Growth Hormone Replacement Therapy Is Not Associated with Retinal Changes

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ABSTRACT

GH and/or growth factors are thought to play a role in the pathogenesis of diabetic retinopathy. In addition, the occurrence of retinal changes mimicking diabetic retinopathy in two GH-deficient (GHD) patients receiving GH replacement therapy (GHRT) has recently been reported. The present study was performed to evaluate whether this was a coincidence or whether GHRT might regularly induce retinal changes.

Sixty-one GHD patients on GHRT with a mean age of 42.5 ± 17.3 yr were examined by one ophthalmologist (AR). The mean duration of GHRT was 8.4 ± 3.7 yr in childhood onset and 3.5 ± 2.1 yr in adult onset patients. Plasma insulin-like growth factor I concentrations were 76.4 ± 49.6 ng/mL before GHRT and 244.3 ± 119.2 ng/mL while receiving GHRT with a dose of 1.7 ± 0.7 IU/day. After pupil dilatation with tropicamide, fundus examinations of both eyes were performed using a Volk 90 diopter fundus lens with a slit lamp (Haag Streit, Bern, Switzerland). In none of the patients were vascular or retinal changes like macular edema, microaneurysms, hemorrhages, hard exudates, cotton wool spots, preproliferative signs, or proliferations found. The optic discs were also normal in all patients.

We conclude, therefore, that long-term GHRT can be administered safely in GHD patients without an increased risk of retinal changes.

(R)etinal neovascularisation is the major cause of untreated blindness. Numerous clinical reports have postulated a causative role for GH in the pathogenesis of proliferative diabetic retinopathy (1–5). In addition, increased serum and vitreous insulin-like growth factor I (IGF-I) concentrations have been reported to be associated with proliferative retinopathy (6, 7). Furthermore, IGF-I has been shown to induce angiogenesis in vivo in rabbit cornea and retina models (8). Ischemia-associated retinal neovascularisation was also inhibited in transgenic mice expressing a GH antagonist gene and in normal mice given an inhibitor of GH secretion (MK678) (9). Whereas this inhibition could be reversed with exogenous IGF-I administration, transgenic mice expressing the GH agonist E117L had no increase in retinal neovascularisation (9). A decreased prevalence of diabetic retinopathy has also been described in GH-deficient (GHD) diabetics (4, 5), and pituitary ablation has been reported to stop deterioration of visual acuity in patients with diabetic retinopathy (3). Furthermore, continuous infusion of somatostatin has been shown to inhibit development and progression of proliferative retinopathy (10).

Recently, retinal changes have been reported in two non-diabetic GHD subjects receiving GH replacement therapy (GHRT) over a period of 14 and 22 months, respectively (11). Because symptoms improved or disappeared after cessation of GHRT, a possible causative role for GH has been suggested. To further analyze a possible relation between GHRT and retinopathy, we have performed fundus examinations in 61 GHD patients receiving long-term GHRT.

 Patients and Methods

Sixty-one adult patients with GH deficiency (36 males, 25 females) receiving long-term GHRT were investigated. Characteristics of the patients are given in Table 1. Forty-three percent of the patients had nonfunctioning pituitary adenomas, 16% had a prolactinoma, 8% had a craniopharyngioma, and 33% had idiopathic GH deficiency. GH deficiency was documented by a GH response of 3 ng/mL or less to either of the following stimulation tests: arginine, insulin-induced hypoglycemia, or GH-releasing hormone. GH was given as a single daily sc injection in the evening. Usually the dose was adjusted to achieve IGF-I serum concentrations within 2 sd of an age-adjusted control population. In some cases, a fixed dose without adjustment was used. The GH preparations used were Genotropin (Pharmacia and Upjohn, Stockholm, Sweden), Humatrope (Lilly Co, Indianapolis, IN), and Norditropin (Novo Nordisk, Copenhagen, Denmark). IGF-I serum concentrations were measured by a RIA after treatment of serum samples with acid ethanol to precipitate and neutralize IGF-I binding proteins according to the method of Blum et al. (12). The minimum detectable IGF-I concentration was 20 ng/mL; intra- and interassay coefficients of variation were 3.1% and 10%, respectively.

All patients were examined by one ophthalmologist (AR). After pupil dilatation with tropicamide fundus, examinations of both eyes were performed with a slit lamp (Haag Streit, Bern, Switzerland) using a Volk 90 diopter fundus lens (Mentor, OH). After inspection of the posterior pole in primary position, patients had to look in all directions for careful midperiphery and periphery examination. Fundus photographs for additional documentation were taken using a Canon CF-60UV (40 degrees; Tokyo, Japan).

Results

Twenty-five percent of the 61 patients studied had hypertension, and 64% had hyperlipidemia. The age of the patients...
patients and the delay until the results of such a study would have been available. Nevertheless, after this report, we plan to follow up on our patients and repeat the ophthalmologic evaluation at yearly intervals. However, because we have found no retinal changes in 61 patients treated for 337 patient years, we feel reassured that GHRT can be regarded as a safe treatment if the contraindications are carefully watched for. In this respect, it is of interest that long-term GHRT does not seem to increase other risk factors for retinal changes. In contrast, long-term GHRT has been shown to be associated with a decrease rather than an increase in blood pressure (16). Whereas a decrease of insulin sensitivity has been shown in short-term studies and studies using pharmacological GH doses (17, 18) long-term studies using physiological GH doses document either an increase or no further decline in insulin sensitivity (19), with no increased rate of development of diabetes.

From this first systematic investigation of 61 patients treated for 337 patient years it might be concluded that long-term GH substitution in GHD subjects does not induce retinal changes. However, it cannot be excluded that mild affections might have been missed by chance due to their transient nature or very low frequency. We recommend, therefore, that ophthalmologic evaluations should be performed in all GHD patients before institution of GHRT and repeated every year until our report will be confirmed by other larger studies over an even more prolonged period of time.

**References**


**TABLE 1.** Characteristics of the patients with GHD (mean ± sd; range)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Sex (m/f)</td>
<td>36/25</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.8 ± 17.3 (17–73)</td>
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<tr>
<td>Duration of GHRT (yr)</td>
<td>2.1 (0.5–7)</td>
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<tr>
<td>GH dose (IU)</td>
<td>1.7 ± 0.7 (0.5–3.5)</td>
</tr>
<tr>
<td>Serum IGF-I concentrations before treatment (ng/mL)</td>
<td>76.4 ± 49.6 (21–229)</td>
</tr>
<tr>
<td>Serum IGF-I concentrations during treatment (ng/mL)</td>
<td>244.3 ± 119.2 (57–522)</td>
</tr>
</tbody>
</table>

Ophthalmologic examination

In none of the patients could retinal changes like macular edema, microaneurysms, hemorrhages, hard exsudates, cotton wool spots, preproliferative signs, or proliferations be detected in any eye. There was no swelling of the optic disc or vascular abnormality of the optic disc vessels.

**Discussion**

In the present study, no retinal changes could be observed in 61 nondiabetic patients with GH deficiency receiving GHRT for a total period of 337 patient years. This seems to be of interest for the growing number of adult GHD patients who receive GHRT because of the well documented beneficial effects on cardiovascular risk factors, body composition, quality of life, and bone mineral density (13–15). Whereas the possibility that mild transient retinal changes in earlier phases of GHRT might have been missed cannot totally be excluded due to the cross-sectional design of the study, this seems unlikely because none of the patients reported visual disturbances or ophthalmologic treatment during GHRT. The pathogenesis of the retinal changes mimicking diabetic retinopathy in the two patients receiving GHRT reported earlier (11) might be multifactorial or independent of GH therapy. In one case, the episode of pericarditis and intermittent hypertension with documented blood pressure values of up to 170 over 99, as well as concomitant therapy for obesity (phentermine, fenfluramine, pemoline), could have influenced the history of blurred vision; in the other case, the unilateral abnormality might have represented acceleration of unrecognized preexisting retinopathy.

Our data represent results of a cross-sectional study. With respect to the alarming above mentioned Food and Drug Administration report (11) a prospective, randomized, controlled trial seemed unjustified due to the risk for the GHD patients and the delay until the results of such a study would have been available. Nevertheless, after this report, we plan to follow up on our patients and repeat the ophthalmologic evaluation at yearly intervals. However, because we have found no retinal changes in 61 patients treated for 337 patient years, we feel reassured that GHRT can be regarded as a safe treatment if the contraindications are carefully watched for. In this respect, it is of interest that long-term GHRT does not seem to increase other risk factors for retinal changes. In contrast, long-term GHRT has been shown to be associated with a decrease rather than an increase in blood pressure (16). Whereas a decrease of insulin sensitivity has been shown in short-term studies and studies using pharmacological GH doses (17, 18) long-term studies using physiological GH doses document either an increase or no further decline in insulin sensitivity (19), with no increased rate of development of diabetes.

From this first systematic investigation of 61 patients treated for 337 patient years it might be concluded that long-term GH substitution in GHD subjects does not induce retinal changes. However, it cannot be excluded that mild affections might have been missed by chance due to their transient nature or very low frequency. We recommend, therefore, that ophthalmologic evaluations should be performed in all GHD patients before institution of GHRT and repeated every year until our report will be confirmed by other larger studies over an even more prolonged period of time.

**References**