

# Is Insulinlike Growth Factor I Associated With Diabetic Retinopathy?

DIANA G. DILLS, SCOT E. MOSS, RONALD KLEIN, BARBARA E.K. KLEIN, AND MARK DAVIS

**Insulinlike growth factor I (IGF-I) is the mediator of the growth-promoting effects of growth hormone and has been suspected of playing a role in the pathogenesis of proliferative diabetic retinopathy (PDR). However, previous attempts to correlate IGF-I levels with PDR have yielded conflicting results. We determined IGF-I levels in a large population-based study of 682 early-onset (diagnosed before 30 yr of age) adult ( $\geq 18$  yr old) insulin-taking diabetic subjects. PDR was found in 25% of the population. IGF-I levels were measured by radioimmunoassay. The mean serum level of IGF-I was  $277 \pm 108 \mu\text{g/L}$  (mean  $\pm$  SD). Spearman rank correlations showed statistically significant negative correlations between IGF-I levels and age ( $r = -0.51$ ,  $P < 0.0001$ ), duration of disease ( $r = -0.36$ ,  $P < 0.0001$ ), and glycosylated hemoglobin ( $r = -0.09$ ,  $P < 0.05$ ). There was a significant trend ( $P < 0.001$ ) toward decreasing risk of PDR with increasing IGF-I. However, after controlling for duration of diabetes, glycosylated hemoglobin, diastolic blood pressure, and the presence of proteinuria and/or creatinine  $\geq 265 \mu\text{M}$  in a multiple logistic regression model, IGF-I was not significantly associated with PDR. These data suggest that IGF-I may not be a risk factor for the development of PDR. *Diabetes* 39:191-95, 1990**

Insulinlike growth factor I (IGF-I), also known as somatomedin C, has been proposed by several investigators to play a role in the pathogenesis of diabetic retinopathy (1-3). Some studies have revealed a relationship between IGF-I and proliferative diabetic retinopathy (PDR) (1),

Creatinine  $1 \mu\text{M} = 0.011 \text{ mg/dl}$

From the Departments of Medicine and Ophthalmology, University of Wisconsin School of Medicine, Madison, Wisconsin.

Address correspondence and reprint requests to Dr. Diana Dills, University of Wisconsin Medical School, Department of Medicine, 600 Highland Avenue, Madison, WI 53792.

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although other studies have had contradictory results (2,3). This may be due in part to the small number of patients studied. In addition, some of the early studies used bioassays that are less reliable than the radioimmunoassays (RIAs) now available. In this study, we describe the relationship of IGF-I levels to PDR in people participating in a large population-based study of diabetes in southern Wisconsin.

## RESEARCH DESIGN AND METHODS

The population has been described in detail in previous reports (4,5). In brief, 452 of 457 physicians who provide primary care to diabetic patients in an 11-county area in southern Wisconsin participated in the study. Participation involved keeping lists of all diabetic patients for whom they provided primary care from 1 July 1979 to 30 June 1980. There were 9283 diabetic patients identified who were still alive and residing in the study area outside of nursing homes. Review of their records established that 1396 (15%) were diagnosed before age 30 yr and 7887 (85%) at age 30 yr or older. A sample of 2990 of these patients was selected for examination. This sample was composed of two groups, younger and older onset. The younger-onset group consisted of all patients diagnosed before 30 yr of age who took insulin ( $n = 1210$ ). In the younger-onset group, 996 (82.3%) were examined between 1980 and 1982, and 891 were reexamined between 1984 and 1986. At the second examination, 714 were  $\geq 18$  yr old.

In addition to diabetic subjects, two groups of nondiabetic subjects participated in the study. The first group consisted of spouses of the diabetic population residing in the most populous county in the study area. The second group consisted of patients who received primary well-child care or care for medical problems unrelated to diabetes at the University of Wisconsin Pediatrics Clinic. This study was conducted with the approval of the Human Subjects Committee of the University of Wisconsin Center for Health Sciences.

Blood pressure was measured with the Hypertension Detection and Follow-up Program protocol (6). Retinopathy sta-

tus was determined by grading stereoscopic fundus photographs of seven standard fields with the modified Wisconsin "191" system (7). Participants were classified according to their more severely involved eye. For this study, the severity of retinopathy was classified into four categories. Briefly, level 10 represents no retinopathy, levels 21–31 represent microaneurysms and various other early nonproliferative abnormalities, levels 41–51 represent microaneurysms and other moderate to severe nonproliferative abnormalities, and levels 60–80 represent PDR consisting of fibrous proliferations, new vessels, vitreous or preretinal hemorrhage, or scars of photocoagulation either in scatter or confluent patches, presumably directed at new vessels. Grading was done in a masked fashion; only identification numbers were available to the graders.

RIA for IGF-I was a double-antibody RIA with antiserum provided by the National Hormone and Pituitary Program (8,9). The standard curve was derived with synthetic IGF-I (AMGEN Biologicals, Thousand Oaks, CA) that was labeled with  $^{125}\text{I}$  by means of the chloramine-T method. All samples were acid-ethanol extracted to remove IGF-I from its binding protein before assay. The intra-assay coefficient of variation was 16% ( $n = 67$ ). Proteinuria was measured by Labstix (Miles, Elkhart, IN).

Glycosylated hemoglobin was measured from a sample of 100–200  $\mu\text{l}$  of capillary blood that was collected in a heparinized capillary tube and, after transfer to a 1-ml tube, was refrigerated at 4°C until analyzed. Samples were analyzed for glycosylated hemoglobin within 4 days by the Quick-Step Fast hemoglobin test system (Isolab, Akron, OH).

Age is defined as age at the time of the follow-up examination in 1984 through 1986. Age at diagnosis of diabetes is defined as age at the time the diagnosis was first recorded by a physician on the patient's chart or on a hospital record. The duration of diabetes is the period between age at diagnosis and age at the follow-up examination. Proteinuria is defined as urine protein concentration of  $\geq 0.3$  g/L.

Statistical analysis was performed with the Statistical Analysis System (10–12). Means were compared by *t* test. The significance of the relationship between variables was evaluated by linear regression and Spearman correlations. Tests for trends in proportions were performed by the Mantel-Haenszel procedure (13). Logistic regression was used to evaluate the effect of IGF-I on the presence of PDR after controlling for other variables (14).

## RESULTS

Of the 714 participants aged  $\geq 18$  yr at the second examination, 172 had either proteinuria or serum creatinine concentrations  $\geq 265$   $\mu\text{M}$ . Thirty-two of these participants had a kidney transplant ( $n = 26$ ) or were on dialysis ( $n = 6$ ). The latter group had significantly higher ( $P < 0.0001$ ) IGF-I levels ( $404 \pm 191$   $\mu\text{g/L}$ , mean  $\pm$  SD) than people who had never received a transplant or who were not on kidney dialysis ( $277 \pm 108$   $\mu\text{g/L}$ ). For the remainder of our analyses, the kidney transplant/dialysis group was not considered. Thus, 682 patients were analyzed, of which 156 had either proteinuria or creatinine  $\geq 265$   $\mu\text{M}$ .

The IGF-I values in the diabetic group ranged from 35 to 670  $\mu\text{g/L}$ . Mean IGF-I levels were significantly lower ( $P < 0.0001$ ) in the diabetic group ( $277 \pm 108$   $\mu\text{g/L}$ ) than in the

TABLE 1

Mean insulinlike growth factor I by sex and age in younger-onset diabetic\* and nondiabetic comparison groups

Age (yr)	Diabetic group		Nondiabetic group	
	<i>n</i>	Mean $\pm$ SD ( $\mu\text{g/L}$ )	<i>n</i>	Mean $\pm$ SD ( $\mu\text{g/L}$ )
<b>Men</b>				
18–29	152	325 $\pm$ 103	22	442 $\pm$ 178
30–39	106	263 $\pm$ 96	15	325 $\pm$ 68
40–49	49	248 $\pm$ 86	10	336 $\pm$ 83
50–59	23	196 $\pm$ 56	7	249 $\pm$ 89
60+	16	203 $\pm$ 62	27	251 $\pm$ 84
Total	346	281 $\pm$ 104	81	327 $\pm$ 137
<b>Women</b>				
18–29	136	343 $\pm$ 112	14	503 $\pm$ 201
30–39	108	247 $\pm$ 86	16	357 $\pm$ 93
40–49	52	207 $\pm$ 64	14	357 $\pm$ 180
50–59	27	179 $\pm$ 87	10	286 $\pm$ 76
60+	13	223 $\pm$ 105	48	220 $\pm$ 78
Total	336	273 $\pm$ 112	102	305 $\pm$ 154
<b>Total</b>				
18–29	288	333 $\pm$ 108	36	466 $\pm$ 187
30–39	214	254 $\pm$ 91	31	341 $\pm$ 82
40–49	101	227 $\pm$ 78	24	348 $\pm$ 146
50–59	50	187 $\pm$ 74	17	271 $\pm$ 81
60+	29	212 $\pm$ 83	75	231 $\pm$ 81
Total	682	277 $\pm$ 108	183	315 $\pm$ 147

\*Excluding kidney dialysis/transplant patients.

nondiabetic comparison group ( $315 \pm 147$   $\mu\text{g/L}$ ). There were no significant differences in the mean IGF-I levels ( $P > 0.05$ ) between men and women in either the diabetic or nondiabetic group. There was a significant trend of decreasing IGF-I levels with increasing age in both the diabetic ( $P < 0.0001$ ) and nondiabetic ( $P < 0.0001$ ) groups (Table 1). For most age-specific groups, the nondiabetic group had significantly higher IGF-I levels than the diabetic group.

IGF-I levels also declined with increasing duration of diabetes (Table 2). However, after controlling for age in a multiple linear regression, duration was not significantly related to IGF-I. Besides being negatively correlated with age ( $r = -0.51$ ,  $P < 0.0001$ ) and duration ( $r = -0.36$ ,  $P < 0.0001$ ; Fig. 1), there was a weak but significant negative correlation of IGF-I level with glycosylated hemoglobin ( $r = -0.09$ ,  $P < 0.05$ ; Fig. 2). Although there was a positive correlation with proteinuria ( $r = 0.05$ ,  $P < 0.20$ ), it failed to reach statistical significance.

The serum IGF-I levels were divided into quartiles with a range of 35–202  $\mu\text{g/L}$  for the lowest quartile, 203–265  $\mu\text{g/L}$  for the second quartile, 266–346  $\mu\text{g/L}$  for the third quartile, and 347–670  $\mu\text{g/L}$  for the highest quartile.

TABLE 2

Mean insulinlike growth factor I by duration of diabetes

Duration (yr)	<i>n</i>	Mean $\pm$ SD ( $\mu\text{g/L}$ )
5–9	129	320 $\pm$ 106
10–14	185	299 $\pm$ 116
15–19	118	293 $\pm$ 103
20–24	86	265 $\pm$ 92
25–29	58	236 $\pm$ 78
30–34	52	198 $\pm$ 69
35+	54	202 $\pm$ 89

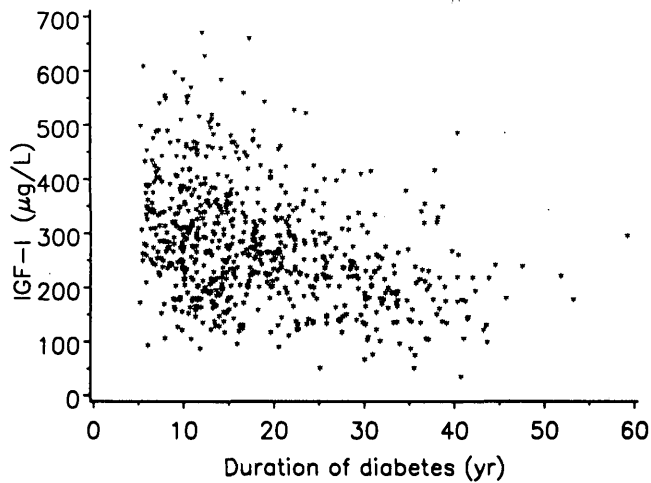


FIG. 1. Scatter plot showing relationship of serum levels of insulinlike growth factor I (IGF-I) and duration of diabetes in 682 people with diabetes diagnosed at <30 yr of age.

A significant inverse trend between IGF-I and the presence of PDR ( $P < 0.001$ ) was found (Table 3; Fig. 3). This relationship remained after controlling for the presence of proteinuria or creatinine  $\geq 265 \mu\text{M}$ . However, after controlling for duration of diabetes, the negative relationship between IGF-I and PDR disappeared (Table 4). There appeared to be a trend toward increasing IGF-I levels with increasing levels of PDR in the patients who had diabetes for >30 yr (Table 4). However, the test for trend did not reach statistical significance ( $P = 0.31$ ).

Because the effects of IGF-I on retinopathy may be influenced by other characteristics, stepwise logistic regression analyses were employed. In the model, the dependent variable was the presence or absence of PDR, and the independent variables were duration of diabetes, glycosylated hemoglobin, diastolic blood pressure, presence or absence of proteinuria and/or creatinine  $\geq 265 \mu\text{M}$ , and the level of IGF-I. The model shows that after controlling for the independent variables, there is no relationship between IGF-I level and the prevalence of PDR (Table 5).

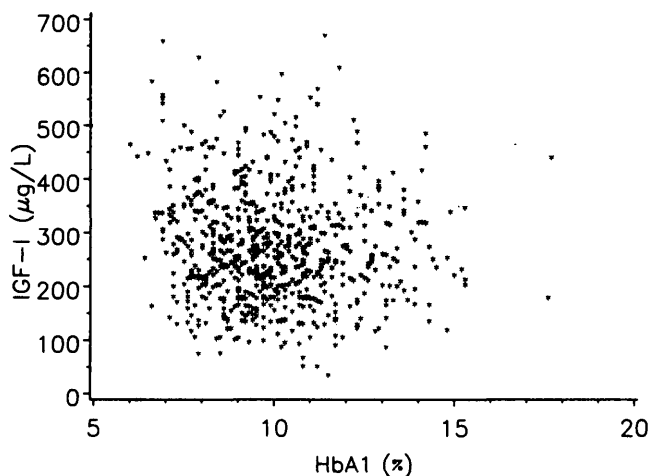


FIG. 2. Scatter plot showing relationship of serum levels of insulinlike growth factor I (IGF-I) with glycosylated hemoglobin (HbA<sub>1</sub>) in 682 people with diabetes diagnosed at <30 yr of age.

TABLE 3  
Relationship of insulinlike growth factor I (IGF-I) to diabetic retinopathy severity

Quartile	IGF-I range ( $\mu\text{g/L}$ )	n	None	Nonproliferative diabetic retinopathy		Proliferative diabetic retinopathy
				Mild	Moderate	
1	35–202	176	6.8	36.4	24.4	32.4
2	203–265	176	5.1	30.7	33.5	30.7
3	266–346	169	12.4	43.8	26.6	17.2
4	347–670	161	14.3	45.3	21.1	19.3
Total		682	9.5	38.9	26.5	25.1

Values are percentages.

## DISCUSSION

IGF-I has been proposed as a growth-promoting factor in PDR (15). Our finding that there is no significant association between PDR and IGF-I levels in people without renal impairment does not support this hypothesis.

A possible relationship between growth hormone or IGF-I and PDR was first suggested by Poulsen (16), who reported the regression of retinopathy in a diabetic patient after pituitary infarction. This led to the limited use of hypophysectomy for treatment of PDR during the 1960s (17). There have been few well-controlled trials of this procedure, but a study by Lundbaek et al. (18) showed slower formation of new vessels in the hypophysectomized group than in the control group. Additional support for a possible relationship between IGF-I and retinopathy came from Merimée's (19) observation of the absence of microvascular complications in growth-hormone-deficient dwarfs with diabetes. Subsequently, Merimée et al. (1) found that IGF-I levels in adult diabetic patients with rapidly progressive retinopathy were twice those in patients without retinopathy, patients with less severe retinopathy, or nondiabetic control subjects. However, our study and numerous other studies found no relationship between IGF-I and PDR (3,20,21). Several factors may account for these apparently discrepant results. Ours was a cross-sectional, population-based study, whereas that

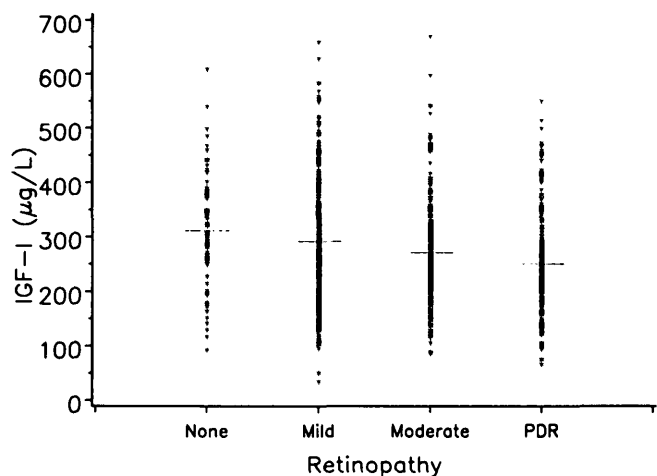


FIG. 3. Scatter plot showing relationship of serum levels of insulinlike growth factor I (IGF-I) with severity of retinopathy. Thin bars represents mean for each group.

TABLE 4

Relationship of insulinlike growth factor I (IGF-I) to proliferative diabetic retinopathy (PDR) severity after controlling for duration of diabetes

Quartile	IGF-I range ( $\mu\text{g/L}$ )	Duration (yr)									
		5-9		10-14		15-19		20-29		30+	
		<i>n</i>	%PDR	<i>n</i>	%PDR	<i>n</i>	%PDR	<i>n</i>	%PDR	<i>n</i>	%PDR
1	35-202	15	0	44	9.1	18	44.4	39	30.8	60	55.0
2	203-265	27	7.4	36	13.9	37	27.0	46	45.7	30	53.3
3	266-346	42	0	44	4.5	33	21.2	40	35.0	10	60.0
4	347-670	45	0	61	14.8	30	30.0	19	42.1	6	83.3

of Merimée et al. (1) was a longitudinal study of a selected ophthalmology clinic population in which the putative relationship between an elevated level of IGF-I and retinopathy was based on very few patients with rapid progression of preproliferative to proliferative retinopathy. Finally, in our study, a transient rise of serum IGF-I during a period of PDR, such as that recently reported by Hyer et al. (22), might have been missed.

IGF-I levels are significantly higher in diabetic kidney disease (2), perhaps because the kidney is an important site of IGF-I degradation (23). However, normalization of kidney function did not reduce IGF-I levels to normal in our diabetic participants who had undergone kidney transplantation. The explanation for this finding is not clear. The presence of IGF-I inhibitors (24) or the multiple drugs that these patients take for immunosuppression may account for elevations of IGF-I levels. Few of our patients had kidney transplants, and additional studies are needed to confirm our findings. Furthermore, in patients with severe kidney failure on dialysis, abnormalities of proteins that bind IGF-I may result in their failure to be removed by the acid-ethanol extraction procedure used to separate IGF-I from its binding protein in this and other studies (1,2,25); this unsaturated binding protein may interfere with the measurement of IGF-I (26). Residual unsaturated binding protein may therefore account for the elevated IGF-I levels in our patients with end-stage kidney disease, either those on dialysis or transplant recipients. These patients were eliminated from our analyses for this reason.

Diabetic participants without kidney disease in our study had lower age-specific IGF-I levels than the nondiabetic

group. This is consistent with the findings of other studies (25). However, Hyer et al. (2) found no significant difference between control subjects and diabetic patients from a retinopathy clinic population, and Merimée et al. (1) reported that patients with diabetes had higher IGF-I levels than nondiabetic control subjects. Failure to control for age in Hyer's study (2) or kidney function in Merimée et al.'s study (1) may account for the difference. Our finding of a marked decline in IGF-I with increasing age, both in healthy subjects and in patients with early-onset diabetes, is consistent with the findings of Tan and Baxter (25). This age-related decline in IGF-I levels has been described previously in nondiabetic populations and is apparently a normal function of aging (27).

We found a significant negative correlation between IGF-I and glycosylated hemoglobin, as have Tan and Baxter (25) and Winter et al. (28). These results suggest that higher levels of glycemia are associated with a reduction of IGF-I levels. Children with extremely poorly controlled diabetes have low IGF-I levels (29,30) and do not grow as well as children with well-controlled diabetes (31). However, Lambertson et al. (3) and Horner et al. (31) found no correlation between IGF-I and level of control.

Local effects of IGF-I on the retina may be more important than systemic levels of IGF-I as a risk factor for PDR. Grant et al. (15) found markedly elevated IGF-I levels in the vitreous from patients with PDR compared with nondiabetic patients. The vitreal concentrations of IGF-I in most of their diabetic patients with severe neovascularization were high enough to stimulate chemotaxis in both bovine and human retinal endothelial cells (32). In Grant et al.'s study (33), there was only a moderate positive correlation between the concentration of IGF-I in vitreous and its concentration in serum in diabetic subjects and none in control subjects. Thus, serum levels of IGF-I may not reflect ocular levels in many patients. Although IGF-I has not been shown to be synthesized in retinal tissue, mRNA for IGF-I has been found in most tissues. In addition, specific receptors for IGF-I have been found in the bovine retina (34), suggesting that the retina may be an important target of IGF-I action.

In summary, after controlling for duration of diabetes, glycosylated hemoglobin, diastolic blood pressure, and the presence of proteinuria and/or creatinine  $\geq 265 \mu\text{M}$ , IGF-I levels were not significantly associated with PDR. Although we cannot exclude either transient rises in serum IGF-I or elevated ocular IGF-I levels as possible risk factors, our data suggest that an elevated serum IGF-I level is not a risk factor for PDR.

TABLE 5

Characteristics significantly associated with proliferative diabetic retinopathy (PDR) in a multivariate logistic regression

Variable	$\beta$ (mean $\pm$ SE)	<i>P</i>
Intercept	-9.300 $\pm$ 1.289	<0.0001
Duration of diabetes	0.122 $\pm$ 0.013	<0.0001
HbA <sub>1c</sub>	0.127 $\pm$ 0.058	0.028
Diastolic blood pressure	0.052 $\pm$ 0.012	<0.0001
Proteinuria and/or creatinine $\geq 265 \mu\text{M}$	1.198 $\pm$ 0.234	<0.0001
IGF-I	-0.0002 $\pm$ 0.0011	0.87

HbA<sub>1c</sub>, glycosylated hemoglobin. IGF-I, insulinlike growth factor I. PDR is more likely with longer duration of diabetes, higher HbA<sub>1c</sub>, higher blood pressure, and presence of proteinuria and/or creatinine  $\geq 265 \mu\text{M}$ .

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