Effect of Diabetes and its Control on Insulin-like Growth Factors in the Young Subject with Type I Diabetes

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SUMMARY

The influence of diabetes and its control on circulating levels of growth hormone and growth hormone-dependent, insulin-like growth factors (IGF) remains controversial. In the present study, the effect of a 1-wk period of intensive insulin therapy on growth hormone and IGF I and II has been determined in 19 young (age 13–22 yr), insulin-dependent (type I) subjects with diabetes mellitus. IGF I was low during conventional insulin therapy (198 ± 20 versus 438 ± 38 ng/ml in nondiabetic subjects, $P < 0.001$), and rose within the week of intensified treatment (to 255 ± 15 ng/ml, $P < 0.005$), concomitant with a reduction in plasma glucose from 233 ± 16 to 110 ± 5 mg/dl. IGF I rose despite a significant fall in mean 24-h growth hormone levels from 14.1 ± 2.2 to 9.0 ± 1.2 ng/ml ($P < 0.02$). The mean IGF II value for the diabetic subjects (504 ± 39 ng/ml) was not significantly different from that of the nondiabetic control group (506 ± 30 ng/ml, $P > 0.3$) and was not altered by intensified therapy. However, four individual patients with very low IGF I also had depressed IGF II (248 ± 16 ng/ml), which was corrected (to 377 ± 35 ng/ml) with improved metabolic control. These data suggest that elevated growth hormone levels in poorly controlled diabetes are ineffective in IGF I generation and that this defect is at least partially corrected by acute improvement in control. The rise in IGF I levels accompanying intensive insulin treatment may suppress the excessive secretion of growth hormone. IGF II levels appear to be affected only by the most severe reductions of growth hormone activity. DIABETES 1984; 33:1175–79.

Hypersecretion of growth hormone in poorly controlled diabetes is well documented[1,2] and is particularly pronounced in diabetic adolescents.[3] The effect of diabetes on other growth factors is less well established. We, and others, have recently reported that the levels of insulin-like growth factor I (IGF I) are relatively low during poor diabetes control.[4,5] It was suggested that the concomitant increase in circulating growth hormone was an attempted compensatory response to a defect in IGF I secretion. This hypothesis was supported by data showing that IGF I rose and growth hormone fell after optimal glycemic control by continuous subcutaneous insulin infusion (CSII).[4] The time sequence, however, was not wholly consistent with this model, in that the decrease in growth hormone levels appeared to precede a significant increment in circulating IGF I.[4,6] Furthermore, lack of unanimity remains; Merimee and colleagues have described elevated IGF I levels in patients with diabetes regardless of their level of control.[7]

The present study was undertaken to further characterize the responses of IGF I and growth hormone to intensified insulin treatment and, in particular, to focus on the short-term responses in adolescent diabetic subjects. We have also investigated the response of the other growth factor, IGF II, to improved diabetes control, about which little information is available.

MATERIALS AND METHODS

Subjects. Nineteen nonobese patients with type I diabetes were studied. Patients ranged in age from 12 to 22 yr (mean ± SEM, 16.7 ± 0.7 yr) and duration of diabetes from 2 yr to 16 yr (8.2 ± 1.0 yr). Clinical data are summarized in Table 1. At entry to the study, all patients were receiving conventional insulin therapy with intermittent subcutaneous (s.c.) injections. One patient was taking L-thyroxine, but otherwise insulin was the only medication taken regularly. Subjects and their parents (for patients below 18 yr of age) gave informed, written consent before taking part in the study. The protocol was approved by the Human Investigations Committee of the Yale University School of Medicine.

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Received for publication 10 February 1984 and in revised form 11 May 1984.

TABLE 1
Clinical characteristics of subjects on entry to the study

Subject no.	Age (yr)	Sex	Stage of puberty	Duration (yr)	HbA_1 (%)	Mean 24-h GH (ng/ml)	IGF I (ng/ml)	IGF II (ng/ml)	Complications*		
									bdr	pdr	n
1	18	F	5	3	13.9	9	193	419	—	—	0
2	15	F	3.5	10	13.6	18	180	407	0	0	0
3	16	M	5	2	13.4	—	306	609	0	0	—
4	19	M	4	12	—	13	126	542	+	0	0
5	16	M	5	4	16.4	—	184	535	+	0	0
6	21	F	5	12	11.3	9	310	829	+	0	+
7	20	F	4	16	12.6	21	151	581	0	0	0
8	13	M	2	2	12.7	—	297	425	0	0	—
9	13	M	2	4	12.2	3	180	598	+	0	0
10	13	F	4	2	16.4	29	286	532	—	—	0
11	14	F	5	12	12.2	11	331	587	0	0	0
12	20	M	5	9	10.6	—	292	545	+	0	+
13	18	F	4	10	14.2	16	153	576	+	+	+
14	13	M	2	8	15.4	18	178	784	0	0	—
15	14	M		10	13.2	22	256	620	0	0	—
16	16	F	4	9	16.4	—	131	282	+	0	0
17	20	M	5	9	—	—	56	207	+	0	+
18	22	F	5	16	16.3	—	59	258	+	+	0
19	17	F	5	6	14.4	26	101	244	+	0	0
Mean	17			8	13.8	14	198	504			
SE	1			1	0.5	2	20	39			

*bdr = Background diabetic retinopathy; pdr = proliferative diabetic retinopathy; n = nephropathy; proteinuria in excess of 0.4 g/24 h, normal serum creatinine; + = present; 0 = absent; — = information not available.

Procedures. All patients were admitted to the Children's Clinical Research Center at the Yale New Haven Medical Center. They were initially studied while receiving their usual conventional insulin therapy (CIT) and a diet that approximated their normal intake at home, as assessed by careful dietary history. On the morning of the second day, after an overnight 10–12-h fast, an indwelling catheter was inserted into a forearm vein. Blood was withdrawn for determination of total glycosylated hemoglobin (HbA_1) and fasting plasma IGF I and IGF II. Subsequently, blood samples were obtained for plasma glucose measurement hourly for 24 h in all subjects.

In 10 patients, serum growth hormone was measured every 2 h for 24 h. In 10 patients, plasma free insulin was measured in blood taken before, and at timed intervals over 4 h after, a standardized breakfast.

On the third hospital day, insulin therapy was given by continuous subcutaneous infusion (CSII) using a battery-powered syringe pump (model AS6C Auto-Syringe, Inc., Hooksett, New Hampshire). The basal infusion rate and premeal bolus doses of regular insulin (Eli Lilly and Company, Indianapolis, Indiana) were adjusted to achieve plasma glucose concentrations as close to normal as possible, as described previously.[8] After 7 days of pump treatment, a catheter was again inserted into a forearm vein and the blood sampling performed on the second hospital day was repeated.

Nondiabetic controls. Fasting plasma IGF I and IGF II levels in 122 healthy, young volunteers have recently been determined by Dr. Hintz and colleagues.[9] From this group, 19 normal controls were selected for comparison with our diabetic subjects based exclusively on matching for age, sex, and stage of sexual development[10] by one of the authors (S.A.A.), who was masked from the IGF results. Blood glucose and growth hormone profiles were also obtained from 6 healthy, nondiabetic volunteers (mean age, 15.7 ± 0.8 yr).

Determinations and calculations. Plasma glucose was measured with a glucose analyzer (Beckman Instrument Company, Fullerton, California). Total glycosylated hemoglobin was measured chromotographically using a commercial microcolumn kit (Isolab, Inc., Akron, Ohio) and growth hormone by radioimmunoassay.[11] Plasma for free insulin determinations was immediately (within 45 min) treated with polyethylene glycol to precipitate anibody-bound insulin and the free insulin subsequently measured within 4 wk by radioimmunoassay.[12] IGF I and II were assayed simultaneously in all samples after acid gel filtration, using methods previously reported.[13] IGF I was measured by a modification of the procedure of Furlanetto et al.[14] using an antibody prepared by Dr. J. J. van Wyk and supplied by the National Human Pituitary Program. Radioimmunoassay of IGF II used a specific C-peptide antibody.[13]

Values are expressed as the mean ± SEM. Student's *t*-test was employed in analysis of the data, with the use of the paired *t*-test where applicable. Correlations between variables were examined by least-squares linear regression analysis.

RESULTS

Glycemic control. Glycosylated hemoglobin was elevated in all patients upon entry to the study, indicating suboptimal control with CIT (HbA_1 13.8 ± 0.5%, normal range 5.5–8.0%). After 1 wk of CSII, plasma glucose levels during 24-h monitoring were markedly reduced. The mean hourly plasma glucose concentration fell from 233 ± 16 mg/dl to 110 ± 5 mg/dl ($P < 0.001$) (Table 2). Neither the total daily insulin dosage nor the free insulin concentrations before and

TABLE 2
Glucose, insulin, and growth hormone on conventional treatment (CIT) and after 1 wk of CSII

	CIT	CSII
Mean 24-h glucose (N = 19) (mg/dl)	233 ± 15	110 ± 5*
Insulin dose (N = 19) (U/day)	61 ± 6	72 ± 5
Plasma free insulin (N = 10) basal (μU/ml)	19 ± 7	19 ± 4
Integrated area postbreakfast (mU · min/ml)	11.8 ± 4.0	17.6 ± 4.3
Mean 24-h GH (N = 10) (ng/ml)	14 ± 2.2	9.0 ± 1.2†

*Significantly different from CIT value, $P < 0.001$.
†Significantly different from CIT value, $P < 0.05$.

after the standard breakfast meal were significantly altered by pump therapy (Table 2).

Growth factor levels. As shown in Figure 1, plasma IGF I levels in conventionally treated diabetic subjects were reduced when compared with those in age- and sex-matched, nondiabetic controls (198 ± 20 ng/ml versus 438 ± 34 in controls, $P < 0.01$). At the start of the study, IGF I levels in the diabetic subjects were inversely correlated with HbA_1 values ($r = 0.55$, $P = 0.02$). After 1 wk of CSII, mean IGF I concentrations rose by 29% (to 255 ± 15 ng/ml, $P < 0.005$ versus CIT). However, this brief period was insufficient to normalize IGF I concentrations (Figure 1).

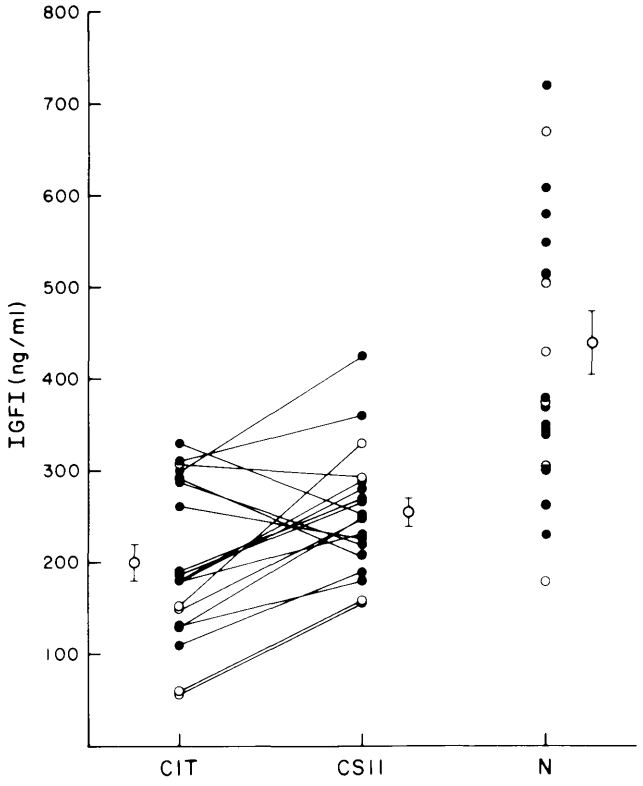

FIGURE 1. IGF I levels by subject on CIT and after 1 wk of CSII, and of age- and sex-matched, nondiabetic controls (N). ● = Subjects of age ≤18 yr, ○ = subjects aged over 18 yr, and ⊖ = mean 1 SE.

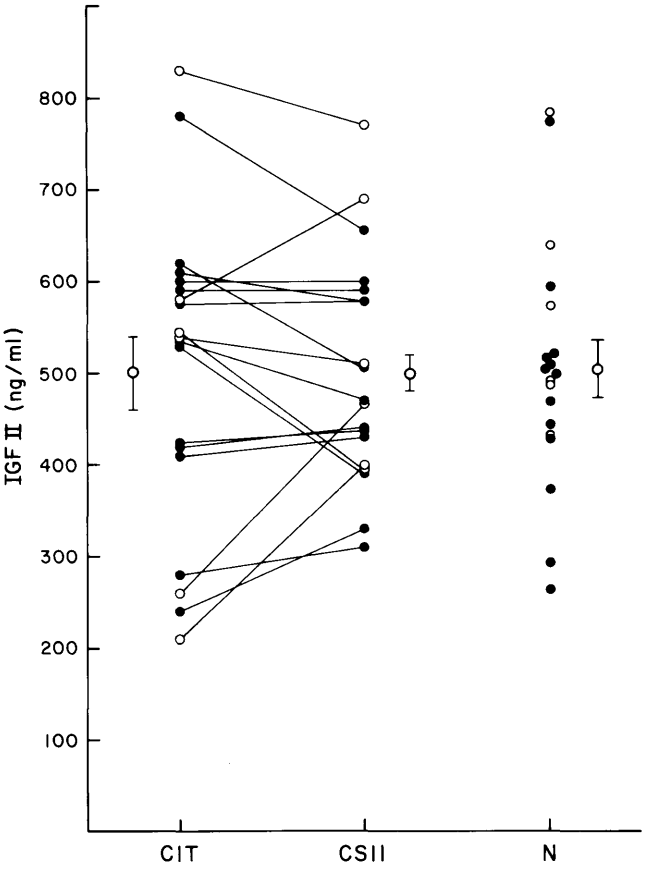

FIGURE 2. IGF II levels by subject on CIT and after 1 wk of CSII, and of age- and sex-matched, nondiabetic controls (N). Symbols are as for Figure 1.

During CIT, mean plasma IGF II levels for the entire diabetic group were comparable to values in nondiabetic controls and did not change with CSII (Figure 2). However, when the 4 subjects with subnormal IGF II values during CIT (nos. 16–19) were considered separately, a consistent rise toward normal was observed in each (from 248 ± 16 to 377 ± 35 ng/ml, $P < 0.05$) (Figure 2). These patients also had the lowest IGF I values at the start of the study (Table 1).

In the 10 patients with growth hormone profiles, mean 24-h growth hormone levels were significantly elevated during CIT (14.1 ± 2.2 ng/ml versus 7.0 ± 1.1 ng/ml in nondiabetic controls, $P < 0.02$), whereas IGF I concentrations were reduced ($P < 0.001$). CSII treatment produced a 36% reduction in circulating growth hormone (to 9.0 ± 1.2 ng/ml, $P < 0.05$) to values indistinguishable from those in nondiabetic controls ($P > 0.3$). This was associated with a simultaneous rise in IGF I (from 188 ± 22 to 256 ± 13, $P < 0.05$) that was comparable to the increment seen in all 19 subjects.

There was no significant difference between the IGF I or IGF II levels of patients who had retinopathy and those of the patients who did not (Table 1).

DISCUSSION

A substantial body of evidence indicates that IGF I plays an important role in mediating the somatotropic effects of growth hormone. Since growth hormone concentrations are elevated rather than reduced in adolescents with poorly con-

trolled diabetes,[1,2] a defect in IGF I generation would provide an attractive explanation for the impaired growth observed in such patients. An adverse effect of poor metabolic control on circulating IGF I concentrations has been difficult to establish, however. This is perhaps not surprising, in view of the difficulties of assessing metabolic control before the development of glycosylated hemoglobin assays and the limited ability to alter glucose regulation before the introduction of intensive treatment techniques. Variations in assay methods (bioassays and radioimmunoassay), as well as failure to account for the changes in IGF I levels that accompany normal growth and development,[9] may also help explain why elevated, normal, and reduced IGF I values have been reported in diabetes.[15-18]

We have chosen to study young diabetic subjects, because this is the time that growth factors assume greatest physiologic importance.[9] The IGF I values we observed in our young diabetic subjects while they were on CIT were significantly reduced in comparison with those of a group of nondiabetic controls selected on the basis of identical age, sex, and degree of sexual maturation. The IGF I concentrations were reduced in the face of elevations in circulating growth hormone and were inversely related to the degree of metabolic control as reflected by glycosylated hemoglobin levels. Clearly, growth hormone in the poorly controlled diabetic subject is failing to effectively stimulate IGF I production. Our findings are similar to those reported by Blethen et al., who also noted a negative correlation between glycosylated hemoglobin and age-adjusted IGF I values in poorly controlled, adolescent diabetic subjects.[5] In contrast, Merimee and colleagues have recently reported significant elevations of IGF I levels in adults with type I (but not type II) diabetes.[7] This discrepancy could be attributed to the greater age of their patients or to the lack of age-adjusted control data. There was no conventional assessment of metabolic control in that study.

Because of the inherent limitations of such cross-sectional surveys, we examined the effects of a brief period of intensive treatment; 1 wk of CSII resulted in a significant rise in IGF I values, albeit not to normal control values (Figure 1). Whether IGF I would continue to rise during more prolonged treatment is uncertain. However, earlier studies would support this view.[4] The current findings extend our previous observations in a much smaller group of six adults and two adolescents with type I diabetes.[4] That study failed to establish whether the rise in IGF I actually coincided with the fall in growth hormone during CSII. The current data demonstrate that IGF I values increased acutely and in conjunction with restoration of circulating growth hormone to normal. This supports the hypothesis that the hypersecretion of growth hormone during CIT represents an attempt to compensate for defective production (or increased clearance) of IGF I. Partial correction of this defect with CSII may allow feedback suppression of the excessive growth hormone secretion. IGF I has been demonstrated to exert such negative feedback of growth hormone secretion in vitro.[19] The mechanism(s) responsible for the stimulating effect of CSII on IGF I remain to be established. While insulin has been shown to enhance IGF production in vitro,[20] our findings cannot readily be explained by changes in daily insulin dosage or in circulating concentrations of free insulin (see Table 2).

The influence of diabetes and its control on IGF II has not been examined in adolescents, although there has been a recent report of normal levels in adults.[7] Studies in nondiabetic subjects suggest that IGF II, like IGF I, is growth hormone dependent. In patients with growth hormone deficiency, IGF II levels are low and rise on replacement therapy.[13] However, unlike IGF I, IGF II is not increased in acromegaly or when normal subjects are given excess amounts of exogenous growth hormone.[13,21] Therefore, it is not surprising that IGF II values were not elevated during CIT even in the face of elevations in circulating growth hormone concentrations. Indeed, the compensatory increases in growth hormone generally appear to have been sufficient to maintain adequate IGF II production. The mean level of IGF II was normal in our poorly controlled, conventionally treated adolescents and did not rise during CSII. There were, however, 4 patients who did have IGF II deficiency while on CIT and it is noteworthy that those patients also had the lowest IGF I concentrations. Assuming that IGF I levels reflect growth hormone activity, these patients would seem to have been the most deficient in this respect. If, as suggested by the improvement in IGF I levels, CSII reverses a defect in growth hormone activity of diabetic subjects, IGF II in the most severely affected patients would be expected to rise.

The observation that most diabetic children appear to be growing at a normal rate despite a host of metabolic and hormonal derangements is a testament to compensatory mechanisms that help sustain growth. On the other hand, Tattersall and Pyke found that adults who had developed type I diabetes before puberty were shorter than their nondiabetic identical twins.[22] Recent studies indicate that intensive insulin treatment with either CSII or multiple daily injections is accompanied by a sharp increase in growth velocity even in children with normal stature and apparently normal growth rates.[23] It is reasonable to speculate that accelerated growth in children with diabetes is mediated, at least in part, by stimulation of IGF production: IGF I and, in some cases, possibly IGF II.

The present observations may have negative clinical implications for adults. In Merimee's study, the greatest IGF I elevations were observed in patients with fulminant proliferative diabetic retinopathy.[7] Since this study was not longitudinal, it could be argued that elevated IGF I levels were merely a secondary phenomenon. Deteriorating retinal status may have led to more vigorous insulin therapy, which produced the increased IGF I values. Further studies are needed to determine whether IGF I actually plays a role in the proliferation of new retinal blood vessels in diabetes.

ACKNOWLEDGMENTS

We are indebted to the nurses and staff of the Children's Clinical Research Center, JoAnn Ahern, R.N., Sue Bates, R.N., and Patricia Davis, R.N., M.S.N., for the excellent care given our patients; to Tatiana Sergievsky and Francis Liu for their expert technical assistance; to Elizabeth Salvati, who prepared the manuscript; and to Dr. Richard Donabedian of the Department of Laboratory Medicine, Yale-New Haven Hospital, for his help in the measurement of growth hormone.

This study was supported by grants AM-20495, AM-24085, and RR-125 from the NIH and by a grant from the Juvenile Diabetes Foundation International. Dr. Amiel is the

recipient of a grant from the Wellcome Foundation, London, United Kingdom.

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