Association of Elevated IGF-I Levels With Increased Retinopathy in Late-Onset Diabetes

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Insulinlike growth factor I (IGF-I) has been suggested to play a role in the pathogenesis of proliferative diabetic retinopathy (PDR). We determined IGF-I levels in subjects in a large population-based study of 928 people with diabetes diagnosed at 30 yr of age or older. PDR was found in 15.7% of the insulin-using group (n = 517) and in 2.8% of those not using insulin (n = 397). The mean serum level of IGF-I was 208 μg/L in individuals using insulin and 222 μg/L in those not using insulin, both significantly lower than in a nondiabetic comparison group (278 μg/L, $P < 0.0001$). Logistic regression analysis was used to examine the relationship between IGF-I and PDR while controlling for other factors associated with the presence of PDR. After controlling for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, presence of proteinuria, and age at diagnosis, higher levels of IGF-I were significantly associated with an increased frequency of PDR (P = 0.025) in the group using insulin. In individuals not using insulin, higher levels of IGF-I were associated with an increased frequency of PDR or moderate non-PDR (P = 0.08). These data suggest that higher IGF-I levels may be a risk factor for the development of severe retinopathy in people with diabetes diagnosed at 30 yr of age or older.
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Insulinlike growth factor I (IGF-I), or somatomedin C, is the major mediator of the growth-promoting effects of growth hormone, and may play a role in the progression of diabetic retinopathy (1). Some studies have shown higher IGF-I levels in patients with proliferative diabetic retinopathy (PDR) (1), whereas others have not (2–4). The relationship of IGF-I to retinopathy in adult-onset diabetes has not been previously examined in a large population. Lamberton et al. (2) examined 33 patients with adult-onset diabetes and found no correlation of serum IGF-I with retinopathy severity, proteinuria, age, or glycosylated hemoglobin. Likewise, Merimee et al. (1) also found no correlation between IGF-I and retinopathy in 41 patients with non-insulin-dependent diabetes mellitus (NIDDM). In a large clinic-based study, Hyer et al. (3) examined 371 patients, 127 of whom were not being treated with insulin. They found a lower level of IGF-I in the oldest group, with inactive proliferative retinopathy, compared with patients with less severe retinopathy. Nardelli et al. (4) examined 69 patients with adult-onset diabetes, all non-insulin-treated, and found no relationship between IGF-I level and degree of retinopathy. Although the study of Sato et al. (5) of 72 patients with non-insulin-treated diabetes has shown higher IGF-I levels in diabetic patients with proliferative retinopathy when compared with control subjects, IGF-I levels in their diabetic patients with different stages of diabetic retinopathy did not differ significantly from each other. In this study we report the relationship between IGF-I levels and retinopathy in a large population-based study of individuals with diabetes diagnosed at 30 yr of age or older.

RESEARCH DESIGN AND METHODS

The method of identification and description of the population have appeared in detail in previous reports (6,7). In summary, 10135 diabetic patients were identified as having received primary medical care in an 11-county area in southern Wisconsin 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. The diagnosis of diabetes had been made in 1396 (15%) before 30 yr of age, and in 7887 (85%) at 30 yr of age or older. Eligibility criteria for all

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persons diagnosed at 30 yr of age or older included the diagnosis of diabetes by the primary-care physician, confirmed by a random or postprandial serum glucose level of a least 11.1 mM or a fasting serum glucose of at least 7.8 mM on at least two occasions, and residence in the 11-county area (n = 5431).

Of the 5431 patients meeting the eligibility criteria for the group diagnosed at ≥30 yr of age, 2341 individuals had diabetes for 0–4 yr, 2465 had diabetes for 5–14 yr, and 625 had diabetes for ≥15 yr. A random sample of 576 people from the first group, 579 people from the second group, and all 625 people from the third duration group was selected for examination. Of these three groups, 451, 452, and 467, respectively, were examined in 1980–1982, and 987 were reexamined in 1984–1986. Data from these subjects are the subject of this report.

The nondiabetic control subjects were spouses of the diabetic population residing in the most populous county in the study area. 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 by the Hypertension Detection and Follow-up Program protocol (8). Retinopathy status was determined by grading stereoscopic color fundus photographs of seven standard fields by the modified Wisconsin "191" system (9). 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 proliferation(s), new vessels, vitreous or preretinal hemorrhage(s), 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 readers.

Radioimmunoassay (RIA) for IGF-I was a double-antibody RIA with antiserum provided by the National Hormone and Pituitary Program (10,11). The standard curve was derived with synthetic IGF-I (Amgen, Thousand Oaks, CA) labeled with ^{125}I by 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). Urine protein was measured by Labstix (Miles, Elkhart, IN). Glycosylated hemoglobin was measured from a sample of 10 ml of venous blood that was collected in a syringe with 0.5 ml heparin and, after transfer of 100–200 μl to a 1-ml tube, was refrigerated at 4°C until analyzed. Samples for glycosylated hemoglobin were assayed within 7 days with the Quick-Step Fast Hemoglobin Test System (Isolab, Akron, OH).

Plasma C-peptide was measured in a random fashion, neither fasting nor at a standard time after a meal. With a 5-ml vacutainer tube that contained 7.5 mg EDTA and 0.2 ml Trasylol (10,000 KIU/ml), 4 ml of blood was collected and spun immediately at 4°C. Plasma was frozen at −20°C and sent to the University of Chicago for determination of the C-peptide level. Plasma C-peptide was measured as described by Faber et al. (12) with Heding's M1230 antiserum. The lower limit of detection of C-peptide was 0.03 nM, and the interassay coefficient of variation was 8%.

Age is defined as age at the time of the follow-up examination in 1984–1986. 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 ≥0.3 g/L (≥1+).

Statistical analysis was performed with the Statistical Analysis System (SAS) (13–15), and means were compared by t test. The significance of the relationship between variables was evaluated by linear regression, Pearson correlations, and Spearman correlations. Tests for trends in proportions were performed by the Mantel-Haenszel procedure (16). Logistic regression was used to evaluate the relationship of IGF-I to the presence of PDR after controlling for other variables (17).

RESULTS

Of the 987 participants who were reexamined, 53 were missing IGF-I data (24 using insulin and 29 not using insulin) and 6 (all using insulin) were on dialysis or had received a kidney transplant. These participants were excluded from analysis.

Of the remaining 928 participants at the time of the second examination, 527 were taking insulin and 401 were not taking insulin. Of the insulin-using group, 19.5% (n = 103) had undetectable C-peptide (<0.03 nM), 25.2% (n = 133) had low but detectable C-peptide (0.03–0.29 nM), and 54.7% (n = 285) had normal C-peptide levels (≥0.3 nM). Of the group not using insulin, 0.2% (n = 1) had undetectable C-peptide, 2.0%

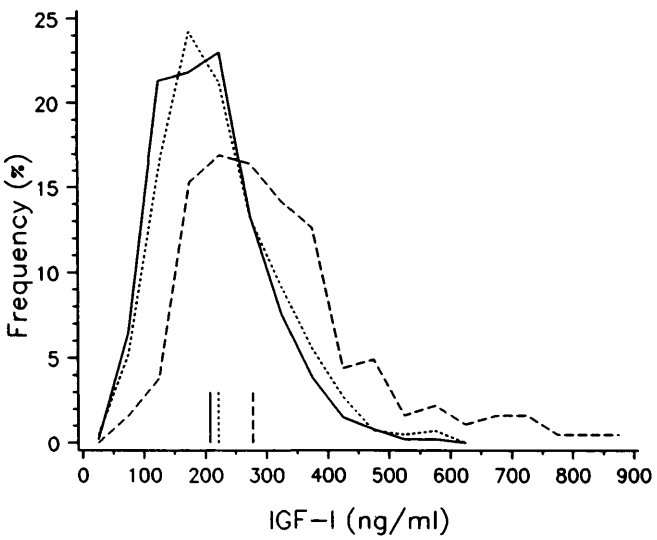

FIG. 1. Frequency distribution of insulinlike growth factor I (IGF-I) in insulin-taking diabetic subjects (*solid line*), diabetic subjects not taking insulin (*dotted line*), and nondiabetic subjects (*dashed line*). Vertical lines indicate mean IGF-I.

TABLE 1
Mean insulinlike growth factor I by age in study subjects

Age (yr)	Diabetic subjects						Nondiabetic controls (μg/L)	
	Using insulin (μg/L)			Not using insulin (μg/L)				
	n	Mean ± SD	*P**	*n*	Mean ± SD	*P**	*n*	Mean ± SD
30–54	74	226 ± 78	<0.0001	34	233 ± 96	<0.0001	61	336 ± 113
55–64	135	213 ± 92	<0.05	89	230 ± 97	0.12	30	261 ± 82
65–74	184	201 ± 82	0.16	140	226 ± 101	0.71	45	220 ± 76
75+	134	202 ± 83	0.17	138	210 ± 83	0.29	11	238 ± 93
Total	527	208 ± 84	<0.0001	401	222 ± 94	<0.0001	147	278 ± 108

**P* value for comparison with nondiabetic subjects.

(*n* = 8) low but detectable C-peptide, and 96.8% (*n* = 388) normal C-peptide. C-peptide data were missing in 1.1% (*n* = 10) individuals.

IGF-I levels in the diabetic group using insulin ranged from 27 μg/L to 578 μg/L; IGF-I levels in the diabetic group not using insulin ranged from 43 μg/L to 590 μg/L. Mean ± SD IGF-I levels were 208 ± 84 μg/L in the group using insulin and 222 ± 94 μg/L in the group not using insulin. Mean values in both diabetic groups were significantly ($P < 0.0001$) lower than in the nondiabetic comparison group (278 ± 108 μg/L). Figure 1 shows the frequency distributions of IGF-I in the two groups of diabetic people and in the nondiabetic comparison group.

There was a trend of decreasing IGF-I levels with increasing age in the diabetic insulin-using group ($P < 0.05$) and in the nondiabetic group ($P < 0.0001$); the trend was of borderline significance in the diabetic group not using insulin ($P = 0.08$; Table 1). Mean IGF-I levels of the diabetic groups were significantly lower than in the nondiabetic comparison group only in the youngest age-groups (Table 1).

In both diabetic groups, females had lower mean IGF-I levels than males overall and in most age-groups. However, the differences were not all statistically significant (Table 2).

IGF-I levels were not associated with duration of diabetes in either the group using insulin (test of trend, $P = 0.16$) or the group not using insulin (test of trend, $P = 0.40$) (Table 3).

At the time of the second examination 171 diabetic participants had either gross proteinuria or serum creatinine concentrations >265 μM. Of this group, 124 were using insulin and 47 were not using insulin. No proteinuria or serum creatinine data were available for 29 people using insulin and 17 people not using insulin. In the insulin-using group, mean IGF-I was not significantly different ($P = 0.49$) in those with proteinuria or elevated serum creatinine (203 ± 84 μg/L) when compared with those without gross proteinuria or with normal serum creatinine (209 ± 84 μg/L). In those not using insulin, mean IGF-I was also not significantly different ($P = 0.09$) in those with proteinuria or elevated serum creatinine (245 ± 105 μg/L) when compared with those without these signs (220 ± 92 μg/L).

In addition to being negatively and weakly correlated with age ($r = -0.10$, $P < 0.05$) in the insulin-using participants, IGF-I was also negatively and weakly associated with glycosylated hemoglobin ($r = -0.09$, $P < 0.05$) and systolic blood pressure ($r = -0.10$, $P < 0.05$). In the group of participants not using insulin, there were no significant correlations of IGF-I with age, glycosylated hemoglobin, or blood pressure.

In the diabetic group taking insulin, photographs of 10 people could not be graded for retinopathy severity. Of the remaining 517 subjects, 81 (15.7%) had PDR. In this group, the frequency of PDR increased with increasing quartile of IGF-I (Table 4). However, this trend was not statistically significant ($P = 0.16$).

Because the non-insulin-using group had too few

TABLE 2
Mean insulinlike growth factor I (IGF-I) by age and sex in study subjects

Age (yr)	Using insulin (μg/L)					Not using insulin (μg/L)				
	Male		Female			Male		Female		
	n	Mean ± SD	*n*	Mean ± SD	*P**	*n*	Mean ± SD	*n*	Mean ± SD	*P**
30–54	34	239 ± 76	40	216 ± 79	0.21	18	263 ± 100	16	199 ± 81	<0.05
55–64	69	206 ± 90	66	220 ± 94	0.38	43	235 ± 109	46	224 ± 85	0.60
65–74	83	213 ± 76	101	191 ± 86	0.07	66	246 ± 104	74	209 ± 96	<0.05
75+	46	213 ± 90	88	197 ± 79	0.29	57	215 ± 83	81	206 ± 83	0.54
Total	232	215 ± 83	295	203 ± 85	0.11	184	235 ± 99	217	210 ± 88	<0.01
P†		0.36		<0.05			0.06		0.68	

*Test for difference between males and females.
†Test for association between IGF-I and age.

TABLE 3
Mean insulinlike growth factor I by duration of diabetes in diabetic study subjects

	Using insulin (μg/L)		Not using insulin (μg/L)*	
Duration (yr)	*n*	Mean ± SD	*n*	Mean ± SD
5–9	115	210 ± 84	205	221 ± 95
10–14	106	211 ± 88	99	225 ± 98
15–19	68	216 ± 98	38	228 ± 92
20–24	136	209 ± 83	40	213 ± 77
25–29	61	200 ± 78	8	194 ± 69
30+	41	190 ± 67	8	206 ± 121

*Three people with diabetes for 4 yr excluded from analyses.

people with PDR, we combined PDR with moderate nonproliferative diabetic retinopathy (NPDR). The photographs of four subjects could not be graded for retinopathy severity. Of the diabetic subjects not using insulin, 56 (14.1%) had either PDR or moderate NPDR. No trend was found between increasing IGF-I and increasing frequency of PDR and moderate NPDR in the diabetic group not using insulin (Table 5).

To determine whether IGF-I was related to PDR after controlling for other known factors associated with PDR, we used logistic regression. After controlling for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, proteinuria, and age at diagnosis in the group using insulin, higher IGF-I levels were significantly associated with the presence of PDR ($P = 0.025$; Table 6). With this model and the values of the covariates for each case, a predicted probability of having PDR could be computed. These are plotted against IGF-I in Fig. 2, which illustrates the association between IGF-I and PDR after controlling for the other factors. Although there is much scatter, a trend toward higher predicted probability of PDR at higher IGF-I is apparent. After controlling for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, proteinuria, and body mass in the group not using insulin, there is a weak association between IGF-I and the presence of moderate NPDR and PDR (Table 6); this is of borderline significance ($P = 0.08$). Figure 3 shows the predicted probability of having moderate NPDR to PDR as a function of IGF-I levels after controlling for the other risk factors.

DISCUSSION

IGF-I has been proposed as a growth factor for the proliferation of new vessels in diabetic retinopathy. Our finding that higher IGF-I levels are associated with PDR in the diabetic group using insulin supports this hypothesis.

Growth hormone and IGF-I, the mediator of many of growth hormone's growth-promoting effects, have long been suspected of playing a role in the development of PDR. Merimee (18) reported the absence of microvascular complications in growth hormone–deficient dwarfs with diabetes, and later found higher IGF-I levels in diabetic patients with rapidly progressive retinopathy (1). We undertook this study to examine the relationship between IGF-I and retinopathy as well as confounding factors such as age, kidney impairment, and level of glycemic control.

After controlling for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, proteinuria, and age at diagnosis in the group using insulin, higher IGF-I levels were significantly associated with the presence of PDR. After controlling for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, proteinuria, and body mass in the group not using insulin, there was a weak association between IGF-I and the presence of moderate NPDR and PDR; this is of borderline significance. Our results, like those of Sato et al. (5), show higher IGF-I levels in people with PDR. However, this relationship has not been found by others in patients with NIDDM (2–4) or in a population of subjects with insulin-dependent diabetes mellitus (IDDM) (19); this suggests that the relationship is weak.

IGF-I has been found to be related to age in the general population: levels are low in childhood, rise with puberty to reach a peak in the second decade of life, and then gradually decline with age. In our population, as in nondiabetic subjects, there was a trend of decreasing IGF-I levels with increasing age in both diabetic groups, but in the group not using insulin the trend was of borderline significance. Our findings are similar to those of Tan and Baxter (20), who found a marked decline in IGF-I with increasing age in 46 adult-onset patients and significantly lower IGF-I levels than in age-matched control subjects. Nardelli et al. (4) also found significantly lower levels of IGF-I in their study of non-insulin-using NIDDM subjects than in control subjects. However, Nardelli et al. found no correlation between IGF-I and age

TABLE 4
Severity of retinopathy by quartile of insulinlike growth factor I (IGF-I) in diabetic subjects using insulin (%)

Quartile of IGF-I	Range (μg/L)	*n*	None	Minimal NPDR	Moderate NPDR	PDR
1	27–144	130	16.2	45.4	25.4	13.1
2	145–201	129	22.5	41.9	22.5	13.2
3	202–257	130	20.0	34.6	27.7	17.7
4	258–578	128	21.9	33.6	25.8	18.8
Total		517	20.1	38.9	25.3	15.7

PDR, proliferative diabetic retinopathy. NPDR, nonproliferative diabetic retinopathy.

TABLE 5
Severity of retinopathy by quartile of insulinlike growth factor I (IGF-I) in diabetic subjects not using insulin (%)

Quartile of IGF-I	Range (μg/L)	*n*	None	Minimal NPDR	Moderate NPDR to PDR
1	43–156	98	52.0	32.7	15.3
2	157–205	99	48.5	39.4	12.1
3	206–268	100	56.0	34.0	10.0
4	269–590	100	52.0	29.0	19.0
Total		397	52.1	33.8	14.1

PDR, proliferative diabetic retinopathy. NPDR, nonproliferative diabetic retinopathy.

TABLE 6
Association of insulinlike growth factor I (IGF-I) and other independent risk factors with presence of PDR in insulin-using subjects and moderate NPDR to PDR in non-insulin-using subjects in multivariate logistic regression models

Using insulin			Not using insulin		
	β ± SE	*P*		β ± SE	*P*
Intercept	−4.95 ± 1.59	<0.005	Intercept	−7.76 ± 1.67	<0.0001
Duration of diabetes (yr)	0.075 ± 0.019	<0.0001	Duration of diabetes (yr)	0.069 ± 0.022	<0.005
Glycosylated hemoglobin (%)	0.184 ± 0.082	0.024	Glycosylated hemoglobin (%)	0.256 ± 0.076	<0.001
Systolic blood pressure (mmHg)	0.0097 ± 0.0061	0.11	Systolic blood pressure (mmHg)	0.014 ± 0.007	0.030
Proteinuria (≥0.3 g/L) and/or creatinine ≥265 μM	0.341 ± 0.297	0.25	Proteinuria (≥0.3 g/L) and/or creatinine ≥265 μM	0.509 ± 0.406	0.21
Age at diagnosis (yr)	−0.0526 ± 0.0162	<0.005	Body mass (kg/m^2)	−0.0020 ± 0.0300	0.95
IGF-I (μg/L)	0.0036 ± 0.0016	0.025	IGF-I (μg/L)	0.0027 ± 0.0016	0.08

PDR, proliferative diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy.

in either insulin-using or non-insulin-using diabetic groups, but did find a negative correlation between IGF-I and age in their healthy control population. We may have been able to detect age-related differences in our insulin-using group possibly because of our larger population and the broader age range examined than in the study by Nardelli et al.

The kidney is a major site of IGF-I degradation (21); therefore, one might expect higher IGF-I levels in patients with impaired kidney function. In both the insulin-using and non-insulin-using groups, the mean IGF-I is not significantly different in those with proteinuria or elevated serum creatinine than in those without proteinuria and normal creatinine levels. This result is similar to those of Dills et al. (19), Lamberton et al. (2), and Sato et al. (5), but different from the results of Hyer et al. (3), who have shown higher IGF-I levels in diabetic patients with kidney impairment. It is possible that the failure to find such a relationship may be secondary to proteinuria being related to cardiovascular disease and not kidney disease, thus confounding this relationship.

IGF-I levels have been shown to fluctuate with glycemic control (22) and to increase after the institution of tight glycemic control using continuous subcutaneous insulin infusion (23). In our study, IGF-I levels in the insulin-using participants were negatively but weakly associated with glycosylated hemoglobin, but in the group of participants not using insulin, the correlation of IGF-I with glycosylated hemoglobin was not significant. Glycosylated hemoglobin was not associated with IGF-I in other studies of patients with NIDDM (2,5). Our findings are similar to those of Tan and Baxter (20), who reported an inverse correlation of glycosylated hemoglobin and IGF-I in younger patients with IDDM (21–40 yr of age) but not in older diabetic patients. Our results suggest that IGF-I levels may be affected more by hyperglycemia in younger- than in older-onset patients with diabetes. Poorly controlled diabetes (particularly with insulin defi-

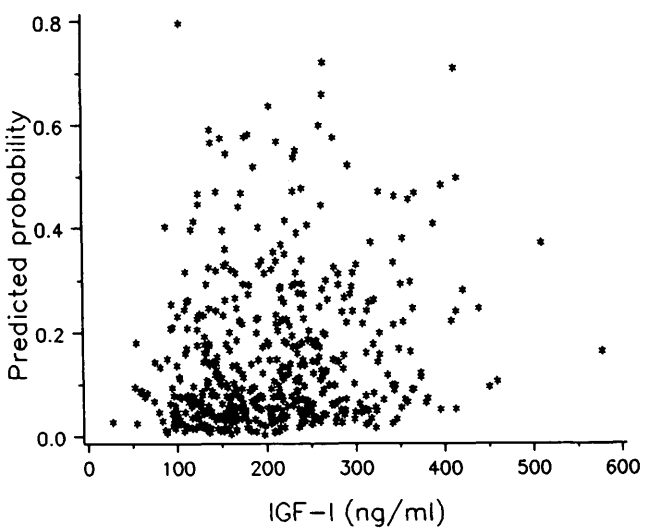

FIG. 2. Predicted probability of having proliferative diabetic retinopathy by insulinlike growth factor I (IGF-I) corrected for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, proteinuria and/or creatinine >265 μM, and age at diagnosis of diabetes in insulin-taking diabetic subjects.

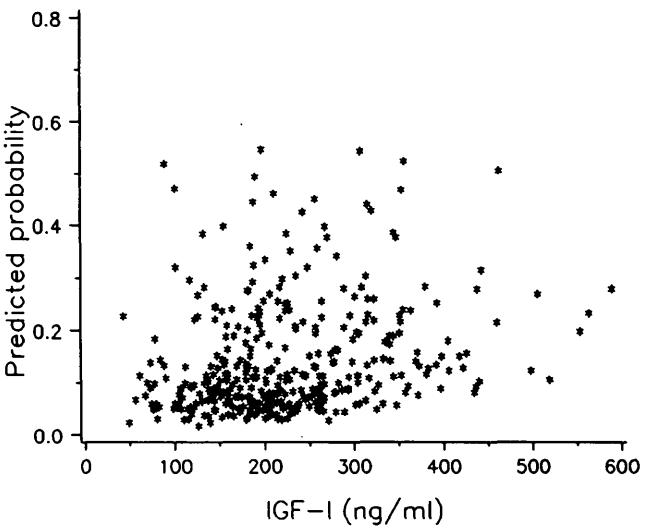

FIG. 3. Predicted probability of having moderate nonproliferative to proliferative diabetic retinopathy by insulinlike growth factor I (IGF-I) corrected for duration of diabetes, glycosylated hemoglobin, systolic blood pressure, proteinuria and/or creatinine >265 μM, and body mass in diabetic subjects not taking insulin.

ciency) resembles starvation, which is known to lower IGF-I levels (24). This may explain why people with diabetes have lower IGF-I levels than nondiabetic people, and may also explain why the lowering is more prominent in younger patients, who are more likely to be insulin deficient.

Our finding of a correlation between PDR and IGF-I in the older-onset patients is different than in our previous study (19) of younger-onset (diagnosed before age 30 yr) insulin-taking patients. This either suggests that the relationship is weak or that there are confounding unmeasured variables. Vitreous concentration of IGF-I may be more important than systemic levels. Grant et al. (25) found markedly elevated IGF-I levels in the vitreous from patients undergoing vitrectomy with PDR compared with levels in nondiabetic patients. In addition, concentrations of IGF-I in the vitreous of patients with PDR can stimulate proliferation and migration of cultured human retinal pigment epithelial cells (26). Concentrations of IGF-I in the vitreous of nondiabetic subjects are usually low or undetectable and do not correlate with serum IGF-I levels. In contrast, concentrations of IGF-I in patients with PDR are much higher and show a strong correlation between serum and vitreous levels (27). Breakdown of the blood-retinal barrier in diabetic retinopathy may allow leakage of serum IGF-I into the vitreous (28), possibly accounting for our apparently paradoxical observation that nondiabetic subjects have higher serum IGF-I levels than diabetic subjects even though higher serum levels of IGF-I in diabetes are associated with PDR.

In our study, significant transient rises in IGF-I preceding an exacerbation of retinopathy could have been missed. Studies by Hyer et al. (23,29) suggest that transient rises in IGF-I may precede exacerbation of PDR in both patients with IDDM and NIDDM and in patients recently brought under tight control with continuous subcutaneous insulin infusion. Additional prospective studies are needed to evaluate the potential etiologic significance of IGF-I as a risk factor in the development or progression of retinopathy.

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