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Chapter 12. Graves' Disease: Complications

THYROID STORM

Thyroid (or thyrotoxic) storm is an acute, life-threatening syndrome due to an exacerbation of thyrotoxicosis. It is now an infrequent condition, because of earlier diagnosis and treatment of thyrotoxicosis, better pre- and postoperative medical management. However, acute exacerbation of thyrotoxicosis caused by intercurrent illness, especially infections, may still occur. Thyroid storm in the past most frequently occurred after surgery, but now it is usually a complication of untreated or partially treated thyrotoxicosis, rather than a postoperative complication.

Clinical pattern

Classic features of thyroid storm are indicative of a sudden and severe exacerbation of thyrotoxicosis, with fever, marked tachycardia, tremor, nausea and vomiting, diarrhea, dehydration, restlessness, extreme agitation, delirium or coma. Fever is typical and may be higher than 105.8 oF (41 oC). Patients may present with a true psychosis or a marked deterioration of previously abnormal behavior. Sometimes thyroid storm takes a strikingly different form, called apathetic storm, with extreme weakness, emotional apathy, confusion, absent or low fever

Signs and symptoms of decompensation in various organ systems may be present. Delirium is one example. Congestive heart failure may also occur, with peripheral edema, congestive hepatomegaly, and respiratory distress. Marked sinus tachycardia or tachyarrhythmias, such as atrial fibrillation, are common. Liver damage and jaundice may derive from congestive heart failure or a direct action of thyroid hormone on the liver coupled with malnutrition (Chapter 10). Fever and vomiting may produce dehydration and prerenal azotemia. Abdominal pain may be a prominent feature. The clinical picture may be masked by a secondary infection such as pneumonia, a viral infection, or infection of the upper respiratory tract. Death may be caused by cardiac arrhythmia, congestive heart failure, hyperthermia, or other unidentified factors.

Storm is typically associated with Graves' disease, but it may occur in patients with toxic nodular goiter[1] . In the past, death was the usual final outcome of thyroid storm[2] . In a large series reported in 1969, three-fourths of patients with thyroid storm died[3] . These patients typically were malnourished, had severe thyrotoxicosis, and had coincident serious disease, such as heart failure[4]. In later series mortality was 30-75%[1,5] . At present, although still life-threatening, death from thyroid storm is rarer if it is promptly recognized and aggressively treated in an intensive care unit[6] .

Incidence

In Nelson and Becker's series reported in 1969[3] , there were 21 cases of thyroid storm among 2,329 admissions due to thyrotoxicosis (about 1%). Other series, which included all cases with fever of 38.3 oC or more in the postoperative period, reported an incidence of thyroid storm as high as 10% of patients operated on[4] . Few patients are now seen with the classic pattern of thyroid storm, but patients are occasionally encountered with marked accentuation of symptoms of thyrotoxicosis in conjunction with infection. Most recent reports described single cases. The incidence of thyroid storm currently is very low.

Cause

Thyroid storm classically began a few hours after thyroidectomy performed on a patient prepared for surgery by potassium iodide alone. Many such patients were not euthyroid and would not be considered appropriately prepared for surgery by current standards. Exacerbation of thyrotoxicosis is still seen in patients sent too soon to surgery, but it is unusual in the antithyroid drug-controlled patient. Thyroid storm occasionally occurs in patients operated on for some other illness while severely thyrotoxic. Severe exacerbation of thyrotoxicosis is rarely seen following 131-I therapy for hyperthyroidism; some of these may be defined as thyroid storm7.

Thyroid storm appears most commonly following infection3, which seems to induce an escape from control of thyrotoxicosis. Pneumonia, upper respiratory tract infection, enteric infections, or any other infection can cause this condition. Pathophysiology is incompletely understood8 . Interestingly, serum free T4 concentrations were higher in patients with thyroid storm than in those with uncomplicated thyrotoxicosis, while serum total T4 levels did not differ in the two groups9 , suggesting that events like infections may decrease serum binding of T4 and cause a greater increase in free T4 responsible for storm occurrence.

The decreased incidence of thyroid storm can be largely attributed to improved diagnosis and therapy. In most cases, thyrotoxicosis is recognized early and treated by measures of predictable therapeutic value. Patients are routinely made euthyroid before thyroidectomy or 131-I therapy. Using thionamides preoperatively, thyroid glands have only minimal amounts of stored hormones, thus minimizing thyroid hormone release due to manipulation. Postoperative storm, formerly the most frequent kind of storm, has now been largely eliminated. 131-I is increasingly being used as a first-line treatment of hyperthyroidism (Chapter 10 and Chapter 17), but thyroid storm is rarely seen after this treatment, due to adequate medical pretreatment, and only isolated cases have been reported 10,11 .

Diagnosis

Diagnosis of thyroid storm is made on clinical grounds and involves the usual diagnostic measures for thyrotoxicosis. There are no distinctive laboratory abnormalities. Free T4 and, if possible, free T3 should be measured. T3 may rarely be normal or even decreased because of coexisting nonthyroidal illness12 . Electrolytes, blood urea nitrogen (BUN), blood sugar, liver function tests, and plasma cortisol should be monitored.

Therapy

Thyroid storm is a major medical emergency that has to be treated. in an intensive care unit (Table 12-1).

Table 1. Treatment of Thyroid Storm

Supportive Measures 1. Rest 2. Mild sedation 3. Fluid and electrolyte replacement 4. Nutritional support and vitamins as needed 5. Oxygen therapy 6. Nonspecific therapy as indicated 7. Antibiotics 8. Cardio-supportive 9. Cooling
Specific therapy 1. Propranolol (20 to 200 mg orally every 6 hours, or 1 to 3 mg intravenously every 4 to 6 hours) 2. Antithyroid drugs (150 to 250 mg PTU or 15 to 25 mg methimazole, every 6 hours) 3. Potassium iodide (one hour after first dose of antithyroid drugs): 4. 100 mg KI every 12 hours 5. Dexamethasone (2 mg every 6 hours)
Possibly useful therapy 1. Ipodate (Oragrafin) or iopanoic acid (Telepaque) 2. Plasmapheresis or exchange 3. Oral T4 and T3 binding resins 4. Dialysis

It should be noted that if any possibility is present that orally given drugs will not be appropriately absorbed (e.g. due to stomach distention, vomiting, diarrhea or severe heart failure), the intravenous route should be used13. If the thyrotoxic patient is untreated, an antithyroid drug should be given. PTU, 150-250 mg every 6 hours should be given, if possible, rather than methimazole, since PTU also prevents peripheral conversion of T4 to T3, thus more rapidly reduces circulating T3 levels. Methimazole (15-25 mg every 6 hours) can be given orally, or if necessary, the pure compound can be made up in a 10 mg/ml solution for parenteral administration. Methimazole is also absorbed when given rectally in a suppository14 . An hour after thiocarbamide has been given, iodide should be administered. A dosage of 100 mg twice daily is more than sufficient. Unless congestive heart failure contraindicates it, propranolol or other <61538><61485>blocking agents should be given at once, orally or parenterally in large doses, depending on the patient's clinical status. Permanent correction of the thyrotoxicosis by either 131-I or immediate thyroidectomy should be deferred until euthyroidism is restored. Other supporting measures should fully be exploited,

including sedation, oxygen, treatment for tachycardia or congestive heart failure, rehydration, multivitamins, occasionally supportive transfusions, and cooling the patient to lower body temperature down. Antibiotics may be given on the presumption of infection while results of culture are awaited.

The adrenal gland may be limited in its ability to increase steroid production during thyrotoxicosis15 . If there is any suspicion of hypoadrenalism, hydrocortisone (100-200 mg/day) or its equivalent should be given. The dose can rapidly be reduced when the acute process subsides. Pharmacological doses of glucocorticoids (2 mg dexamethasone every 6 h) acutely depress serum T3 levels by reducing T4 to T3 conversion. This effect of glucocorticoids is beneficial in thyroid storm and supports their routine use in this clinical setting. Propranolol controls tachycardia, restlessness, and other symptoms16,17 .

Usually rehydration, repletion of electrolytes, treatment of concomitant disease, such as infection, and specific agents (antithyroid drugs, iodine, propranolol, and corticosteroids) produce a marked improvement within 24 hours. A variety of additional approaches have been reported, but indications for their use are not well defined. For example, oral gallbladder contrast agents such as ipodate and iopanoic acid in doses of 1-2 g, which inhibit peripheral T4 to T3 conversion, may have value18 . Peritoneal dialysis can remove circulating thyroid hormone, and plasmapheresis can do likewise, but at the expense of serum protein loss. Orally administered ion-exchange resin19 (20-30g/day as Colestipol-HCl) can trap hormone in the intestine and prevent recirculation. These treatments are rarely needed.

Antithyroid treatment should be continued until euthyroidism is achieved, when a final decision regarding antithyroid drugs, surgery, or 131-I therapy can be made.

GRAVES' ORBITOPATHY

Graves' orbitopathy (GO) is the complex of ocular manifestations that are often found in patients with Graves' disease and, less frequently, in patients with Hashimoto's thyroiditis or apparently without thyroid abnormalities (so-called Euthyroid Graves' disease)20. GO is the most frequent extrathyroidal expression of Graves' disease.

Epidemiology

Data on the incidence of GO are limited21. In a population-based setting in USA, an adjusted rate of 16 cases per 100.000 per year in women and 2.9 cases per 100.000 in men was reported22. Clinical evident ocular manifestations are present in about 50% of Graves' patients, but subclinical abnormalities can be demonstrated (e.g., by CT or MRI of the orbit23, or by measurement of intraocular pressure in upward gaze24) also in the majority of the remaining 50%. GO is severe and potentially sight-threatening in 3-5% of cases25. Ocular involvement is in most cases bilateral, although often asymmetrical, but it may be unilateral in up to 15% of cases20. The onset of GO apparently has a bimodal peak in the fifth and seventh decades of life, but eye disease may occur at any age22. It is more frequent in women, but men tend to have a more severe disease26,27, as suggested by a decrease in the female/male ratio from 9.3 in mild GO, to 3.2 in moderately severe GO, and 1.4 in severe GO27.

There is a close temporal relationship between the onset of GO and the onset of hyperthyroidism. In approximately 85% of cases GO and hyperthyroidism occur within 18 months of each other25,26, although GO may both precede (about 20% of cases) or follow (about 40% of cases) the onset of hyperthyroidism25,26.

The natural history of GO is poorly understood. However, in a longitudinal cohort study, spontaneous amelioration was observed in two thirds of cases, while ocular involvement did not change with time in 20% and progressed in 14%28. It is worth noting that GO seems to be less frequent than in the past. A review of the first 100 consecutive patients seen at the same joint thyroid-eye unit in 1960 and 1990 revealed

a decrease in the proportion of Graves' patients with clinical relevant GO from 57% to 32%29; likewise, a reduction in the proportion of severe forms of GO compared to milder forms was observed29, likely reflecting an earlier diagnosis and treatment of both hyperthyroidism and orbitopathy. The latter finding is, however, controversial, since in a recent multicenter study carried out by the European Group on Graves' Orbitopathy (EUGOGO), 40% of GO patients had mild disease, 33% had moderate GO, and 28% had severe eye disease30. It should be noted that these figures may have been influenced by the fact that EUGOGO centers are all referral centers where it is likely to see more complicated cases of GO.

An important epidemiologic feature of GO is its relation with cigarette smoking31. The prevalence of smokers among Graves' women with orbitopathy is much higher than that in Graves' women apparently without GO or in normal controls (Figure 1)32. Smoking is a predictor of Graves' hyperthyroidism, with a hazard ratio of 1.93 in current smokers, 1.27 in ex-smokers, and 2.65 in heavy smokers33. In a case-control study, the odds ratio of cigarette smoking for Graves' hyperthyroidism without GO was 1.7, but raised to 7.7 for Graves' disease with GO34. Whether passive smoking may have the same impact as active smoking is unsettled; however, in a recent European survey of GO in childhood, the highest prevalence of Graves' children with GO was found in countries where the prevalence of smokers among teenagers was also highest: since >50% of children were <10 years of age, it is likely that passive smoking rather than active smoking influenced GO occurrence35. Mechanisms whereby smoking may affect the development and course of GO are unclear. In addition to direct irritative effects and modulation of immune reactions in the orbit36, smoking was associated with an increase in the orbital connective tissue volume as assessed by MRI37, and with an increased adipogenesis and hyaluronic acid production in in vitro cultured orbital fibroblasts38.

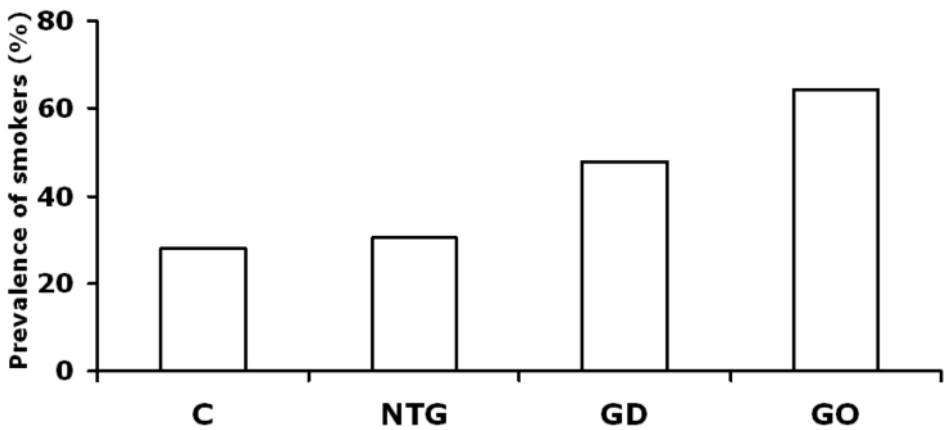

Figure 1. Prevalence of smokers among women with Graves' disease with (GO) or without (GD) associated orbitopathy. NTG: Non-toxic goiter; C: controls. Derived from Bartalena et al32.

Pathogenesis

Clinical manifestations of GO reflect the enhanced orbital volume, due to an increase in retroocular fibroadipose tissue and swelling of extraocular muscles39. Orbital tissues, including muscles, are infiltrated by inflammatory cells, including lymphocytes, mast cells, and macrophages. Proliferation of orbital fibroblasts and adipocytes, both in the retroocular space and in the perimysial space, is also associated with an increased production of glycosaminoglycans, which are the ultimate responsible for edematous changes both in the connective tissue and the muscles, owing to their

hydrophilic nature. The relative contribution of the increase in fibroadipose tissue volume and extraocular muscle swelling is not always the same, and a predominance of either component may be observed in different patients with similar clinical features40. Because the orbit is a rigid, bony structure anteriorly limited by the orbital septum, the increased orbital volume deriving from cell proliferation, inflammatory infiltration and edema, results into enhanced intraorbital pressure, forward displacement of the globe (proptosis or exophthalmos), extraocular muscle dysfunction causing diplopia and/or strabismus, soft tissue changes with periorbital edema, conjunctival hyperemia and chemosis. If proptosis, which can be considered a form of spontaneous decompression, is severe, subluxation of the eye may occur. Proptosis is responsible for corneal exposure which may be particularly dangerous at night for the incomplete eyelid closure (lagophthalmos), and may result into sight-threatening corneal ulceration. The enlarged muscle volume may cause optic nerve compression (dysthyroid optic neuropathy), especially if the orbital septum is tight and proptosis is minimal. Optic nerve compression is particularly evident at the orbital apex and may be responsible for sight loss. Orbital inflammation and related anatomical changes may cause venous and lymphatic congestion that contribute to periorbital edema and chemosis. With time inflammation subsides and muscle fatty degeneration and fibrosis may contribute to further extraocular muscle restriction and strabismus, which, at this stage, can only be corrected by surgery.

Although it is widely accepted that GO is an autoimmune disorder, its pathogenesis is not completely clear. A still leading pathogenic hypothesis, based on the link between thyroid disease and eye disease41, is that autoreactive T lymphocytes directed against one or more antigens shared by thyroid and orbit infiltrate the orbital tissue and the perimysium of extraocular muscles. Recruiting of T cells to the orbit may be facilitated by adhesion molecules42. Following shared antigen(s) recognition, facilitated by HLA class II antigen expression on antigen-presenting cells, CD4+ T lymphocytes secrete cytokines which amplify the immune response by activating either CD8+ T lymphocytes or autoantibody-producing B cells43, and by stimulating orbital fibroblast proliferation44. Analysis of T-cell clones from GO orbital tissues has shown both Th1 cytokine (interleukin-2, interferon-gamma, tumor necrosis factor-alpha) and Th2 cytokine (interleukin-4, interleukin-5, interleukin-10) secretory profiles, possibly related to different stages of the disease, with Th1 cytokines predominating early and Th2 cytokines late in the course of GO45. Cytokines produced by T cells, macrophages and fibroblasts perpetuate the ongoing inflammatory process through several mechanisms, including induction of expression of HLA class II antigens, heat-shock proteins, CD40, prostaglandins, adhesion molecules, proliferation of fibroblasts, differentiation of preadipocyte fibroblasts into adipocytes, and stimulation of fibroblasts to synthesize and secrete glycosaminoglycans40,43. The observation that immunoglobulins G from GO patients induce glycosaminoglycan synthesis in their orbital fibroblasts through the IGF-I receptor might suggest that the latter may represent a possible pathway in GO pathogenesis46. Increased adipogenesis in the orbit of GO patients might be related to overexpression of adipocyte-related genes, such as secreted frizzled-related protein-1, PPAR-<61543>, adiponectin47, and immediate early genes which act as triggers of the subsequent transcriptional cascade leading to adipocyte phenotype48. Interestingly, ligands of PPAR gamma, such as rosiglitazone, have been shown to stimulate adipocyte differentiation in orbital tissue in culture49; in addition, progression of GO has been reported in a patient submitted to rosiglitazone treatment for diabetes mellitus type 250. The role of PPAR-gamma <61472>agonists in GO pathogenesis is, however, not unequivocal, since in GO orbital fibroblasts and preadipocytes in culture rosiglitazone suppresses the release of IFN-gama-inducible <61485>chemokine CXCL10, which plays an important role in the initial phases of autoimmune thyroid disorders51.

The nature of autoantigen(s) shared by thyroid and orbit is still unclear52. Because Graves' hyperthyroidism is caused by TSH-receptor (TSH-R) antibodies (TRAb), TSH-R might be a plausible candidate autoantigen. TSH-R expression has been shown in the orbital tissue of GO patients, both at the mRNA and protein levels53, 54; however, TSH-R is also expressed in several other tissues not involved in Graves' disease and orbitopathy55, and, although at lower levels, in normal orbital

fibroadipose tissue samples and cultures56. On the other hand, BALB/c mice injected with spleen cells primed either with a TSH-R fusion protein or with TSH-R cDNA developed thyroiditis with blocking-type TRAb, but also showed orbital pathological changes (lymphocytic and mast cell infiltration, edema, presence of glycosaminoglycans) similar to those seen in human GO57. In addition, one study showed a correlation between GO activity, as assessed by the Clinical Activity Score, and TRAb58. Thus, although evidence is not conclusive, TSH-R may have a role in GO pathogenesis. Other autoantigens have been proposed as putative shared antigens, including several eye muscle antigens59, acetylcholine receptor, thyroperoxidase, thyroglobulin60, alpha-fodrin61 (Table 2), but their true role is, to say the least, uncertain52.

Table 2. List of putative autoantigens, shared by thyroid and orbit, involved in pathogenesis of Graves' orbitopathy.

1. TSH receptor
2. Thyroglobulin
3. Thyroperoxidase
4. alpha-Fodrin (cytoskeleton protein)
5. 64 kDa protein (and other eye muscle antigens)
6. 23 kDa protein (and other fibroblast antigens)

The role of genetic factors in the pathogenesis of GO is not very well defined, and no striking differences have been observed between Graves' patients with or without associated GO62. An association between GO and Major Histocompatibility Complex (MHC), cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) or intercellular adhesion melecule 1 gene polymorphisms has been looked for63-65, but results are not unequivocal. GO likely stems from a complex interplay between endogenous factors and exogenous (environmental) risk factors 21,36. The latter are probably more important and include cigarette smoking, thyroid dysfunction, and, in a subset of patients, radioiodine therapy for Graves' hyperthyroidism21,36. The relationship between cigarette smoking and GO has been discussed above (see paragraph on Epidemiology). Both hyperthyroidism66,67 and hypothyroidism68 seem to influence negatively the course of the orbitopathy. TRAb are independent risk factors for GO and can help to predict severity and outcome of eye disease69. Radioiodine therapy for Graves' hyperthyroidism is associated with GO progression in about 15% of cases, although this effect may be transient70,71. This effect is more frequently observed in patients who already have GO prior to radioiodine therapy, smoke, have high TRAb levels, or whose post-radioiodine hypothyroidism is not promptly corrected by L-thyroxine replacement therapy21,36. Radioiodine-associated progression of GO can be prevented by a short course of prednisone71,72. Neither thyroidectomy nor antithyroid drugs influence the course of the orbitopathy73. The above observations have important practical implications in terms of GO prevention (Table 3), because GO patients should be urged to refrain from smoking, their thyroid dysfunction (both hyper- and hypothyroidism) should be promptly corrected, and, in case of radioiodine therapy, a short course of oral prednisone should be administered21,36.

Table 3. Risk factors for the occurrence/progression of Graves' orbitopathy and preventive measures

Risk factor	Preventive measure
Cigarette smoking	Refrain from smoking

Risk factor	Preventive measure
Hyperthyroidism	Restore euthyroidism by antithyroid drugs and/or obtain a permanent control by thyroid ablation (thyroidectomy, radioiodine, both)
Hypothyroidism	Restore euthyroidism by L-thyroxine replacement therapy
Radioiodine therapy for hyperthyroidism	Give oral prednisone concomitantly with radioiodineadministration. Avoid to leave the patient with untreated post-radioiodine. Hypothyroidism
High TSH-receptor antibody levels	Control hyperthyroidism as soon as possible

Clinical Features

Signs & Symptoms. Clinical features of GO include soft tissue changes, proptosis, extraocular muscle dysfunction, corneal abnormalities, and optic nerve involvement (Figures 2-5). The NOSPECS classification (Table 4) is a useful memory aid of GO abnormalities74. Recommendations for GO assessment in clinical practice have recently been reviewed by EUGOGO75. Soft tissue changes include eyelid edema and periorbital swelling, eyelid erythema, conjunctival hyperemia and chemosis, inflammation of the caruncle or plica: their assessment and grading can be done with the aid of an atlas76, which can be downloaded from EUGOGO website (www.eugogo.org). Proptosis, i.e., protrusion of the eye (exophthalmos), is usually measured by Hertel exophthalmometer; normal values are usually less than 20 mm, but vary with race, age, gender, degree of myopia, and should be established in each center or institution. Extraocular muscle dysfunction is responsible for diplopia (double vision), which can be subjectively defined as intermittent (i.e., present only when fatigued or when first waking), inconstant (i.e., present only at extremes of gaze), or constant (i.e., present also in reading positions and primary gaze); objective assessment of extraocular muscle functioning can be done by several methods, including measurent of ductions in degrees75,76. Palpebral aperture may be increased due to several factors, including upper and/or lower lid retraction, proptosis. Lid retraction and proptosis are responsible for corneal exposure, which may lead to corneal epithelium damage (punctate keratopathy), corneal ulceration and perforation. The incomplete eye closure at night (lagophthalmos) and the absence of Bell's phenomenon (no upward eye rotation on attempted eye closure) are risk factors for corneal damage75,76. Intraocular pressure is often increased, particularly in upward gaze24, but this abnormality rarely progresses to true glaucoma. Dysthyroid optic neuropathy, due to optic nerve compression at the orbit apex by swollen extraocular muscles, or, less frequently, to optic nerve stretching in cases of marked proptosis or eye subluxation, is a sight-threatening expression of GO. It can be diagnosed by fundoscopy showing disc swelling, reduced visual acuity, abnormal color vision test, contrast sensitivity, perimetry, visual-evoked potentials, and pupillary responses75,76.

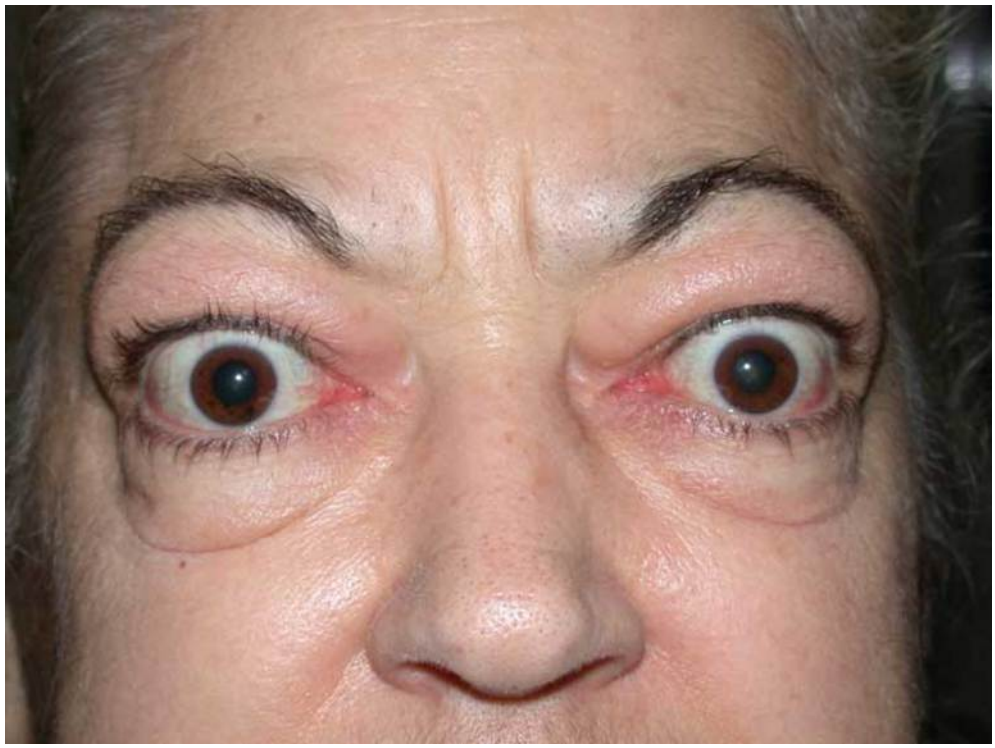

Figure 2. Female patient with moderately severe GO. Note periorbital swelling, injection of conjunctival vessels, proptosis, marked lid retraction, and proptosis.

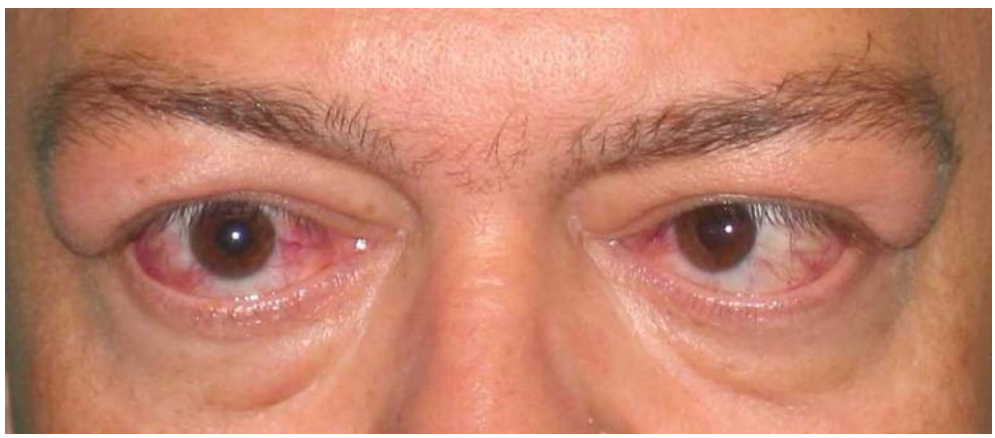

Figure 3. Male patient with moderately severe GO. Note marked periorbital swelling, conjunctival hyperemia, esotropia (strabismus) in the left eye.

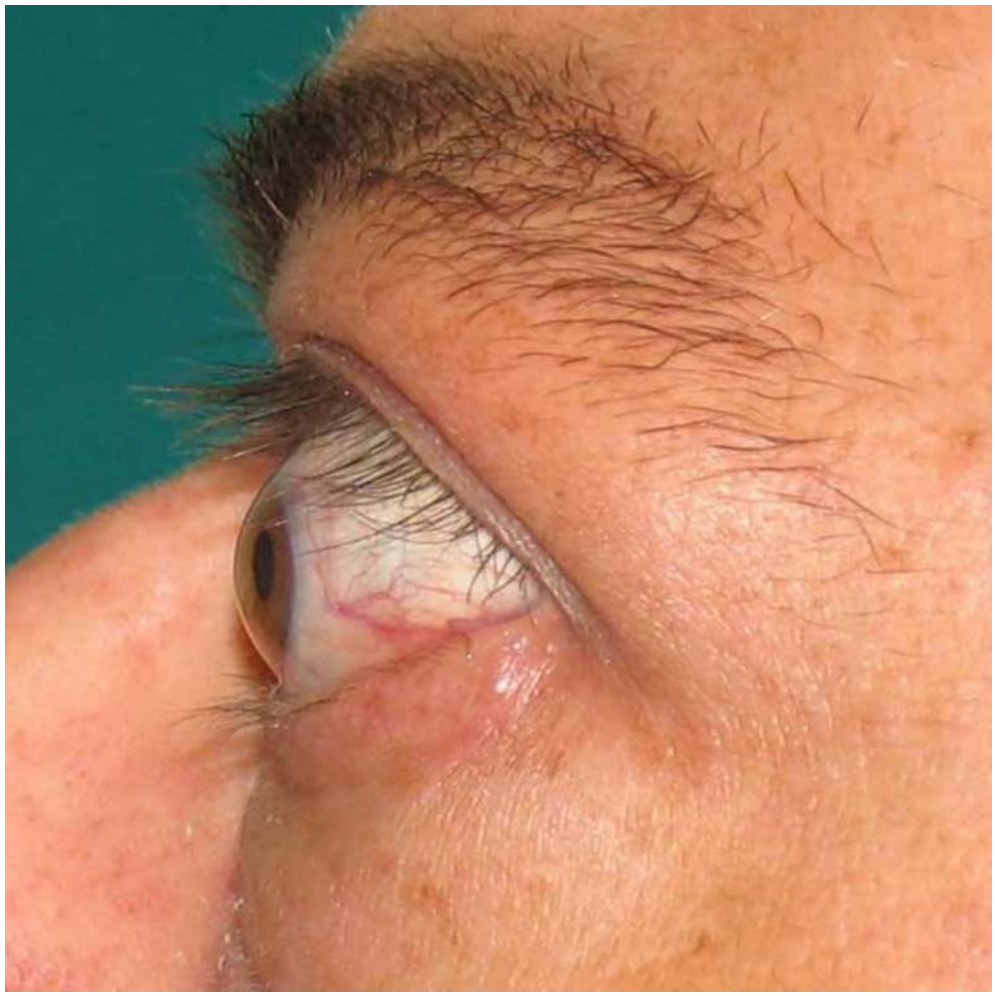

Figure 4. Male patient with moderately severe GO. Note the superior eyelid edema, mild conjunctival vessel injection, marked proptosis, and marked upper lid retraction.

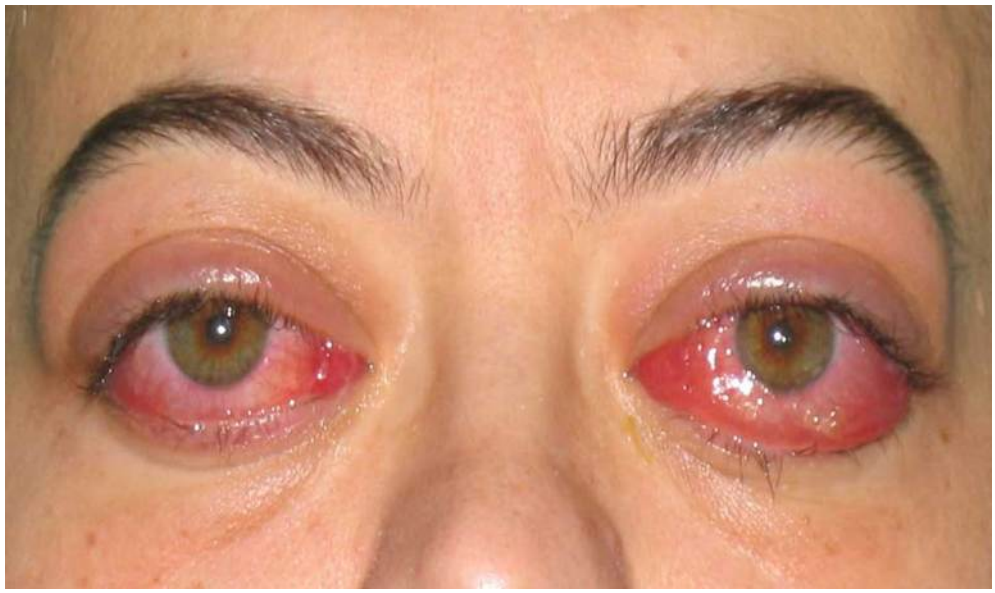

Figure 5. Female patient with severe GO. Note marked periorbital swelling, palpebral hyperemia, conjunctival hyperemia, proptosis (particularly in the left eye), caruncle edema. Eye motility was markedly reduced, lagophthalmos was present, there were two corneal ulcers in the left eye, and corneal punctate staining in the right eye, reduced visual acuity in the left eye (5/10). CT scan showed enlargement of extraocular muscles (particularly medial rectus and inferior rectus) in both eyes, but no relevant compression of the optic nerve at the orbit apex.

Table 4. NOSPECS classification of eye changes of Graves' disease

Class	Grade	Symptoms and Signs
0		No symptoms or signs
1		Only signs (upper lid retraction, without lid lag or proptosis)
2		Soft tissue involvement with symptoms (excess lacrimation, sandy sensation, retrobulbar discomfort, and photophobia, but not diplopia);objective signs as follows:
	0	absent
	a	minimal (edema of conjunctivae and lids, conjunctival injection, and fullness of lids, often with orbital fat extrusion, palpable lacrimal glands, or swollen extraocular muscles beneath lower lids)

Class	Grade	Symptoms and Signs
	b	moderate (above plus chemosis, lagophthalmos lid fullness)
	c	marked
3		Proptosis associated with classes 2 to 6 only (specify if inequality of 3 mm or more between eyes, or if progression of 3 mm or more under observation)
	0	absent (20 mm or less)
	a	minimal (21-23 mm)
	b	moderate (24-27 mm)
	c	marked (28 mm or more)
4		Extraocular muscle involvement (usually with diplopia)
	0	absent
	a	minimal (limitation of motion, evident at extremes of gaze in one or more directions)
	b	moderate (evident restriction of motion without fixation of position)
	c	marked (fixation of position of a globe or globes)
5		Corneal involvement (primarily due to lagophthalmos)
	0	absent
	a	minimal (stippling of cornea)
	b	moderate (ulceration)
	c	marked (clouding, necrosis, perforation)
6		Sight loss (due to optic nerve involvement)
	0	absent
	a	minimal (disc pallor or choking, or visual field defect, vision 20/20 to 20/60)

Class	Grade	Symptoms and Signs
	b	moderate (disc pallor or choking, or visual field defect, vision 20/70 to 20/200)
	c	marked (blindness, i.e., failure to perceive light; vision less than 20/200)
From Werner SC74.		

Symptoms of GO (Table 5) include, in addition to changes in ocular appearance related to periorbital swelling and proptosis, excess lacrimation, photophobia, grittiness, pain in or behind the eyes, either spontaneous or with eye movements, diplopia of different severity with or without strabismus, blurred vision, which may clear with blinking (due to excessive lacrimation) or covering one eye (reflecting extraocular muscle impairment), or may persist (probably reflecting optic neuropathy, particularly if associated with gray areas in the field of vision). In addition to reduced visual acuity, optic nerve involvement can be heralded by decreased color perception. Diplopia may be absent if extraocular muscle involvement is symmetrical in both eyes.

Table 5. Symptoms associated with Graves' orbitopathy

1. Changes in eye appearance, particularly eyelid or periorbital swelling, eye bulging
2. Excessive lacrimation, often more pronounced on waking
3. Incomplete closure of eyes at night, as reported by the partner
4. Photophobia, need to protect eyes with dark lenses
5. Increased eye "sensitivity" to irritative factors other than light (e.g., wind, smoke, pollution)
6. Ocular discomfort, described as grittiness, foreign body or sandy sensation, often defined as "allergy"
7. Ocular pain, either related or unrelated to eye movements
8. Neck ache, with abnormal head posture (torcicullum)
9. Diplopia
    a. Intermittent: present only when tired or on waking
    b. Inconstant: present only at extremes of gaze
    c. Constant: present also in primary and reading positions
10. Blurred vision
    a. Disappearing with blinking
    b. Not disappearing with blinking
11. Reduced color perception

Clinical manifestations of GO have a profound negative impact on quality of life and daily activities of affected individuals77. By the use of general health-related quality of life (HRQL) questionnaires, such as the SF-36 or its shorter forms, it was shown that GO is associated with significant changes in several functions, including physical functioning, role functioning, social functioning, mental health, general health perception, and bodily pain78. Interestingly, these changes in HRQL parameters were similar to those found in patients with inflammatory bowel disorders, and even more marked than those observed in patients with diabetes mellitus, heart failure or emphysema78. Since HRQL questionnaires are broad and may not address items speficic for a given disease, a GO-speficic quality of life (GO-QoL) questionnaire was developed and validated in clinical studies77,79-81. This questionnaire (dowloadable from EUGOGO website at www.eugogo.org) is composed of 16 questions, 8 concerning the consequences of diplopia and decrased visual acuity on visual functioning, and 8 regarding the consequences of changes in physical appearance on social functioning77. The Go-QoL is a useful tool for self-assessment of treatment outcomes for GO82.

Activity & Severity. Definition of GO severity is somehow arbitrary and may reflect different views20,30. According to the most recent EUGOGO definition30, mild GO is characterized my minimal to moderate soft tissue swelling, proptosis <25 mm, no or intermittent diplopia, no corneal or optic nerve involvement; moderate (or moderately severe) GO by marked soft tissue swelling, and/or proptosis >25 mm, and/or inconstant diplopia, and/or punctate corneal staining, with no evidence of optic neuropathy; severe GO by constant diplopia and/or optic neuropathy (Table 6). A value of 25 mm proptosis is probably too high for mild GO, since it is 9 mm above the median value and 7 mm above the upper normal limit in normal controls, at least in Italy20, and also the NOSPECS classification indicated a value of 24 mm as indicative of moderate (or moderately severe) proptosis74. Independently of this argument, clinical optic neuropathy, constant diplopia, as proposed by EUGOGO30, but also marked proptosis are, taken individually, sufficient to define GO as severe, but GO may be defined as severe also if less marked degrees of each feature are present at the same time20 (Table 7). Assessment of severity is particularly relevant to decide on whether a given patient should be treated by aggressive treatments (either medical or surgical) or simply by local or general supportive measures (see below).The other important feature of GO is its activity. Although, as stated above, GO natural history is not completely understood, it is commonly accepted that GO undergoes an initial phase of activity, characterized by progressive exacerbation of ocular manifestations until a plateau phase is reached; GO then tends to remit spontaneously, but remission is invariably partial. In the inactive phase (burnt-out GO), only residual ocular manifestations are present (e.g., proptosis, strabismus due to muscle fibrotic changes), but inflammation has subsided and it is unlikely that it may flare up. It is unknown how long this process takes to be completed, but it is widely believed that it takes between 6 months and two years. Recognition of the different phases of the disease is important, because active disease, basically characterized by the presence of inflammation, can respond to immunosuppressive treatments, which are largely ineffective when GO is burnt-out. Different indicators have been proposed to assess GO activity, including short duration of treatment (<18 months), positivity of octreoscan, decreased extraocular muscle reflectivity at orbital ultrasound, prolonged T2 relaxation time at MRI, increased urinary glycosaminoglycan levels, but they lack sufficient specificity and accuracy83. A useful tool to assess GO activity is represented by the Clinical Activity Score (CAS), which can be calculated very easily and is recommended by EUGOGO in the assessment of GO in routine clinical practice, in specialist multidisciplinary clinics, and for clinical trials75. In its original formulation84 it included 10 items, which were subsequently reduced to 7 when revised by an ad hoc Committee of the four sister thyroid societies85 (Table 8). If one point is given to each item when present, CAS, which basically reflect eye inflammation, may range from 0 (absent activity) to 7 (maximal activity); GO is generally defined active if CAS is >3.

Table 6. Assessment of severity of Graves' orbitopathy (1)

Grade of severity	Manifestations
Mild	1. Minimal to moderate soft tissue swelling 2. Proptosis <25 mm 3. No or only intermittent diplopia 4. No corneal or optic nerve involvement
Moderate	Marked soft tissue swelling 1. and/or proptosis >25 mm 2. and/or inconstant diplopia 3. and/or punctate staining of the cornea 4. but no optic nerve involvement
Severe	Constant diplopia 1. and/or optic nerve involvement
From the European Group on Graves' Orbitopathy (EUGOGO) 30	

Table 7. Assessment of severity of Graves' orbitopathy (2)

	Parameter		
Degree of involvement	Proptosis* (mm)	Diplopia**	Optic neuropathy
Mild	19-20	Intermittent	Subclinical***
Modera	21-23	Inconstant	Visual acuity 8/10-5/10
Severe	>23	Constant	Visual acuity <5/10
Severe orbitopathy: at least one severe, or two moderate, or one moderate and two mild manifestations****			

	Parameter		
Degree of involvement	**Proptosis* (mm)**	**Diplopia****	**Optic neuropathy**
*Proptosis by exophthalmometer readings. Median normal value in our Italian population is 15 mm. Normal values show racial variations; accordingly, abnormal values should be considered those 4 mm above the respective median value. **Diplopia: Intermittent, present only when tired or on waking; Inconstant, present in secondary positions of gaze; Constant, present in primary and reading positions. ***Abnormal visual evoked potentials or other tests, with normal or slightly reduced (9/10) visual acuity ****Patients with severe GO will need either medical or surgical treatment depending on GO activity or, in the case of optic neuropathy, the response to intravenous glucocorticoids. From Bartalena et al20			

Table 8. Clinical Activity Score (CAS).

1. Spontaneous retrobulbar pain 2. Pain on eye movements 3. Eyelid erythema 4. Conjunctival injection 5. Chemosis 6. Swelling of the caruncle 7. Eyelid edema or fullness
One point is given to each item, if present. CAS is the sum of single scores, ranging from 0 (no activity) to 7 (maximal activity). Active GO: CAS>3
From Mourits et al84, modified from an ad hoc Committee of the four Thyroid sister Societies85.

Diagnosis

Diagnosis of GO is usually easy on clinical grounds and by careful ophthalmological examination. Although not necessary in most Graves' patients, CT scan or MRI of the orbit confirm diagnosis by showing enlarged extraocular muscles (without involvement of the tendon) and/or increased orbital fibroadipose tissue86. Modest extraocular muscle enlargement and increased fibroadipose tissue volume are often found in Graves' patients without clinical manifestations of ocular involvement. Orbital imaging is very useful to detect signs of optic nerve compression, which support the diagnosis of optic neuropathy. Imaging is required in asymmetrical or, particularly, unilateral forms of GO, to rule out that proptosis, periorbital swelling, inflammation, or diplopia be due to disorders other than GO. The latter include primary or metastatic orbital tumors, vascular abnormalities (e.g., carotid-cavernous sinus fistula, carotid aneurysm, cavernous sinus thrombosis, subarachnoid hemorrhage, sub-

dural hematoma), granulomatous disorders. Occasionally, angiograms or venograms may be required for diagnosis. Octreoscan may be useful to identify patients with active GO86, but its role in clinical practice is limited, also in view of its high cost.

Management

Management of GO is based on a multidisciplinary approach which involves endocrinologists, ophthalmologists, orbit surgeons, radiologists and radiotherapists. In a recent survey of GO management based on a questionnaire distributed among members of the European Thyroid Association, European Society of Ophthalmic Plastic and Reconstructive Surgery, and European Association of Nuclear Medicine, 96% of responders stated that a multidisciplinary setting for GO management is valuable, although 21% of patients were in the end not treated in a multidisciplinary setting87. The therapeutic approach to a GO patient should be based on both severity and activity of the disease, the former being the feature to assess first (Figure 2)

Mild GO. Most patients have mild (nonsevere) GO, which does not require particularly aggressive treatments and often is self-limiting20,88. If GO activity is modest, simple local measured can be suggested to obtain symptomatic relief until GO is burnt-out (Table 9). Photophobia can be mitigated by sunglasses; grittiness due to corneal exposure can be controlled by artificial tears and topical lubricants, particularly indicated in the presence of lagophthalmos; the latter may require taping the eyelids shut at night; eyelid retraction can be controlled (with a variable degree of success) by <61538>-blocking drops (useful for the increased intraocular pressure) or by botulinum toxin injections89; elevation of the bed may be helpful to reduce periorbital swelling due to congestion; mild diplopia often is controlled by prisms (if they are tolerated) 20. Reassurance is an important issue, and the patient must be informed that his/her eye disease is unlikely to progress to more severe forms, usually stabilizes, and often ameliorates spontaneously. Control of thyroid dysfunction is fundamental, because progression often is associated with hyper- or hypothyroidism21,36; refrain from smoking is also essential, because it is associated with a decreased chance of developing proptosis and diplopia90, and decreases the likelihood to develop severe GO34. Patients who do not succeed to quit smoking by themselves, should be helped by professional stop-smoking clinics, organizations, groups, where they can receive counseling, behavioral therapies, pharmacological treatments.

Table 9. Management of mild Graves' orbitopathy

Sign and/or symptom and/or associated problem	Therapeutic measure
Photophobia	Sunglasses
Foreign body or sandy sensation	Artificial tears and ointments
Eyelid retraction	alpha-blocking eye drops. Botulinum toxin injections
Increased intraocular pressure	alpha-blocking eye drops
Lagophthalmos	Nocturnal eye taping
Thyroid dysfunction (hyper/hypo)	Restoration of euthyroidism, as appropriate
Smoking	Refrain from smoking
Anxiety about possible further progression	Reassurance on the natural history of mild GO

Moderate-to-severe GO. Management of moderate-to-severe GO depends not only on severity, but also on activity of the orbitopathy (Figure 6; Table 10). Medical treatment is likely to be beneficial in patients with active GO, with florid signs and symp-

toms of inflammation, recent-onset extraocular muscle dysfunction, recent progression of the ocular abnormalities as a whole. On the contrary, in long-standing GO, with chronic proptosis and residual, stable diplopia and/or strabismus, but no no evidence of inflammation, medical treatment has little chances to produce favorable effects, and the surgical, rehabilitative approach is preferable20. Dysthyroid optic neuropathy, the most severe expression of the orbitopathy, is a clinical, sight-threatening emergency, which requires immediate treatment. If there is no response to medical treatment (high-dose intravenous glucocorticoids), orbital decompression is warranted20,30.

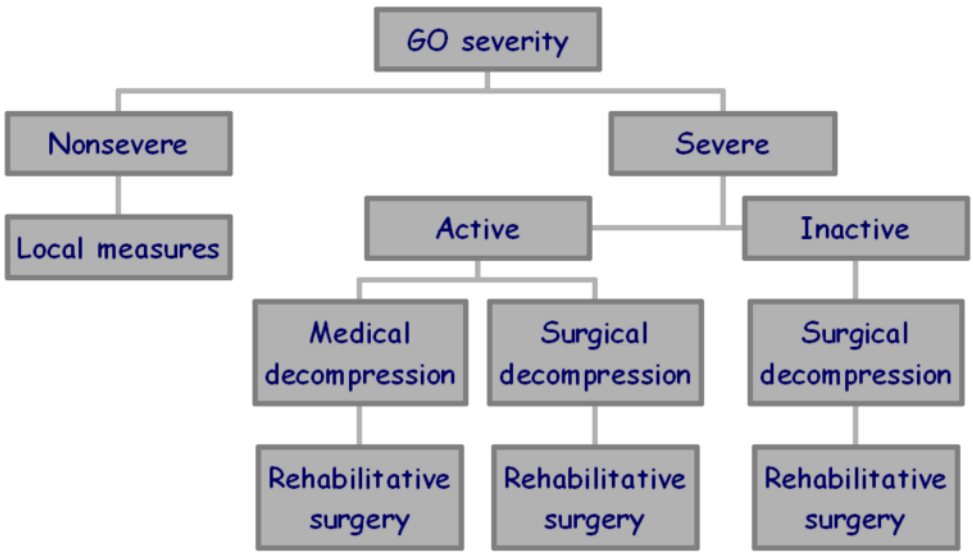

Figure 6. Therapeutic algorithms for Graves' orbitopathy (GO). For assessment of GO severity, see Tables 6 and 7; for assessment of GO activity, see Table 8. Medical decompression: high-dose glucocorticoids and/or orbital radiotherapy; Rehabilitative surgery: extraocular muscle surgery, eyelid surgery.

Table 10. Management of moderate-to-severe Graves' orbitopathy

Established methods

1. Glucocorticoids
    a.
        i. Local (retrobulbar, subconjunctival)
        ii. Oral
        iii. Intravenous
2. Orbital irradiation
3. Orbital decompression
4. Rehabilitative surgery
    a.
        i. Extraocular muscle surgery
        ii. Eyelid surgery

Non-validated treatments

1. Thyroid ablation
2. Somatostatin analogs
    a.
        i. Octreotide
        ii. Lanreotide
3. Intravenous immunoglobulins
4. Cyclosporine
5. Antioxidants
    a.
        i. Pentoxifylline
        ii. Allopurinol
        iii. Selenium

Future perspectives
1. Immunotherapy
a.
i. Rituximab
ii. Etanercept
iii. CTLA-4 Ig
iv. PPAR<61543>-antagonists
v. IL-1 receptor antagonists

Glucocorticoids are the mainstay in the medical treatment of GO20,91-93. They have been used for decades because of their anti-inflammatory effects, but also because they exert immunosuppressive actions useful to control the course of the orbitopathy20,91-94. The latter include interference with the function of T and B lymphocytes, decreased recruitment of neutrophils and macrophages, down-regulation of adhesion molecules, inhibition of cytokine secretion, inhibition of glycosaminoglycan secretion20,91-93. Locally (subconjunctivally or retrobulbarly) given glucocorticoids are less effective than systemically given glucocorticoids20,91-93, although favorable responses in terms of improvement of diplopia and reduction in extraocular muscle dysfunction have been reported with in a recent randomized clinical trial of periocular injections of triamcinolone acetate95. Glucocorticoids have for a long time been given orally, but high doses are required, treatment lasts for several months, recurrences are frequent upon drug tapering or withdrawal, side effects (particularly Cushing's syndrome) are frequent20,91-93. In the last 20 years the intravenous route has become the most commonly used96. Intravenous glucocorticoids are more effective, with a rate of favorable responses of about 80-90% versus 60-65% with oral glucocorticoids96, and better tolerated than oral glucocorticoids97. Glucocorticoids are most effective on soft tissue, inflammatory changes, recent-onset extraocular muscle dysfunction, and dysthyroid optic neuropathy, whereas proptosis and long-lasting eye muscle impairment are less responsive20. However, it should be noted that severe liver damage, heralded by a marked rise in serum concentrations of hepatic enzymes, was noted in 7 of about 800 treated patients (approximately 0.8%), three of whom died98. The causes of this hepatotoxicity are unclear, but might include direct liver toxicity of glucocorticoids, precipitation of virus-induced hepatitis, sudden reactivation of the immune system upon drug withdrawal leading to autoimmune hepatitis96. The cumulative dose of glucocorticoids might also be important, since no cases of liver damage were reported in a recent randomized clinical trial in which lower, but equally highly effective, doses of glucocorticoids were employed99. Accordingly, the current recommendation is that the cumulative dose of glucocorticoids should not be higher that 4.5-6 grams96. The early response (or lack of response) to first-week with intravenous glucocorticoids may be of help to predict long-term treatment outcome100.

Orbital radiotherapy is the other non-surgical mainstay in the management of GO20,93. The rationale for its use and the indications are quite similar to those of glucocorticoids; in addition, irradiation exploits the radiosensitivity of T lymphocytes which infiltrate the orbit101. Irradiation is currently carried out by linear accelerators, using a cumulative dose of 20 Gray fractionated in 10 daily 2-Gray doses over a 2-week period103, although other regimens (and lower doses) might be equally effective104. Favorable responses are observed in about 60% of treated patients102. Recent years have witnessed a lively debate on the true effectiveness of orbital radiotherapy104, and, compared to a previous survey

of 1996, a recent questionnaire-based survey promoted by EUGOGO in Europe, showed that, among treatments for moderate-to-severe GO, there was greater use of steroids and lesser use of irradiation87. However,the results of several randomized studies confirmed, with one exception, its efficacy103,105-108. In addition, orbital radiotherapy is a safe procedure devoid of relevant short-term and long-term side effects or complications109,110. Preexistent retinopathy associated with diabetes mellitus or hypertension represents a contraindication to its use109,110. As for glucocorticoids, orbital radiotherapy is mostly effective on soft tissue inflammatory changes and recent-onset extraocular muscle dysfunction102. Orbital radiotherapy can be used either alone or in combination with glucocorticoids20. The association exploits the prompter effect of glucocorticoids and the more sustained action of irradiation; in two randomized prospective studies, combined therapy proved to be more effective than either treatment alone111,112.

Among other medical treatments recently proposed, particular attention was given to somatostatin analogs, octreotide and lanreotide. Their use in GO was supported by the observation that somatostatin receptors are expressed on the surface of both orbital fibroblasts113 or orbital lymphocytes114 from GO patients, and that positivity of orbital octreoscan could predict subsequent GO response to immunosuppressive therapy86. After an initial optimism based on the positive results of small and often uncontrolled studies115, four recent randomized and controlled clinical trials have shown that both octreotide and lanreotide have only marginal and clinically poorly relevant effects on GO116-119; accordingly, their use is presently not justified120,121. Whether novel somatostatin analogs currently under investigation, such as SOM230, may be more effective remains to be demonstrated. Cyclosporine, used in GO for its immunosuppressive properties, has been reported in only two randomized and controlled studies122,123 . Cyclosporine has a lower efficacy than glucocorticoids as a single-agent therapy, although a combination of both drugs might be more effective than either treatment alone122,123. Thus, the use of cyclosporine might be maintained in patients who are relatively resistant to glucocorticoids in whom persistent GO activity warrants continuing medical intervention. Side effects of cyclosporine are not negligible and should be carefully considered. Intravenous immunoglobulins (IVIGs) have been reported to have favorable effects on GO in some studies, but not in others20; only two studies were randomized. Thus, IVIGs use is currently not recommended, also in view of their high cost and the possible risk deriving from the use of plasma-derived products20.

Orbital decompression is, with glucocorticoids and orbital radiotherapy, a milestone in the management of GO. It is aimed at increasing the space available for the increased orbital content by removing part of the bony walls of the orbit and/or the orbital fibroadipose tissue20. It is indicated in patients who have impending sight loss due to optic neuropathy and do not respond promptly to intravenous glucocorticoids124. Other important indications for decompressive surgery are represented by corneal damage due to eyeball exposure in patients with marked proptosis, or by recurrent subluxation of the globe, which may stretch the optic nerve and cause sight loss. In recent years, thanks to the improved surgical techniques and the diminished surgical risk, the indications for orbital decompression have expanded, including also correction of residual cosmetic problems125,126. Several techniques of orbital decompression are available, aimed at removing part of one, two, three or four orbital walls (floor, roof, lateral wall, medial wall) as well as part of the retroorbital fibroadipose tissue. The different surgical options should be discussed with the patient, as well possible complications of the procedure, particularly the de novo occurrence or worsening of diplopia, particularly frequent after extensive removal of the orbital floor127. Removal of fibroadipose tissue can be done together with or without bone removal, but removal of fat alone is associated with a lower reduction of proptosis20.

Rehabilitative surgery includes surgery for strabismus or eyelid retraction. Extraocular muscle surgery is aimed at correcting residual diplopia after medical and/or surgical treatment of GO. Timing of surgery is crucial, because it should not be performed when GO is active, but when it has been inactive for 6 months20. The goal of

eye muscle surgery is to align the eyes, avoiding abnormal head posture and restoring single binocular vision in primary and reading positions; multiple operations may be required to achieve this goal. Eyelid surgery may rarely be an emergency procedures in patients with exposure keratitis and corneal ulcerations, but it usually is carried our to correct eyelid malposition after medical treatment or orbital decompression. Eyelid surgery usually constitutes the last step of rehabilitation.

Thyroid ablation. The question of whether in a patient with the orbitopathy, Graves' hyperthyroidism should be treated by non-ablative (i.e., thionamides) or ablative (i.e., radioiodine therapy, thyroidectomy, both) therapy is unanswered128. Supporters of thyroid ablation justify this approach by mentioning the pathogenic link between thyroid and orbit: removal of thyroid-orbit shared antigen(s) and autoreactive T lymphocytes might be beneficial to the eye129; supporters of non-ablative thyroid treatment suggest that control of thyrotoxicosis by antithyroid drugs may be associated with a reduction of autoimmune phenomena which might be reflected by an amelioration of ocular conditions; furthermore, once triggered, GO might proceed independently of thyroid treatment130. Two retrospective studies showed that total thyroid ablation (thyroidectomy followed by radioiodine therapy, as in thyroid cancer) was associated with an improvement of clinical GO131,132. A recent randomized, controlled clinical trial demonstrated that, as compared to total thyroidectomy alone, total thyroid ablation is followed by a better outcome of GO in patients given intravenous glucocorticoids133. Probably this is not enough to support total thyroid ablation in all patients with clinically relevant GO; however, current evidence justifies it in GO patients in whom thyroidectomy is the treatment of choice for their hyperthyroidism.

Future perspectives. GO is only partially preventable, but environmental factors play an important role in its pathogenesis21,36. Accordingly, preventive measures, including refrain from smoking, control of thyroid dysfunction, and a cautious use of radioiodine therapy should be adequately applied21,36 (Table 3). However, this is not enough. Our better understanding of GO pathophysiology has led to unraveling immunologic mechanisms responsible for its occurrence and progression39-41.

As a consequence, it is possible that in the future, immunotherapy can be developed for Graves' disease and, in particular, for the orbitopathy134. In this regard, attention has recently been focused on rituximab, a chimeric murine-human monoclonal antibody targeting the CD-20 antigen expressed on the B lymphocyte surface; rituximab kills CD-20+ cells by several mechanisms, and for this reason it has been used successfully in the treatment of non-Hodgkin lymphomas, but also of several autoimmune disorders134. A possible role of rituximab has been postulated for Graves' disease135,136, but this remains to be established. This drug has been used in a limited number of GO patients137-139; preliminary results seem encouraging, but confirmation by large, randomized clinical trials is warranted134. The same considerations can be made for etanercept, which is an anti-TNFalpha monoclonal antibody, and, in a small, open and uncontrolled study was reported to have beneficial effects on GO140. Whether other immunotherapies, e.g., with CTLA-4 Ig, PPAR gamma-antagonists, IL-1 receptor antagonists, might have a role in the management of GO presently remains purely speculative134. The contribution of oxygen reactive species to the changes occurring in the orbit of GO patients141 supported the hypothesis that antioxidants might play a role in GO management. Insofar only two small, non-randomized studies are available on the use of pentoxifylline, and nicotinamide or allopurinol, showing some effects of these drugs142,143; EUGOGO is currently carrying out a large multicenter, randomized, placebo-controlled study on the effects of pentoxifylline or selenium in mild GO, the results of which should be available in one year.

LOCALIZED MYXEDEMA AND THYROID ACROPACHY

Localized myxedema (also called pretibial myxedema or thyroid dermopathy) is

an uncommon extrathyroidal manifestations of Graves' disease (less frequently of chronic autoimmune thyroiditis). It almost always occurs in Graves' patients who also have GO. In a review of 178 consecutive patients with pretibial myxedema, only 4 patients had no evidence of eye disease144. However, in a community-based epidemiologic study, only 4% of GO patients also had pretibial myxedema, although the latter was more frequent in patients with severe orbitopathy145..It is more common in older than in younger patients, with a large preponderance in women146. Skin lesions are edematous and thickened plaques, typically localized in the pretibial area; however they can be less frequently found in other skin areas, such as feet, toes, upper extremities, shoulders, upper back, nose. Prevalent localization in the pretibial area is related to mechanical and dependent position. The occurrence of lesions in less common sites is often preceded (triggered?) by local trauma147,148. There can be three clinical types: nodular, diffuse, and elephantiasic149,150 (Figures 7 and 8).

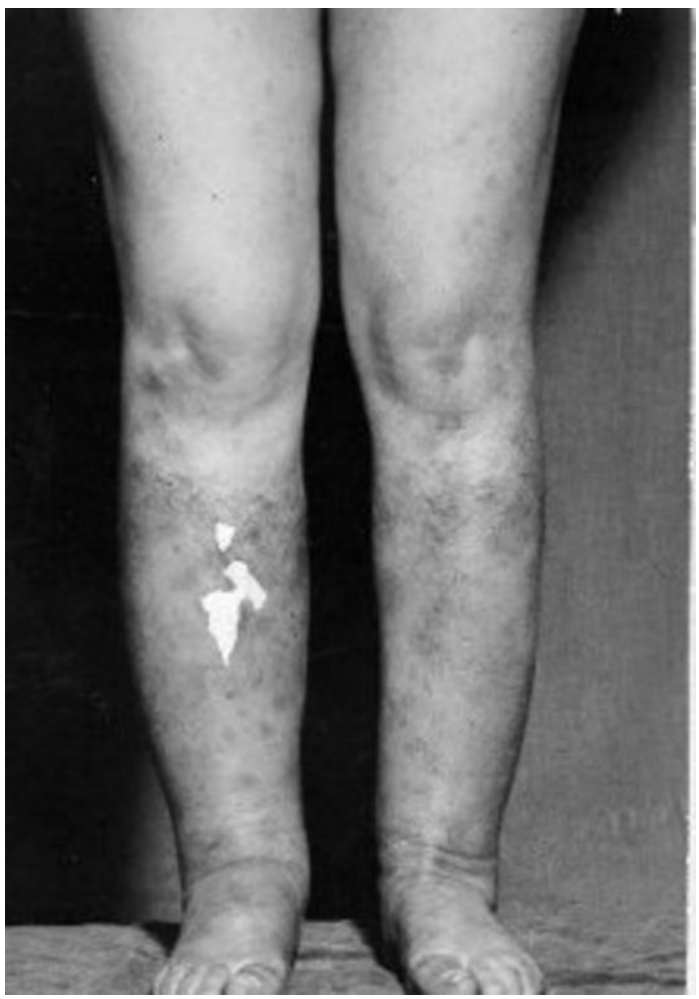

Figure 7. A case of severe pretibial myxedema showing the coarsened, nodular, infiltrated, pigmented lesions on the lower extremities.

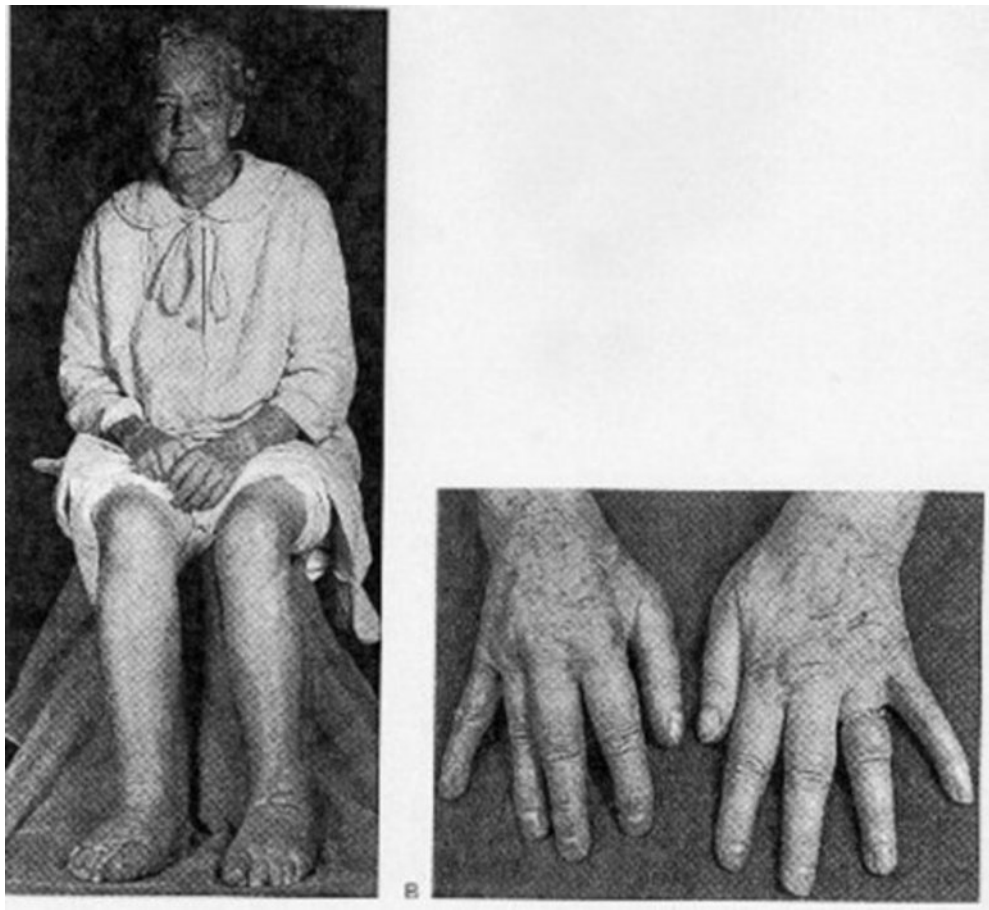

Figure 8. (a) Massive infiltrative, localized myxedema in a female patient with Graves' disease and orbitopathy. The skin lesions have become confluent over the lower extremities. (b) In the same patient, localized myxedema, involving the phalanges, is evident.

Histopathologically, skin lesions are characterized by the accumulation of activated fibroblasts (and, to a lesser extent, mast cells), with a markedly increased production of glycosaminoglycans in the dermis and subcutaneous tissues151. Whereas in normal skin approximately 5% of the acid mucopolysaccharides are hyaluronic acid, in pretibial myxedema this amount increases to 90%. Glycosaminoglycans are responsible for fluid retention, subsequent compression and occlusion of lymphatic vessels, and lymphedema152. Thus, as in GO, fibroblasts seem to play a central role in the pathogenesis of localized myxedema. This notion is further supported by the finding of limited variability of T cell receptor V gene usage in pretibial myxedema, pointing to a primary immune response of antigen-specific T lymphocytes153. Furthermore, as is the case with acropachy, lymphocytes do recognize local fibroblasts154. IgG from patients with pretibial myxedema was shown to stimulate proteoglycan synthesis by human skin fibroblasts155. Fibroblasts from control pretibial tissues were found to increase synthesis of hyaluronic acid when exposed to sera of patients with Graves' hyperthyroidism, while fibroblasts from pretibial myxedema were stimulated by both normal and patient's sera156. As for GO, TSH-R has been implicated uin the pathogenesis of localized myxedema. TSH-R is expressed in peripheral skin fibroblasts from patients with localized myxedema, both at the mRNA157 and protein level158. However, TSHR is expressed also in skin from normal subjects157,158. Likewise, TSH-R immunoreactivity was detected in cultured fibroblasts from pretibial myxedema159-161, although the specificity of this finding remains to be established. As mentioned above, IgG from Graves' patients with localized myxedema was reported to stimulate glycosaminoglycan production in cultured skin fibrob-

lasts155, but this data is not unequivocal, because IgG from normal subjects were equally effective in other studies162. To summarize, although pathogenic mechanisms remain to be fully elucidated, localized myxedema appear to result from autoimmune reactions leading to fibroblast proliferation and increased glycocosaminoglycan secretion.

From a clinical standpoint, localized myxedema presents as light-colored (sometimes yellowish brown) skin lesions, frequently with an orange peel texture (Figures 6 and 7). Skin lesions may be characterized by hyperpigmentation and hyperkeratosis. They usually represent only a cosmetic problem and are asymptomatic, but sometimes they may be associated with itching and pain, or may be functionally important, e.g., they may cause problems to wear shoes, especially the elephantiasic form of localized myxedema. Localized myxedema may remain stable, but frequently improves with time, partially or completely163. Many cases of mild localized myxedema do not require any treatment, but in moderately severe lesions or when there is cosmetic concern, topical glucocorticoids applied with occlusive plastic dressing produce beneficial effects in a relevant proportion of patients163. If necessary, treatment is repeated until clinical remission occurs164. When localized mxedema is severe and extensive, steroid pulse therapy, or decongestive physiotherapy, a combination of manual lymphatic drainage, bandaging, exercise, and scrupulous skin care, may be tried165,166. In a patient with very severe and debilitating pretibial myxedema, a combined treatment of surgical excision and octreotide treatment showed a successful effect that was still present after 9 years of follow-up167. However, no substantial effect was reported by long-term octreotide treatment in three patients with localized myxedema168. Two studies on the use of intravenous IgG in a small nymber of patients have reported discrepant effects (reviewed in169). Thus, measures such as compression bandaging and topical glucocorticoids still are the most cost effective treatments for localized myxedema

Acropachy is a very uncommon extrathyroidal expression of Graves' disease, usually associated with severe GO144 and localized myxedema170, thus reflecting severity of the autoimmune process. It seems more common in women than in men144. It is characterized by clubbing of fingers and toes, with concomitant soft-tissue swelling of hands and feet. These abormalities are usually painless and may be asymmetric144. As for GO, there seems to be a strong relation with cigarette smoking171. X-ray of affected sites shows soft-tissue swelling and subperiosteal bone formation. There is currently no treatment that can solve the esthetic and (less frequent) functional abnormality of thyroid acropachy, which occasionaly may remit spontaneously in the long-term.

CLINICAL ABNORMALITIES OF THE HEART

The biochemical actions of thyroid hormone on the heart are described in Chapter 10.

Hyperthyroidism is usually associated with relevant cardiovascular symptoms and changes in cardiovascular hemodynamics172.Thyrotoxicosis increases the demands on the heart both by chronotropic and inotropic alterations. Cardiac output is markedly increased owing to increased stroke volume and rapid heart rate172. It is possible that the metabolic efficiency of heart muscle is decreased172. Irritability of the heart is increased. Investigation with stress echocardiography shows in hyperthyroidism impaired chronotropic, contractile, and vasodilatatory cardiovascular reserves, that are reversible upon conversion to euthyroidism173. In a recent, large, matched case-control study, cardiovascular symptoms and signs, including palpitations, chest pain, dyspnea, cough, orthopnea, displaced apex, cardiac murmur, chest wheeze/crepitus were much more frequent in hyperthyroid patients than in controls, and some of them persisted despite effective restoration of euthyroidism by antithyroid drug treatment174 (Table 11). This common finding of cardiovascular alterations in hyperthyroid patients may result

from thyroid hormone excess itself, by hyperthyroidism-related worsening of preexisting cardiovascular disorders, or by the occurrence of novel cardiovascular abnormalities172. The importance of cardiovascular abnormalities is underscored by the observation that mortality of hyperthyroid patients is increased, mainly due to cardiovascular events175,176. Similar conclusions were reached also in a community-based study of elderly people177, in which, however, definition of hyperthyroidism was based on the finding of low/suppressed serum TSH, which may not necessarily reflect thyroid hormone excess, but rather be the result of non-thyroidal illness syndrome.

Table 11. Cardiovascular symptoms and signs in hyperthyroid patients and matched euthyroid controls at baseline and after restoration of euthyroidism by antithyroid drugs.

At baseline	Hyperthyroid patients	Controls	p-value
Palpitations	73%	20%	<0.0001
Chest pain	25%	11%	<0.0001
Dyspnea	60%	14%	<0.0001
Cough	35%	12%	<0.0001
Orthopnea	6%	1%	<0.0001
Displaced apex beat	4%	1%	<0.01
Cardiac murmur	15%	5%	<0.0001
Chest wheeze/crepitus	9%	2%	<0.0001
After restoration of euthyroidism			
Palpitations	31%	21%	<0.0007
Chest pain	16%	11%	0.2
Dyspnea	30%	13%	<0.0001
Cough	35%	12%	<0.0001
Orthopnea	3%	2%	0.5
Displaced apex beat	0.5%	1%	0.6
Cardiac murmur	8%	6%	0.7
Chest wheeze/crepitus	4%	2%	0.4
Derived from Osman et al174.			

Mitral valve prolapse was found more commonly in hyperthyroid patients (43%) than in controls (18%)174 . This incresed incidence might be due to increased adrenergic tone, autoimmunity, or the augmented cardiac output associated with thyrotoxicosis. Most patients with thyrotoxicosis are adults. Many, especially those with toxic nodular goiter, are in the 50- to 70-years age group, which has a relatively high incidence of organic heart disease anyway179. Thus, it is not surprising that cardiac abnormalities are prominent among the symptoms of thyrotoxicosis. Frequent premature beats and paroxysmal tachycardia sometimes appear in thyrotoxic patients and may be disturbing to the patient. Atrial fibrillation occurs in thyrotoxicosis with or without preexisting heart disease, but it is more frequent in older patients180, probably reflecting an increase in the prevalence of underlying cardiac abnormalities of ischemic or different origin179,. It may be paroxysmal or persistent during the thy-

rotoxic period. Attempts to correct this arrhythmia to normal in patients with persistent atrial fibrillation are usually unsuccessful while they are hyperthyroid. Once euthyroidism has been restored, atrial fibrillation may revert spontaneously or may be converted pharmacologically or by electroconversion. About two-thirds of patients undergo spontaneous reversion to sinus rhythm after receiving therapy for thyrotoxicosis, usually within 4 months181; later on, spontaneous conversion is unlikely181. It is wise to always evaluate thyroid function in clinically euthyroid patients with atrial arrhythmias with or without heart disease, because in about 20% of patients TSH tests and/or FT4 point to an overactive thyroid and in 50% of these patients normal sinus rhythm resumes after treatment with antithyroid drugs182. It is widely accepted that subclinical hyperthyroidism is asssociated, in individuals aged 60 years or more with a 3-to-5-fold increased risk of developing atrial fibrillation183,184.

Congestive heart failure is a frequent complication in thyrotoxic patients with preexisting organic heart disease, particularly if old185,186. These patients mostly have a toxic multinodular goiter. Low output congestive heart failure has also described in 25 patients with Graves' disease with a mean age of 45 years187. In the elderly hyperthyroid patient, cardiac symptoms may so dominate the clinical picture that diagnosis of thyrotoxicosis may be overlooked. Careful attention should be given to this possibility in all patients with congestive heart failure, especially if goiter is detected. Congestive heart failure may occur in patients who have no detectable preexisting organic heart disease177. It is often difficult to establish whether an underlying heart disease is present in a hyperthyroid patient who also has a disorder of rhythm, a cardiac murmur, or congestive heart failure, because all these conditions may be ascribed to thyrotoxicosis per se. It is frequently gratifying to observe normalization of cardiac findings once euthyroidism has been restored.

In hyperthyroidism, owing to the increased metabolic demand, angina can be worsened if pre-existing, or induced de novo172,188,189. Evidence of myocardial lactate production when the heart is paced at an accelerated rate190, and normal coronary arteries are found at angiography after episodes of angina or infarction191, have suggested that changes in thyrotoxicosis are due to an imbalance between O2 demand and supply rather than to arterial obstruction. This possibility is corroborated by the finding that coronary artery spasm of an otherwise normal vessel may occur during thyrotoxicosis188,189.

Cardiac abnormalities found in Graves' disease often are entirely reversible, except that longstanding atrial fibrillation due to hyperthyroidism is not always convertible after euthyroidism is restored. In addition, a recent case-matched study showed that some cardiovascular may persist even after restoration of euthyroidism174. It has become evident that even in the mildest forms of thyrotoxicosis subtle cardiac abnormalities may be present. Thus, in patients with so-called "subclinical" thyrotoxicosis, i.e. suppressed TSH and normal serum free T4 and T3 concentrations, due to multinodular, autonomous goiter or TSH-suppressive T4 treatment, mean basal 24-h heart rate is increased, there is an augmented risk of atrial premature beats and atrial fibrillation, and left ventricular function and wall thickness are increased192,193. A recent report shows an increased standardized mortality ratio of about 2, both for cardiovascular and all causes, in elderly patients over 60 years of age in subclinical hyperthyroidism177. There is controversy whether TSH suppressive T4 treatment leads to functional cardiac abnormalities194.

Treatment of heart failure in the presence of thyrotoxicosis does not differ from its treatment in euthyroid patients, but it may be more difficult. Rest, salt restriction, diuretic therapy, digitalization and administration of afterload-reducers, like angiotensin converting enzyme (ACE) inhibitors, betablockers, aldosterone antagonists and other specific measures, are in order172. Larger than normal doses of digoxin are required, but there is probably no change in the toxic-to-therapeutic dose ratio. Atrial fibrillation may be controlled by digoxin, propranolol, or both. Electroconversion is usually successful only after thyrotoxicosis has been resolved for a few months195.

Hyperthyroidism should be controlled as expeditiously as possible. Congestive heart

failure is a contraindication to operation. Most patients with thyrotoxicosis and clinically relevant heart disease are now treated with RAI. This treatment may be preceded by a 3-to-6-month course of antithyroid drug therapy to deplete their glands of stored thyroid hormone, a program that lessens any chance of an exacerbation of the heart disease caused by a radioiodine-induced release of thyroid hormone from the gland. Administration of 131I followed by antithyroid drugs, and potassium iodide or ipodate, that also inhibit T4 to T3 conversion, may be used in severely ill patients in whom a prompt response is needed. This method is described in Chapter 11.

Propranolol has been used successfully in the control of tachycardia, and also in patients with congestive heart failure if tachycardia appeared to be adding substantially to the problem. In these instances, possible depression of myocardial contractility by the drug was outweighed by the benefit derived from controlling the rate. In such circumstances, one must proceed with caution and often digoxin should be added.

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