Indium-111-Pentetreotide Scintigraphy in Graves' Ophthalmopathy

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The radiolabeled somatostatin analog ^{111}In-pentetreotide can sensitively demonstrate somatostatin receptor-positive localizations in diseases where activated lymphocytes play a role. Lymphocyte infiltration of retrobulbar tissue in Graves' ophthalmopathy is the rationale of receptor imaging with radionuclide-coupled ^{111}In-pentetreotide. **Methods:** Forty patients with Graves' ophthalmopathy, 5 patients with orbital myositis and 10 control subjects were included in this prospective study. Indium-111-pentetreotide (110 MBq) was intravenously injected and SPECT images were obtained at 4 and 24 hr after injection. The scans were analyzed by a region of interest technique. An uptake ratio between the orbits and the brain was determined. **Results:** Compared to controls (4-hr ^{111}In-pentetreotide uptake: median 6.0 counts/voxel/MBq, orbit-to-brain ratio 5.6), ophthalmopathy patients showed two- to threefold increased uptake (15.8 counts/voxel/MBq versus controls $p = 0.0032$; ratio 12.6 versus controls $p = 0.003$). When considering patients with active disease only, even higher uptake was registered (16.8 counts/voxel/MBq versus controls $p = 0.0048$, ratio 15.6 versus controls $p = 0.0006$). Untreated patients showed markedly higher uptake (23 counts/voxel/MBq) compared to patients under steroid therapy (12.6, $p = 0.001$). In myositis, high uptake (20 counts/voxel/MBq) was also registered. **Conclusion:** In contrast to controls, ophthalmopathy patients showed markedly increased orbital accumulation of labeled ^{111}In-pentetreotide. This sensitive nuclear medicine technique could possibly select those patients who might benefit from treatment with immunosuppressive agents and/or octreotide.

Key Words: indium-111-pentetreotide; Graves' ophthalmopathy; somatostatin receptor scintigraphy

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Somatostatin, a small peptide hormone of 14 amino acids, is present in high concentrations in the hypothalamus, cerebral cortex, brain stem and pancreas (*1*). In the central nervous system, it acts as a neurotransmitter and its hormonal activities include the inhibition of the release of growth hormone and insulin (*2*). Somatostatin receptors have been identified on many cells of neuroendocrine origin as well as on lymphocytes (*1,3*). Because of the short plasma half-life of somatostatin (2–4 min), analogs more suitable for medical treatment have been developed. The somatostatin analog octreotide, which is eight amino acids long, has been shown to bind to somatostatin receptors on both tumorous and nontumorous tissues (*4,5*). Because of its relatively long effective half-life, ^{111}In-DTPA-D-Phe1 (^{111}In-pentetreotide) is a radionuclide-coupled somatostatin analog that can be used to visualize somatostatin-receptor-bearing cells efficiently 4 and 24 hr after injection when interfering background radioactivity has been minimized by renal clearance (*6,7*).

The histologic findings in Graves' ophthalmopathy, including orbital infiltration with mononuclear cells and local release of cytokines, suggest that activated T cells are involved in the pathogenesis of this disorder (*8,9*). In the early stages of the disease, the retrobulbar tissue shows marked lymphocytic infiltration and interstitial edema, whereas in later stages, fibrosis and fatty infiltration are seen (*10,11*). However, this process of inflammation and subsequent fibrosis is not always reflected in the clinical severity of the disease. Quantitative analyses of eye movement recordings were shown to be a useful adjunct in assessing the severity of ophthalmopathy (*12,13*). Thus, it can be difficult to distinguish clinically active inflammatory disease from the stable fibrotic end stage. It is conceivable that immunosuppression is effective only during the active phase, and that patients not responding to immunosuppression already have inactive disease. Hence, establishing the activity of ophthalmopathy at initial presentation might have important clinical use. The use of steroids and radiation could then be restricted to patients with active disease,

FIGURE 1. Semiquantitative evaluation was performed using SPECT slices with irregular ROIs placed over the orbits and as references over both hemispheres.

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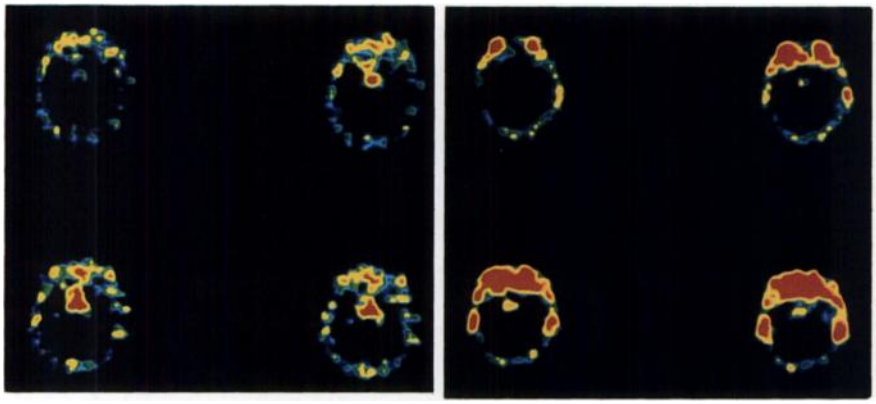

FIGURE 2.
Indium-111-pentetreotide scan (four transversal slices through the orbit) of a normal control (A) and a patient with Graves' ophthalmopathy (B).

whereas rehabilitative surgery could be initiated without prior therapy in inactive ophthalmopathy.

Therefore, taking into account the marked lymphocytic infiltration and the interstitial edema of the retrobulbar tissue in the active stage, as well as the demonstrated somatostatin receptors on lymphocytes, we performed a prospective clinical study to establish whether the degree of ^{111}In-pentetreotide uptake in the orbit could serve as a new way to assess disease activity in Graves' ophthalmopathy.

MATERIALS AND METHODS

Patients

Indium-111-pentetreotide scintigraphy was performed in 40 patients (31 females, age 29–71 yr, mean 46.5) with Graves' ophthalmopathy (American Thyroid Association Classes 1–6; duration of disease: range 1–144 mo, mean 20.7 mo) of whom 34 were suffering from active disease (eyelid erythema and edema, conjunctival injection, chemosis, retrobulbar pain on eye movement) according to the recently published classification of eye changes of Graves' disease and recommendations of the joint committees of the World Thyroid Associations (*14*). The diagnosis was based on endocrinological and ophthalmological investigation according to the World Thyroid Associations (*14*) which encompassed laboratory determination of thyroid hormones and antibodies as well as ultrasonography of the orbit. Eighteen patients had untreated ophthalmopathy of recent onset (<6 mo), whereas 11 patients were already undergoing steroid therapy (prednisone starting with 50 mg/day and tapering the dose by 5 mg/wk). Thirty-two patients were euthyroid and eight were hyperthyroid at the time of scanning. Five patients with orbital myositis (3 female, 30–65 yr, median age 45 yr; duration of disease 1–89 mo, median duration 23.5 mo) and 10 patients (5 female, 27–70 yr, median age 44 yr) without any history of ophthalmic/thyroid or autoimmune disease, but with suspected endocrine tumor (carcinoid, pheochromocytoma) served as controls. Diagnosis of ocular myositis was based on ophthalmological investigation (unilateral involvement of one extraocular muscle, mostly horizontal, restriction of motility in the direction of the involved muscle, orbital pain, lid erythema and ptosis), as well as on sonography (low reflectivity of the involved eye muscle) and CT (thickened insertion of the involved rectus muscle) of the orbit.

Indium-111-Pentetreotide Scintigraphy

Planar and SPECT images were obtained with a large field of view gamma camera at 4 and 24 hr after intravenous injection of 110 MBq ^{111}In-pentetreotide. The gamma camera was equipped with a high-resolution, medium-energy, parallel-hole collimator and connected to a computer system. Acquisition was performed in a step-and-shoot mode using a zoom factor of 1.45. For SPECT, 64 frames of 40 sec each were collected during a 360° rotation (matrix 64 × 64, magnification 1.6, thickness 4.5 mm). The filtered data were reconstructed with a modified ramp filter, and two slices were added during reconstruction, resulting in a voxel size of 4 × 4 × 9 mm. The scans were analyzed visually and by a region of interest technique (ROI). Semiquantitative evaluation was performed using the SPECT slices with irregular ROIs placed over the orbits and as reference over both hemispheres (Fig. 1). Accumulation of radioactivity was registered in calculated counts/voxel per MBq injected activity (decay-corrected). For dosimetry, the biologic half-life of the orbit and brain activity was calculated by analyzing the computer images 4 and 24 hr after injection. An ^{111}In-pentetreotide uptake ratio between the orbits and the brain was also determined.

The two-sample Wilcoxon test was applied to compare the values of both patients and controls, and an alpha adjustment

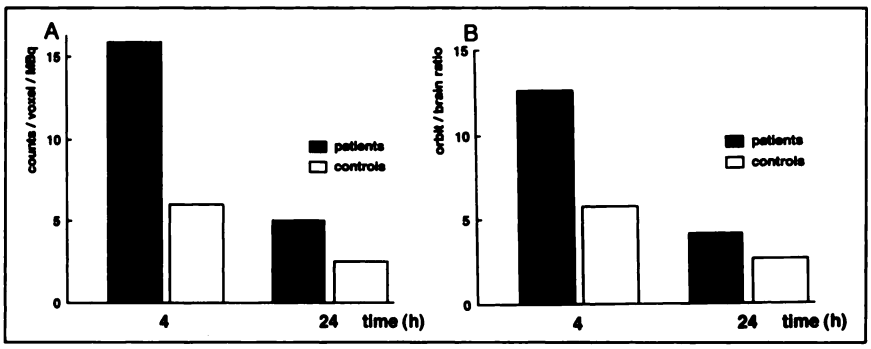

FIGURE 3. Orbital uptake (median) (calculated counts/voxel/MBq) (A), and orbit-to-brain ratio of ^{111}In-pentetreotide (B) 4 hr (patients versus controls: uptake $p = 0.0032$; ratio $p = 0.003$ respectively) and 24 hr after intravenous injection of ^{111}In-pentetreotide in 40 patients with Graves' ophthalmopathy and 10 controls.

TABLE 1
Orbital Uptake and Orbit-to-Brain Ratios of ^{111}In-Pentetreotide

		^{111}In-Pentetreotide			
		Uptake		Orbit-to-brain ratio	
		4 hr	24 hr	4 hr	24 hr
Controls	(n = 10)	9.0 ± 2.0	3.8 ± 2.1	5.0 ± 1.5	2.6 ± 1.1
Graves' ophthalmopathy	(n = 40)	17.3 ± 2.9	5.0 ± 1.8	14.0 ± 2.9	5.1 ± 1.8
Active ophthalmopathy	(n = 34)	19.2 ± 1.8	5.8 ± 1.8	15.6 ± 2.9	5.3 ± 1.8
Inactive ophthalmopathy	(n = 6)	6.0 ± 1.8	2.3 ± 0.7	6.2 ± 1.5	3.6 ± 1.3
Untreated ophthalmopathy	(n = 29)	23.0 ± 2.9	5.9 ± 2.0	17.0 ± 2.9	7.0 ± 2.0
Treated ophthalmopathy*	(n = 11)	14.0 ± 2.9	3.8 ± 1.6	13.0 ± 2.8	4.4 ± 1.5
<6 mo	(n = 18)	20.9 ± 2.6	5.3 ± 1.9	14.3 ± 2.8	6.0 ± 1.6
≥2 yr	(n = 7)	12.0 ± 2.1	3.0 ± 1.0	12.4 ± 3.0	3.8 ± 1.4
ATA I–III	(n = 6)	11.0 ± 2.0	3.0 ± 1.0	11.7 ± 2.7	4.0 ± 1.3
ATA IV–VI	(n = 34)	20.6 ± 3.0	5.2 ± 1.9	15.7 ± 2.9	5.6 ± 1.9
Hyperthyroid	(n = 8)	18.0 ± 2.6	4.6 ± 1.9	15.6 ± 2.5	5.1 ± 1.8
Euthyroid	(n = 32)	17.0 ± 3.0	3.8 ± 1.2	13.9 ± 2.9	4.9 ± 1.6
Myositis	(n = 5)	22.0 ± 3.0	4.3 ± 1.1	41.0 ± 4.0	5.0 ± 0.8

* Patients with thyroid eye disease undergoing steroid therapy.
Values are means ± s.e.m. ATA = American Thyroid Association. ATA I–III and IV–VI are Classes 1–3 and 4–6, respectively. <6 mo is time span of duration of opthalmopathy.

(Bonferroni-Holm) was performed. Probability values < 0.05 were considered significant.

RESULTS

Compared to controls (Fig. 2A; 4 hr ^{111}In-pentetreotide uptake: median 6.0 calculated counts/voxel/MBq injected activity, orbit-to-brain ratio 5.6), ophthalmopathy patients (Fig. 2B) showed a two- to threefold increase in uptake (15.8 counts/voxel/MBq versus controls, p = 0.0032, ratio 12.6 versus controls, p = 0.003, Fig. 3 and Table 1). For patients with active disease only, an even higher uptake was registered (16.8 counts/voxel/MBq versus controls, p = 0.0048, Fig. 4A; ratio 15.6 versus controls, p = 0.0006, Fig. 4B; 24-hr uptake: 4.0 counts/voxel/MBq versus controls, p = 0.028; ratio 5.3 versus controls, p = 0.033). Patients with inactive disease had uptake comparable to controls (4-hr: 5 counts/voxel/MBq versus active disease, p = 0.0048; ratio 6 versus active ophthalmopathy, p = 0.0006, Fig. 4B; 24-hr: 2.3 counts/pixel/MBq versus active, p = 0.005). Untreated patients (especially with ophthalmopathy of recent onset) showed markedly higher ^{111}In-pentetreotide uptake (4 hr: 23 counts/voxel/MBq) compared to patients undergoing steroid therapy (12.6 counts/voxel/MBq, p = 0.001; Fig. 5). Furthermore, patients with ophthalmopathy of recent onset (<6 mo) had a significantly higher uptake (16.3 counts/voxel/MBq) than patients with a disease duration of more than 2 yr (8.6 counts/voxel/MBq, p = 0.01, Fig. 6). Accumulation of radioactivity in the orbit was also markedly higher (16.5 counts/voxel/MBq) in patients with optic neuropathy and eye muscle involvement (Classes 4–6 of the American Thyroid Association) compared to patients with Classes 1–3 only (7.4 counts/voxel/MBq, p = 0.01, Fig. 7). In hyperthyroid ophthalmopathy patients, octreotide uptake was slightly higher in the orbit (13.7 versus 11.2 counts/voxel/MBq, p = 0.06) as well as in the thyroid (12.6 versus 11.8 counts/voxel/MBq, p = 0.08; planar investigation) in comparison to euthyroid patients. In the five cases of ocular myositis, a high uptake of radioactivity in the orbit was also registered (4 hr: 20 counts/voxel/MBq versus controls, p = 0.0006; Fig. 8).

DISCUSSION

This prospective study demonstrated marked orbital accumulation of ^{111}In-pentetreotide in patients with Graves'

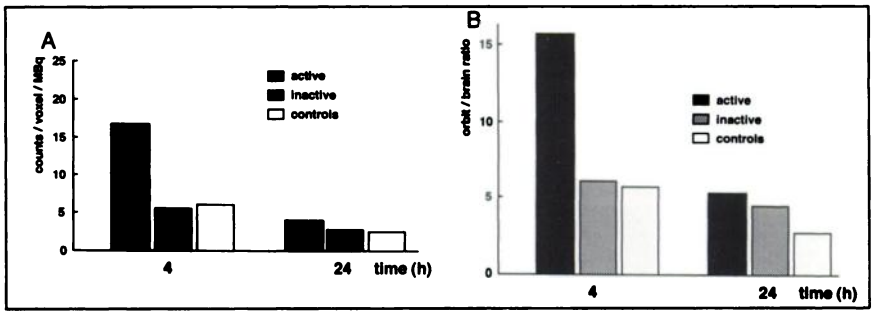

FIGURE 4. Orbital uptake (median) (calculated counts/voxel per MBq injected activity) (A) and orbit-to-brain ratio of ^{111}In-pentetreotide (B) 4 hr (active versus inactive ophthalmopathy/controls: uptake p = 0.0048, ratio p = 0.0006, respectively) and 24 hr after intravenous injection of ^{111}In-pentetreotide in 34 patients with active Graves' opthalmopathy, six patients with inactive Graves' ophthalmopathy and 10 controls.

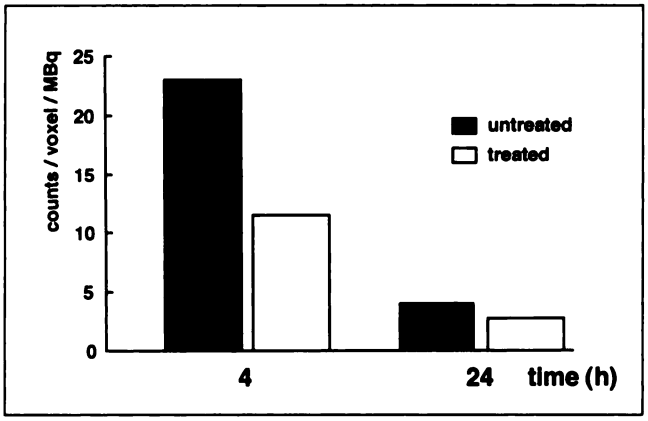

FIGURE 5. Orbital uptake of ^{111}In-pentetreotide (counts/voxel/MBq) 4 hr ($p = 0.001$) and 24 hr after intravenous injection of ^{111}In-pentetreotide in 29 untreated and 11 treated (glucocorticoids) patients with Graves' ophthalmopathy.

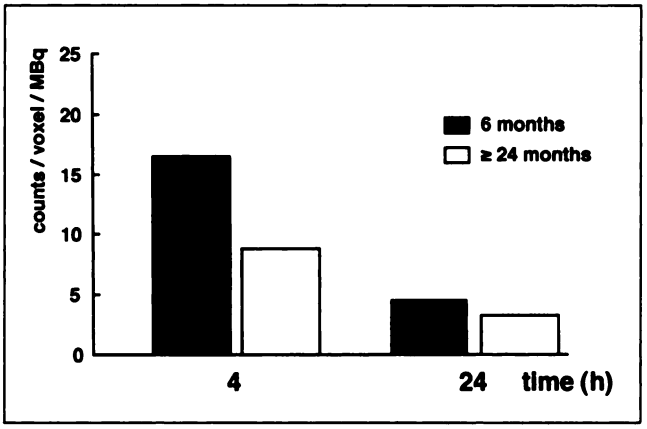

FIGURE 6. Relationship between orbital uptake (median) (counts/voxel/MBq) 4 hr (<6 versus >24 mo, $p = 0.01$) and 24 hr after intravenous injection of ^{111}In-pentetreotide and duration of Graves' ophthalmopathy.

ophthalmopathy in contrast to controls. Untreated patients with active thyroid eye disease of recent onset and involvement of eye muscles/optic nerve had especially high radionuclide uptake values. As patients with myositis also revealed an increased orbital radioactivity, the diagnostic value of ^{111}In-pentetreotide scintigraphy lies in its ability to measure inflammation acuity and intensity. Nevertheless, although a sensitive nuclear medicine technique, the high ^{111}In-pentetreotide uptake in patients with orbital myositis limits the specificity of this method.

The assessment of disease activity in patients with Graves' ophthalmopathy can be done by a variety of methods as recently reviewed (*15*). After initial active inflammation, an inactive stage of fibrosis follows. Thus, it is possible that disease activity rather than disease duration is the prime determinant of the effect of immunosuppression. The natural course of ophthalmopathy is characterized by spontaneous exacerbations and regressions, and the duration of active disease varies extremely (*15,16*). Assuming that immunosuppression is more effective during the active stage, we hypothesized that due to inflammation, enhanced vascularization and edema of retrobulbar tissue, ^{111}In-pentetreotide uptake would be high during active disease where there is presumably more lymphocytic infiltration, and low in the fibrotic end stage. Indeed, we found a striking difference in orbital accumulation of radioactivity between patients with apparently active and inactive disease and/or patients undergoing steroid therapy. This implies that high ^{111}In-pentetreotide uptake represents active orbital inflammation similar to acute myositis. In both diseases, the radioactivity peak was registered 4 hr after intravenous injection, with a stronger decline in uptake after 24 hr in myositis. In this disease, due to inflammation and vascular congestion, early unspecific ^{111}In-pentetreotide uptake is observed, whereas, in contrast to autoimmune thyroid-associated ophthalmopathy, less marked lymphocyte infiltration and lower binding affinity would explain the rapid orbital clearance of the radionuclide.

Planar thyroid and SPECT orbital ^{111}In-pentetreotide

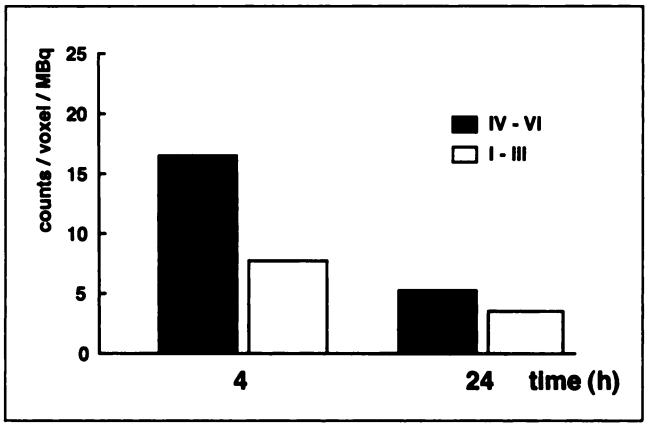

FIGURE 7. Relationship between orbital uptake (median) (counts/voxel/MBq) 4 hr (ATA IV–VI versus ATA I–III, $p = 0.01$) and 24 hr after intravenous injection of ^{111}In-pentetreotide and classes of the American Thyroid Association (ATA) in patients with Graves' ophthalmopathy.

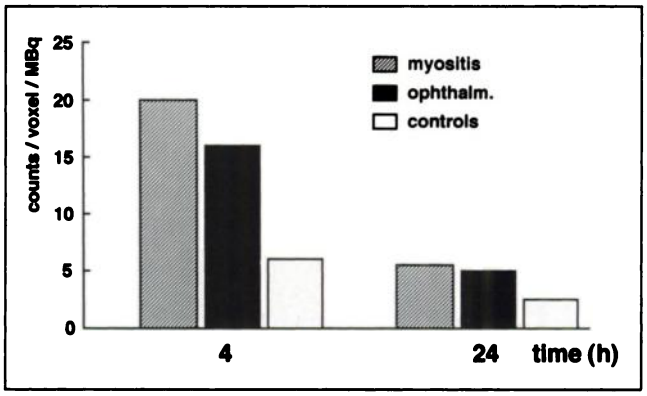

FIGURE 8. Orbital uptake (median) (counts/voxel/MBq) 4 hr (myositis versus controls, $p = 0.0006$) and 24 hr after intravenous injection of ^{111}In-pentetreotide in five patients with orbital myositis, 40 patients with Graves' ophthalmopathy and 10 controls.

(222 MBq) scintigraphy was performed by Krenning et al. in 28 patients with Graves' disease (20 with eye symptoms) and 15 controls (*17*). Thyroidal ^{111}In-pentetreotide accumulation in Graves' disease patients was increased sevenfold in thyrotoxicosis ($p < 0.01$ versus controls) and was almost absent after radioiodine-induced hypothyroidism. In patients with Graves' ophthalmopathy, orbital ^{111}In-pentetreotide activity was elevated and decreased during or after specific treatment (steroids and/or retrobulbar irradiation). A relationship between the clinical activity score and orbital ^{111}In-pentetreotide accumulation was noted. Thus, along with these findings, ^{111}In-pentetreotide scintigraphy might be seen as a parameter of disease activity in Graves' ophthalmopathy.

Extraocular muscles and fat cells show immunoreactivity to insulin-like growth factor 1 (IgF-1) (*18*). Octreotide, a potent long-acting somatostatin analog, suppresses IgF-1 activity either indirectly, by reducing plasma concentrations of growth hormone, or directly, by blocking the effect of IgF-1 on peripheral tissue (*19*). Since somatostatin is a potent inhibitor of a variety of secretion processes, somatostatin receptors might also mediate a directly antiproliferative effect of somatostatin on different cells, an effect described for somatostatin and somatostatin analogs under normal and tumoral conditions in various endocrine tumors (*20*). Octreotide may also inhibit local synthesis of IgF-1 from inflammation or through postreceptor inhibition (*21*) and thereby inhibit glycosaminoglycan synthesis by fibroblasts in the orbit. Glycosaminoglycans accumulate in the tissue of patients with ophthalmopathy (*22*). Binding of water by these hydrophilic macromolecules, which increases the volume of orbital tissue, is the proximate cause of many of the clinical manifestations of ophthalmopathy (*8,16*). Recently, highly significant increased plasma and urinary glycosaminolglycans in ophthalmopathy patients compared to controls were reported (*23–26*). After one week's treatment with octreotide (100 μg thrice daily), elevated urinary glycosaminoglycan values decreased significantly (*26*). Lymphocytes may produce lymphokines that stimulate production of glycosaminoglycans (*8,27*), and octreotide can inhibit responsiveness of T lymphocytes (*28*). Octreotide may therefore directly inhibit the release of lymphokines, resulting in inhibition of the production of glycosaminoglycans.

In conclusion, somatostatin receptor scintigraphy with ^{111}In-pentetreotide may be useful as a diagnostic tool for measuring the acuity of inflammation in patients with thyroid eye disease. A SPECT scan is necessary to properly quantify this orbital scintigraphy. This method could possibly select those patients who might benefit from treatment with immunosuppressive agents and/or octreotide.

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