The Role of Growth Hormone in the Development of Diabetic Retinopathy

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OBJECTIVE — To determine the role of growth hormone (GH) in the development of diabetic retinopathy.

RESEARCH DESIGN AND METHODS — Medical records of 1,423 patients who had undergone insulin tolerance tests (1976–1991) at the Mayo Clinic were examined, and diabetic subjects were identified as either GH-deficient (GH increment after hypoglycemia <5 μg/L and peak <10 μg/L) or GH-sufficient. Prevalence of retinopathy was determined in these cases and in a cohort group of diabetic subjects selected to match the GH-deficient cases. These control patients (32 cases) were selected from medical records of individuals who had received medical care at Mayo during the same interval but who had not undergone insulin tolerance testing.

RESULTS — Twenty-four patients with diabetes were identified, of whom 16 were GH-deficient and 8 GH-sufficient. Despite comparable age, duration of diabetes, and metabolic control, the prevalence of diabetic retinopathy in the GH-deficient group (2 of 16; 12.5%) was less ($P < 0.05$) than that observed in the GH-sufficient group (5 of 8; 62.5%). Prevalence in the GH-deficient group also was lower than that observed in the cohort control group (15 of 32, 47%).

CONCLUSIONS — These data strongly suggest that GH contributes to the development of diabetic retinopathy in humans.

The pathogenesis of diabetic retinopathy remains ill defined, but a role of growth hormone (GH) in this process has been long suspected. Poulsen (1) reported in 1953 that preexisting diabetic retinopathy completely resolved following postpartum pituitary infarction. Subsequent studies suggested that hypophysectomy or pituitary ablation slowed the rate of progression of proliferative retinopathy (2–4), but these procedures were later abandoned because of the high risk of hypophysectomy (5) and the advent of laser photocoagulation therapy. Furthermore, Merimee (6) reported that the prevalence of diabetic complications, including nonproliferative retinopathy, in a group of GH-deficient dwarfs was lower than that which would be predicted from previous population-based studies. However, many of the subjects in this study had only mild glucose intolerance rather than overt diabetes, and the results were not compared with an appropriately matched control group (7). Nevertheless, taken together, these observations, although not definitive, imply that GH may influence the rate of progression of diabetic proliferative retinopathy.

If GH is important in the pathogenesis of diabetic retinopathy, the recent availability of agents that can inhibit GH secretion (e.g., somatostatin or its analogues) offers a potential means of delaying or preventing this complication (8,9). On the other hand, because use of such agents is not without risk, it is important to establish whether creation of a state of GH deficiency alters the rate of development of diabetic retinopathy. To examine this question, we took advantage of the large number of insulin tolerance tests performed in our institution to identify a group of GH-deficient individuals who had long-standing, well-documented diabetes. We compared the prevalence of diabetic retinopathy in these people to that present in diabetic individuals with documented GH sufficiency who had also undergone insulin tolerance testing and to that present in a matched cohort of diabetic individuals who had received medical care at Mayo over the same interval but who had not undergone insulin tolerance testing.

RESEARCH DESIGN AND METHODS

Selection of cases

Data from all 1,423 patients who had undergone an insulin tolerance test at the Mayo Clinic Endocrine Testing Center

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GH, growth hormone; IGF, insulin-like growth factor; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

Table 1—*Clinical characteristics of subjects*

	GH-deficient	GH-sufficient	Cohort control
n	16	8	32
Age (years)	50 ± 3	44 ± 8	51 ± 3
Gender (M/F)	5/11	1/7	10/22
IDDM/NIDDM	4/12	5/3	11/21
Duration of diabetes (years)	13.7 ± 2.9	12 ± 2.3	13.5 ± 2
Fasting glucose (mM)	11 ± 1.0	9.4 ± 1.2	9.1 ± 0.6
Glycosylated hemoglobin (%)	10.7 ± 1.2	10.6 ± 0.9	10.4 ± 0.45

Data are means ± SE.

between 1976 and 1991 were reviewed. An intravenous bolus of soluble insulin (0.1–0.2 U/kg) was given, and blood was sampled at 30-min intervals for the next 2 h for measurement of glucose and GH (10). The number of GH-deficient patients was determined to be 316. GH deficiency was defined as an increment in GH of <5 μg/L and peak <10 μg/L in response to adequate hypoglycemia (plasma glucose <2.2 mM). All 1,423 charts were reviewed for the presence of diabetes (defined as a fasting plasma glucose >7.8 mM on at least two occasions). Patients were classified as having type I insulin-dependent diabetes mellitus (IDDM) if the age at onset of diabetes was <35 years and if subjects were treated with insulin from time of diagnosis; all others were classified as having type II non-insulin-dependent diabetes mellitus (NIDDM).

Individuals fulfilling the criteria above were included as cases unless they had no ophthalmic assessment (14 cases); GH deficiency was caused by pituitary ablation for diabetic retinopathy (2 cases); they had a previous history of acromegaly (6 cases); or they had GH-lowering therapy and inconclusive insulin tolerance test results (1 case) (GH increment >5 μg/L but peak <10 μg/L). Remaining after these exclusions were 24 individuals with diabetes, 16 with GH deficiency and 8 with normal GH secretion.

In addition, the medical records of all individuals registered at Mayo between 1976 and 1991 were reviewed to identify all individuals with a diagnosis of diabetes. From this group, two control subjects were matched for age, gender, and duration of diabetes to each GH-deficient index case. Potential control subjects were listed randomly and reviewed in order until a match was found. The review first identified a potential control whose duration of diabetes (i.e., time since first documented) was equal to or less than that of the index case. If this criterion was fulfilled, then the most recent glycosylated hemoglobin in this individual's record was compared with that of the index case. If no glycosylated hemoglobin was available, the mean of the last three glucose concentrations was used as an indication of glycemic control. If the glycosylated hemoglobin concentration (or mean of the last three glucose concentrations) was greater than or equal to that of the index GH-deficient case, the individual was selected as the control subject for that case. This approach was used to maximize the likelihood that the level of glycemic control in the control cohort would be worse, if anything, than that in the GH-deficient cases.

The complete (inpatient and outpatient) medical records of all cases (GH-deficient, GH-sufficient) and control subjects were then analyzed for the prevalence of diabetes complications. The presence or absence of diabetic retinopathy was assessed by detailed fundoscopic examination of the dilated eye by an ophthalmologist. The severity of retinopathy was classified as no diabetic retinopathy, nonproliferative diabetic retinopathy (microaneurysms, exudates, and retinal hemorrhages), or proliferative diabetic retinopathy (neovascularization of the disk and elsewhere and/or vitreous hemorrhages). The presence or absence of maculopathy was also recorded, as was the use of laser therapy. Most of the eye examinations reported included a specific designation of the type of retinopathy (if present) by the examining ophthalmologist. When no specific designation was stated, a diagnosis was inferred by the reviewer according to the criteria above. If there was a disparity in the severity of retinopathy between the two eyes, the type of retinopathy was based on the eye with the more severe disease.

Statistical analysis

The χ^2 test was used to test for differences in the prevalence of retinopathy between groups. Student's *t* test was used for analysis of subjects' characteristics. Results are expressed as means ± SE. $P < 0.05$ was considered significant.

RESULTS — Table 1 describes characteristics of subjects in the three study groups. Age, gender, type of diabetes, duration of diabetes, and glycemic control were similar in the GH-deficient cases and control subjects. The GH-sufficient subjects were somewhat younger and more likely to have IDDM but were otherwise comparable to the GH-deficient subjects. Underlying pituitary disease included pituitary adenoma (four cases), empty sella syndrome (three cases), craniopharyngioma (two cases), pinealoma (one case), and hemochromatosis (one case). The cause of GH deficiency could not be identified in four cases. Six of the GH-deficient cases had not required any form of hormone replacement, two had been treated with cortisol only, four had been treated with cortisol and thyroxine, and four were on a combination of cortisol, thyroxine, and sex hormone therapy. None of the patients had been on GH replacement therapy.

Two of the 16 (12.5%) GH-defi-

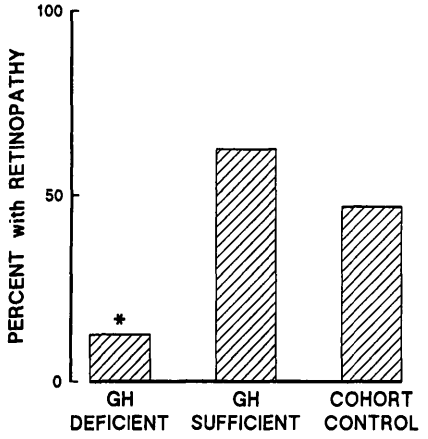

Figure 1—*Prevalence of diabetic retinopathy in the GH-deficient, GH-sufficient, and cohort control subjects. *P < 0.05 compared with other groups.*

cient individuals had diabetic retinopathy (Fig. 1). One individual had only background diabetic retinopathy; the other had proliferative retinopathy and had been treated with photocoagulation therapy. This prevalence was much lower ($P < 0.05$) than that observed in either of the control groups. Five of the eight diabetic individuals who were GH-sufficient had retinopathy (62.5%). Three of the subjects in this group had nonproliferative retinopathy; one had proliferative retinopathy and photocoagulation therapy; and one had proliferative retinopathy, rubeosis iridis, and photocoagulation therapy. The prevalence of retinopathy was also lower than that observed in the cohort of diabetic individuals who did not undergo insulin tolerance testing (15 of 32, 47%). In the latter group, 3 subjects had proliferative retinopathy with photocoagulation, 1 patient had exudative retinopathy and maculopathy, 1 patient had rubeosis iridis, and 10 patients had nonproliferative retinopathy.

CONCLUSIONS— The role of GH in the pathogenesis of diabetic retinopathy remains uncertain (11–15). In this study, we report that diabetic patients with GH deficiency as determined by insulin tolerance testing had a lower risk (approximately one-fifth) of developing diabetic retinopathy than did either diabetic patients with documented normal GH secretion or an appropriately matched cohort of diabetic patients whose GH secretory status was undetermined.

GH deficiency in adults has few if any symptoms. Therefore, formal testing is required for its diagnosis. Because diabetes is common, we reasoned that a substantial number of people who had undergone insulin tolerance testing as part of an evaluation of their pituitary-adrenal function would also be diabetic. Because of the large number of insulin tolerance tests performed at our institution, we were able to identify 24 diabetic individuals, 16 who were GH-deficient and 8 who were GH-sufficient. Because the latter subjects obviously would not have been subjected to an insulin tolerance test unless there was some suspicion of pituitary and/or adrenal disease, we were concerned that they might in some unknown way differ from the typical person with diabetes. Consequently, we also identified a second control group from diabetic individuals who were cared for at the Mayo Clinic over the same interval. Although GH secretory status of these subjects was not evaluated, it is very unlikely that any were GH-deficient on the basis of chance alone. A GH-deficient person included inadvertently in this group would diminish rather than accentuate any differences in retinopathy relative to the GH-deficient group. The prevalence of retinopathy in the GH-sufficient control group (62%) and the cohort control group (47%) was not only similar to one another but also similar to that observed in people with diabetes of comparable duration (40–80%) who have been evaluated as part of population-based studies (16–19). Of importance from the perspective of the present report, the prevalence rates in all of the studies above were four- to fivefold greater than that observed in the GH-deficient subjects (12%).

How GH alters the risk for diabetic retinopathy is not known. Individuals with poorly controlled IDDM secrete excessive amounts of GH (20). GH has both direct and indirect effects on tissue growth and metabolism. Many, if not all, of the indirect effects appear to be mediated via insulin-like growth factor 1 (IGF-1) (21). Indeed, elevated concentrations of IGF-1 have been reported recently, both in plasma and in vitreous fluid in diabetic patients with advanced retinopathy (22–24). On the other hand, other researchers have failed to demonstrate a relationship between plasma IGF-1 concentrations and the severity of retinopathy (25,26). However, these findings are difficult to interpret because of the complex and ill-defined relationships between the IGFs and their binding proteins and GH and its binding protein. GH can antagonize insulin action. By worsening glycemic control, insulin resistance potentially could accelerate the rate of development of retinopathy. Although the GH-deficient and control groups in this study were matched for glycosylated hemoglobin and/or glucose concentrations, this by no means excludes chronic differences in blood glucose levels. Whatever the mechanism, this study suggests that the use of GH supplementation in diabetic (or perhaps even glucose intolerant) individuals who have GH deficiency is likely to accelerate the rate of development of retinopathy. Conversely, our results also suggest that therapies aimed at lowering circulating GH concentrations (e.g., treatment with somatostatin or its analogues) may prevent or delay the development of diabetic retinopathy. The risk/benefit ratios of such therapies remain to be determined.

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