmatic Islet Cell Antibodies. Diabetologia 34:534-535, 1991

19. Christiansen AH: Radioimmunoelectrophoresis in the determination of insulin binding to IgG. Methodological studies. Horm Metab Res 5:147-154, 1973

20. Richter W, Eiermann TH, Endl J, et al: Human monoclonal islet specific autoantibodies share features of islet cell and 64kD antibodies. Diabetologia 36:785-790, 1993

21. Nagakawa S, Nakayama H, Sasaki T, et al: A simple method for the determination of serum free insulin levels in insulin treated patients. Diabetes 22:590-600, 1973

22. Tuomi T, Groop LC, Zimmet PZ, et al: Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with non–insulin dependent onset of the disease. Diabetes 42:359-362, 1993

23. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979

24. Vandewalle CL, Decraene T, Schuit FC, et al: Insulin autoantibodies and high titre islet cell antibodies are preferentially associated with the HLA DQA1*0301-DQB1*0302 haplotype at clinical onset of type 1 (insulin-dependent) diabetes mellitus before age 10 years, but not at onset between age 10 and 40 years. Diabetologia 42:1155-1162, 1993

25. Ziegler AG, Standl E, Albert E, et al: HLA-associated insulin autoantibody formation in newly diagnosed type-1 diabetic patients. Diabetes 40:1146-1149, 1991

26. Keller RJ, Eisenbarth GS, Jackson RA: Insulin prophylaxis in individuals at high risk of type 1 diabetes. Lancet 341:927-928, 1993

27. White NH, Skor DA, Cryer PE, et al: Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 308:485-491, 1983

28. Clarke WL, Gonder-Frederick LA, Richards FE, et al: Multifactorial origin of hypoglycemic symptom awareness in IDDM: Association with defective glucose counterregulation and better glycemic control. Diabetes 40:680-685, 1991

29. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 90:450-459, 1991

30. Hramiak IM, Dupre J, Finegood DT: Determinants of clinical remission in recent-onset IDDM. Diabetes Care 16:125-133, 1993

31. Burcelin RG, Eddouks M, Beylot M, et al: Hypersensitivity to insulin during remissions in cyclosporin treated IDDM patients. Diabetes Care 16:881-888, 1993

32. Yki-Järvinen H, Koivisto VA: Natural course of insulin resistance in type 1 diabetes. N Engl J Med 315:224-230, 1986