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 (≥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 ± 108 μg/L (mean ± 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 ≥265 μM 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), 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.

Creatinine 1 μM = 0.011 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.

Received for publication 3 May 1989 and accepted in revised form 29 September 1989.

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 ≥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}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 μl 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 ≥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 ≥18 yr at the second examination, 172 had either proteinuria or serum creatinine concentrations ≥265 μM. 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 ± 191 μg/L, mean ± SD) than people who had never received a transplant or who were not on kidney dialysis (277 ± 108 μg/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 ≥265 μM.

The IGF-I values in the diabetic group ranged from 35 to 670 μg/L. Mean IGF-I levels were significantly lower ($P < 0.0001$) in the diabetic group (277 ± 108 μg/L) than in the nondiabetic comparison group (315 ± 147 μg/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.

TABLE 1
Mean insulinlike growth factor I by sex and age in younger-onset diabetic* and nondiabetic comparison groups

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

*Excluding kidney dialysis/transplant patients.

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 μg/L for the lowest quartile, 203–265 μg/L for the second quartile, 266–346 μg/L for the third quartile, and 347–670 μg/L for the highest quartile.

TABLE 2
Mean insulinlike growth factor I by duration of diabetes

Duration (yr)	n	Mean ± SD (μg/L)
5–9	129	320 ± 106
10–14	185	299 ± 116
15–19	118	293 ± 103
20–24	86	265 ± 92
25–29	58	236 ± 78
30–34	52	198 ± 69
35+	54	202 ± 89

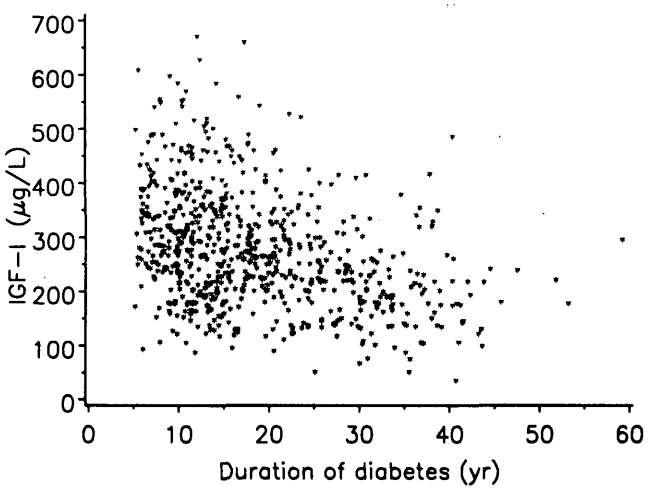

FIG. 1. Scatter plot showing relationship of serum levels of insulinlike growth factor I (IGF-I) and duration of diabetes in 682 people with diabetes diagnosed at <30 yr of age.

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 ≥265 μM. 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 ≥265 μM, 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).

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

Quartile	IGF-I range (μg/L)	*n*	Nonproliferative diabetic retinopathy			Proliferative diabetic retinopathy
			None	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 inpairment 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

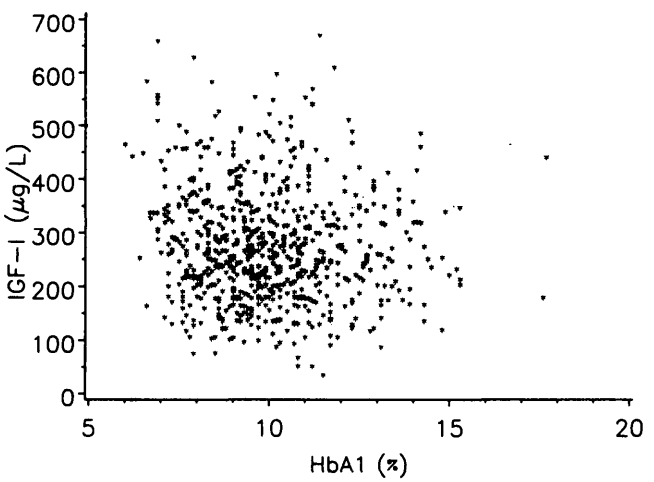

FIG. 2. Scatter plot showing relationship of serum levels of insulinlike growth factor I (IGF-I) with glycosylated hemoglobin (HbA_1) in 682 people with diabetes diagnosed at <30 yr of age.

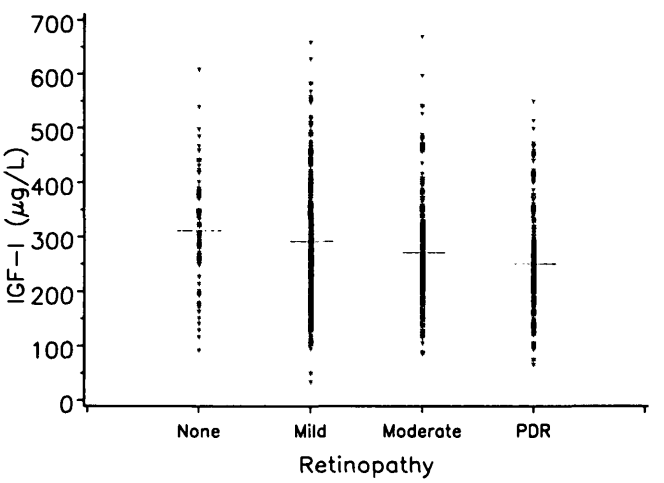

FIG. 3. Scatter plot showing relationship of serum levels of insulinlike growth factor I (IGF-I) with severity of retinopathy. *Thin bars* represents mean for each group.

TABLE 4
Relationship of insulinlike growth factor I (IGF-I) to proliferative diabetic retinopathy (PDR) severity after controlling for duration of diabetes

		Duration (yr)									
		5–9		10–14		15–19		20–29		30+	
Quartile	IGF-I range (μg/L)	*n*	%PDR	*n*	%PDR	*n*	%PDR	*n*	%PDR	*n*	%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, Lamberton 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 ≥265 μM, 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	β (mean ± SE)	*P*
Intercept	−9.300 ± 1.289	<0.0001
Duration of diabetes	0.122 ± 0.013	<0.0001
HbA_1	0.127 ± 0.058	0.028
Diastolic blood pressure	0.052 ± 0.012	<0.0001
Proteinuria and/or creatinine ≥265 μM	1.198 ± 0.234	<0.0001
IGF-I	−0.0002 ± 0.0011	0.87

HbA_1, glycosylated hemoglobin. IGF-I, insulinlike growth factor I. PDR is more likely with longer duration of diabetes, higher HbA_1, higher blood pressure, and presence of proteinuria and/or creatinine ≥265 μM.

ACKNOWLEDGMENTS

This work was supported by Grant EY-03083 (R.K.) from the National Eye Institute and U.S. Public Health Service and by Grant 2P30-DDK-26659 (Dr. Earl Shrago) from the National Institutes of Health.

We are grateful to the 452 Wisconsin physicians and their staffs who participated in and supported this study and Michael J. Grahn for technical assistance.

REFERENCES

1. Merimée TJ, Zapf J, Froesch ER: Insulin-like growth factors: studies in diabetics with and without retinopathy. *N Engl J Med* 309:527–30, 1983
2. Hyer SL, Sharp PS, Brooks RA, Burrin JM, Kohner EM: Serum IGF-I concentration in diabetic retinopathy. *Diabetic Med* 5:356–60, 1988
3. Lamberton RP, Goodman AD, Kassoff A, Rubin CL, Treble DH, Saba TM, Merimée TJ, Dodds WJ: Von Willebrand factor (VIII R:Ag), fibronectin, and insulin-like growth factors I and II in diabetic retinopathy and nephropathy. *Diabetes* 33:125–29, 1984
4. Klein R, Klein BEK, Moss SE, DeMets DL, Kaufman I, Voss PS: Prevalence of diabetes mellitus in southern Wisconsin. *Am J Epidemiol* 119:54–61, 1984
5. Klein R, Klein BEK, Moss SE, Davis MD, Demets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 102:520–26, 1984
6. Hypertension Detection and Follow-up Program Cooperative Group: The hypertension detection and follow-up program. *Prev Med* 5:207–15, 1976
7. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 107:237–43, 1989
8. Furlanetto RW, Underwood LE, Van Wyk JJ, D'Ercole AJ: Estimation of somatomedin-C levels in normals and patients with pituitary disease by radioimmunoassay. *J Clin Invest* 60:648–57, 1977
9. Daughaday WH, Parker KA, Borowsky S, Trivedi B, Kapadia M: Measurement of somatomedin-related peptides in fetal, neonatal and maternal rat serum by insulin-like growth factor (IGF-I) radioimmunoassay, IGF II radioreceptor assay (RRA), and multiplication stimulating activity RRA after acid-ethanol extraction. *Endocrinology* 110:575–78, 1982
10. *SAS User's Guide: Basics. Version 5 Edition*. Cary, NC, SAS Inst., 1985, p. 861–74, 945–65
11. *SAS User's Guide: Statistics. Version 5 Edition*. Cary, NC, SAS Inst., 1985, p. 763–74
12. *SUGI Supplemental Library User's Guide. Version 5 Edition*. Cary, NC, SAS Inst., 1986, p. 269–93
13. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22:719–48, 1959
14. Walker SH, Duncan DB: Estimation of the probability of an event as a function of several independent variables. *Biometrika* 54:167–79, 1967
15. Grant M, Russell B, Fitzgerald C, Merimée TJ: Insulin-like growth factors in vitreous: studies in control and diabetic subjects with neovascularization. *Diabetes* 35:416–20, 1986
16. Poulsen JE: The Houssay phenomenon in man: recovery from retinopathy in a case of diabetes with Simmond's disease. *Diabetes* 2:7–12, 1953
17. McMeel JW, Field RA: Pituitary ablation: treatment of diabetic retinopathy. In *Controversy in Opthalmology*. Brockhurst RJ, Boruchoff SA, Hutchinson BT, Eds. Philadelphia, PA, Saunders, 1977
18. Lundbaek K, Malmros R, Andersen HC, Rasmussen JH, Bruntse E, Madsen PH, Jensen VA: Hypophysectomy for diabetic angiopathy: a controlled clinical trial. In *Symposium on the Treatment of Diabetic Retinopathy*. Goldberg MF, Fine SL, Eds. Arlington, VA, Dept. of Health, Educ., and Welfare, 1969, p. 291–311
19. Merimée TJ: A follow-up study of vascular disease in growth-hormone-deficient dwarfs with diabetes. *N Engl J Med* 298:1217–22, 1978
20. Cohen MP, Jasti K, Rye DL: Somatomedin in insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 45:236–39, 1977
21. Salardi S, Cacciari E, Ballardini D, Righetti F, Capelli M, Cicognani A, Zucchini S, Natali G, Tassinari D: Relationships between growth factors (somatomedin-C and growth hormone) and body development, metabolic control, and retinal changes in children and adolescents with IDDM. *Diabetes* 35:832–36, 1986
22. Hyer SL, Sharp PS, Brooks RA, Burrin JM, Kohner EM: A two-year follow-up study of serum insulin like growth factor-I in diabetics with retinopathy. *Metabolism* 38:586–89, 1989
23. D'Ercole AJ, Decedue CJ, Furlanetto RW, Underwood LE, Van Wyk JJ: Evidence that somatomedin-C is degraded by the kidney and inhibits insulin degradation. *Endocrinology* 101:577–86, 1977
24. Phillips LS, Fusco AC, Unterman TG, del Greco F: Somatomedin inhibitor in uremia. *J Clin Endocrinol Metab* 59:764–72, 1984
25. Tan K, Baxter RC: Serum insulin-like growth factor I levels in adult diabetic patients: the effect of age. *J Clin Endocrinol Metab* 63:651–55, 1986
26. Powell DR, Rosenfeld RG, Baker BK, Liu F, Hintz RL: Serum somatomedin levels in adults with chronic renal failure: the importance of measuring insulin-like growth factor I (IGF-I) and IGF-II in acid-chromatographed uremic serum. *J Clin Endocrinol Metab* 63:1186–92, 1986
27. Hall K, Sara VR: Somatomedin levels in childhood, adolescence and adult life. *Clin Endocrinol Metab* 13:91–112, 1984
28. Winter RJ, Phillips LS, Klein MN, Traisman HS, Green OC: Somatomedin activity and diabetic control in children with insulin-dependent diabetes. *Diabetes* 28:952–54, 1979
29. Winter RJ, Phillips LS, Green OC, Traisman HS: Somatomedin activity in the Mauriac syndrome. *J Pediatr* 97:598–600, 1980
30. Kappy MS: Regulation of growth in children with chronic illness. *Am J Dis Child* 141:489–93, 1987
31. Horner JM, Kemp SF, Hintz RL: Growth hormone and somatomedin in insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 53:1148–53, 1981
32. Grant M, Jerdan J, Merimée TJ: Insulin-like growth factor-I modulates endothelial cell chemotaxis. *J Clin Endocrinol Metab* 65:370–71, 1987
33. Grant MB, Fitzgerald C, Merimée TJ: Vitreous studies of insulin-like growth factors I and II (IGF I and IGF II) in diabetic subjects (Abstract). *Diabetes* 38 (Suppl. 2):56A, 1989
34. Waldbillig RJ, Fletcher RT, Somers RL, Chader GJ: IGF-I receptors in the bovine neural retina: structure, kinase activity and comparison with retinal insulin receptors. *Exp Eye Res* 47:587–607, 1988