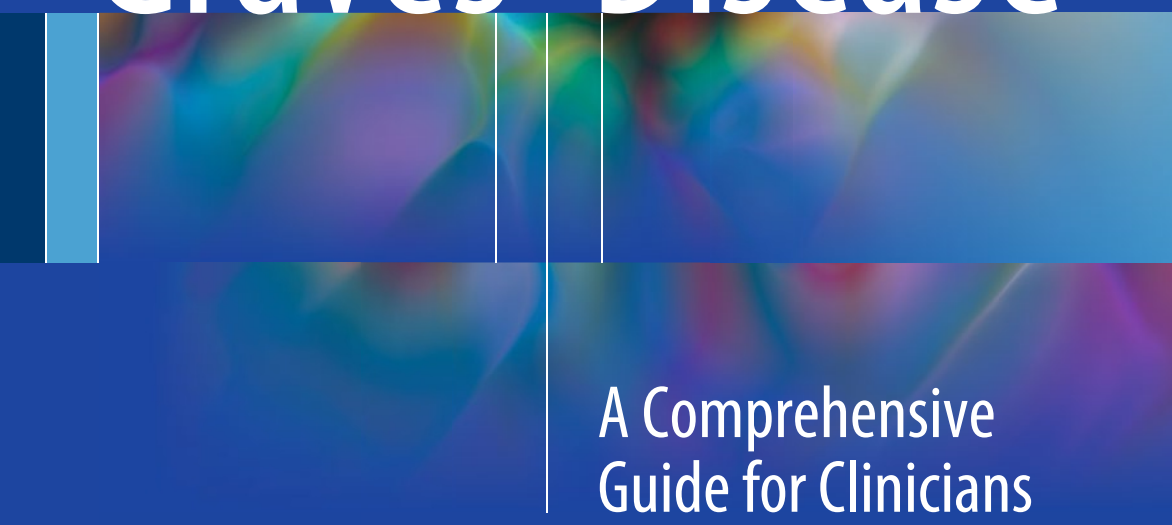
Rebecca S. Bahn
Editor

Graves' Disease

A Comprehensive Guide for Clinicians



Springer

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Preface

Graves' disease combines the clinical symptoms and signs of hyperthyroidism, diffuse goiter, characteristic ocular findings, and less frequently unique dermatologic changes. The earliest descriptions of the triad in modern medical context can be found in writings by Caleb Perry [1], Robert Graves [2], and Carl von Basedow [3]. The eye disease is variously termed Graves' ophthalmopathy or orbitopathy (GO), or simply thyroid eye disease (TED).

Graves' hyperthyroidism is mediated by autoantibody stimulation of the thyrotropin receptor on thyrocytes resulting in excess thyroid hormone production. The fundamental immunologic abnormalities leading to the production of these antibodies is complex and as yet incompletely understood, as is their relationship to the development of GO. Precise targeted therapy of the Graves' disease syndrome will likely become available once pathogenic mechanisms are better understood. Until then treatment options for hyperthyroidism are limited to functional ablation of the thyroid gland using radioactive iodine or surgery, or to pharmacologic inhibition of thyroid hormonogenesis. Therapeutic options for GO are similarly limited to the targeting of disease manifestations, rather than basic mechanisms.

Nevertheless, there have been a number of important refinements in the treatment of Graves' disease in recent years. These include new indications and contraindications for antithyroid drugs, improved approaches to radioactive iodine therapy, the development of novel surgical techniques, and better understanding of the combined use of these modalities. Advances in the treatment of GO include the use of disease activity and severity assessments to inform management decisions and the completion of the first randomized controlled therapeutic trials. The choice of optimal treatment for an individual patient should take into account the preferences of adequately informed patients. This volume was designed to facilitate these physician–patient discussions by providing up-to-date evidence-based information presented in a clinically useful and patient-centric manner. It is my hope that a recognition of the limitations of the currently available therapies will stimulate the development and testing of new disease hypotheses that will translate into novel therapies or preventive strategies for Graves' disease and GO.

We are especially fortunate to have contained in this volume the combined expertise of a group of internationally respected authorities. I am indebted to each author for his or her enthusiastic agreement to participate in this project and for contributing a most scholarly and well-written manuscript. In addition, I wish to thank Michele Aiello from Springer, without whose expert editorial assistance the publication of this volume could not have been accomplished.

Rochester, MN, USA Rebecca S. Bahn, M.D.

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Chapter 1
Professionalism and the Art of Patient-Centric Thyroidology

Michael Brennan

Medicine is an art based upon science

Sir William Osler MD

Medicine is both an art and a science and both make appeal to the true physician

Charles H Mayo MD

The observations of these medical luminaries occurred at a time when the science of medicine was relatively embryonic. Drs. Osler and Mayo surely could not have foreseen the rapid march of medical science that occurred in the latter half of the twentieth century. They understood however that if patients were to fully benefit from advancing knowledge, both the art and science must together be applied. The discipline of endocrinology has been in the forefront of advancing scientific knowledge resulting in modern clinical endocrine practice being firmly established on a sound scientific footing. The discipline of thyroidology has progressed in tandem resulting in new insights into the genetic and biological basis of disease and in the widespread availability of highly reliable and precise laboratory tests and imaging procedures. The natural history of many thyroid disorders has been defined, and the development and publication of evidence-based practice guidelines have equipped clinicians everywhere with the tools and knowledge that promote good practice and better clinical outcomes.

The art of medicine is the means by which physicians can leverage and apply scientific insights in a manner that optimally serves the valid needs of individual patients. This in turn requires an understanding of, and a commitment to, the attributes and behaviors of professionalism. These include integrity, excellence, dutifulness, and honesty combined with superior communication skills and patient advocacy. Altruism is a central tenet of the healing mission which places patient interest over self-interest. The consistent expression of these commitments by physicians promotes the contract

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between society and the medical profession that, in turn, is granted certain rights and privileges through licensure [1].

Concerns over the increasing commercialization of medicine in the early 1980s prompted a call to action that included a recommitment to professionalism values and behaviors [2, 3]. The modern professionalism movement with strong ethical underpinnings arose out of these concerns. A recommitment to professionalism values and behaviors emerged and has been embraced and adopted by learned national and international societies [4, 5]. The American Thyroid Association (ATA) established and has published Clinical and Professional Ethical Guidelines for the Practice of Thyroidology [6]. These guidelines set out membership standards for clinical care, the conduct of research, managing conflict of interest, the equitable use and stewardship of resources, as well as membership responsibility to report conduct and behavior that undermine those standards. They are based upon established ethical principles of respect for persons, beneficence, non-maleficence, and justice. Ethical principles are actualized by professionalism behaviors which together engender trust that is essential for good doctor-patient relationships. The era of paternalistic medicine has passed and has been replaced by a partnership model between physicians and patients. Such a model of care improves clinical outcomes and enhances both patient and physician satisfaction.

The time-tested approach to achieving an accurate and reliable clinical evaluation and subsequent treatment recommendations includes clinical history taking and physical examination supplemented by the selection and insightful interpretation of laboratory tests and imaging procedures. The initial interaction with their physician provides the patient the opportunity to tell their story and can help build and sustain trust essential to good clinical outcome. It is undermined by frequent physician interruptions, displays of impatience, inattentiveness, and lack of eye contact. Increasing productivity expectations has reduced the time that can be spent with patients, making it imperative that whatever time is available is used to optimal effect and patient benefit. It is the mark of the artful physician to provide guidance to patience rather than dominance.

Accuracy of thyroid diagnosis is aided by the availability of highly precise laboratory tests of the pituitary-thyroid axis. Artful patient-centric care requires however that laboratory tests should be used to supplement, rather than replace, time-honored clinical evaluation. Symptoms considered compatible with thyroid dysfunction are many and varied, and several, including fatigue and weight changes, are also very nonspecific and highly prevalent among the general population. Such patients are commonly referred for endocrine consultation. Having access to test results prior to or during the initial evaluation may prompt the endocrinologist, despite his or her best intentions, to prejudge the situation. This may be communicated to patients either verbally or more subtly through body language. Empathetic patient-centric care requires that patients be given the opportunity to tell their story and undergo a focused or, if circumstances warrant, a more detailed physical examination followed by a well-communicated discussion and explanation. Such a process of care builds patient trust and confidence that promotes acceptance and a willingness to consider alternative non-thyroidal explanations for their troubling symptom complex.

Attending physicians have the responsibility to role model and champion such a process especially in the teaching environment. Prompt dismissal of the validity of patient concerns by simply reciting normal test results inevitably leads to patient dissatisfaction and increases the likelihood of further consultations and test duplication that are wasteful of limited resources and inflate healthcare costs. Persistence of such dysfunctional cycles of care leads some patients to become disaffected with the medical profession and drives them to seek help from nontraditional, unqualified individuals with questionable credentials who have achieved a prominent presence on the World Wide Web. The artful practice of medicine guided by behaviors of professionalism and skillful communication can greatly reduce such undesirable outcomes. Medical center leadership must provide support for physicians who aspire to such clinical excellence, and recommended systems approaches to achieving this organizational goal have recently been advocated for and published [7–9].

The international thyroid associations have been proactive in championing and supporting the professionalism of their membership. This is reflected in the international collaboration around clinical practice guidelines that have been published in recent years and are readily available on the American Association website (www.thyroid.org). This represents a good example of patient advocacy in practice. The development of best practice guidelines is demanding of time, requires exhaustive review of available evidence, and is followed by consensus building requiring detailed reviews and in-depth discussions that often occur across multiple time zones. The sharing of evidence-based and expert opinion with the wider medical community translates into improved care and outcomes for patients everywhere. Such a commitment reflects the professionalism of the international thyroid associations and their scholarly and dedicated membership.

The contributions of the European Group on Graves Orbitopathy (EUGOGO) serve as further examples of what can be achieved through professional collaboration [10]. This multidisciplinary, multinational consortium comprises endocrinologists, ophthalmologists, basic scientists, and neuroradiologists. Their mission is to expand the understanding of the pathogenesis of Graves Orbitopathy (GO) through basic and clinical research and to translate new knowledge into improved management of patients. The group also provides initiatives aimed at improving education and training of health professionals involved in the care of GO patients. Progress in the management of this relatively uncommon and multifaceted condition can only occur by establishing agreed-upon diagnostic criteria, measures of both disease activity and severity, combined with well-planned research investigations and knowledge sharing across multiple medical centers. GO may cause not only pain, discomfort, and visual disturbances but may lead to disfigurement with resulting emotional distress and social isolation. Recognition of this led EUGOGO to develop a disease-specific 15-part quality of life (QOL) questionnaire. This is completed by patients prior to their initial physician visit as well as subsequent visits, thereby permitting meaningful assessment of the continuing impact of disease on activities of daily living, social interactions, and other parameters. This is an instructive example of patient-centric care that fosters a trusting partnership between patient and physician translating into greater treatment compliance and improved medical outcomes which is the ultimate goal of medicine.

The advent of illness and disease invariably results in patient vulnerability due to a lessening of control over their destiny. Trust serves as an important foil to vulnerability. Patients, and more broadly society in general, are positively disposed to trust physicians as otherwise they would not seek their help and guidance. A higher level of patient trust is referred to as cognitive based and is formed through observations of the competence, character, and benevolence of physicians and the environment of care. Trustworthiness is nurtured through the consistent expression of professionalism commitments that are foundational of both the art and science of medicine. Patients are benefitted as are physicians who gain a heightened sense of meaning and purpose in their work. This improves morale, engagement, and overall sense of well-being and serves as a counterbalance to burnout that has reached alarming prevalence among the medical community. Hospitals and medical institutions are responsible for providing practice, research, and educational systems and environments that are conducive to professionalism and to the art and science of patient-centric medical care [11]. The provision of such professionalism environments provides rich rewards for the organization through improved teamwork and collaboration, staff recruitment, retention and engagement, improved patient safety and outcomes, enhanced institutional reputation, and brand loyalty [12].

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Chapter 2
Immunopathogenesis of Graves' Disease

Basil Rapoport and Sandra M. McLachlan

Abbreviations

Aire	Autoimmune regulator
APECED	Autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy
APS-1	Autoimmune polyendocrine syndrome type 1
cAMP	3′-5′-Cyclic adenosine monophosphate
CD4	Marker on helper T cells
CD25	Interleukin-2 receptor α chain
CD122	Interleukin-2 receptor β chain
CD8	Marker on cytotoxic T cells
CHO	Chinese hamster ovary cells
ELISA	Enzyme-linked immunoassay
ECD	Extracellular domain of the TSHR
Foxp3	Forkhead box P3 protein
LATS	Long-acting thyroid stimulator
LRD	Leucine-rich repeat domain of the TSHR
LH	Luteinizing hormone
SNP	Single nucleotide polymorphism
TBAb	TSH blocking antibody
TBI	TSH binding inhibition
Treg	Regulatory T cells
TSH	Thyrotropin

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TSHR	Thyrotropin receptor
TMD	Transmembrane domain of the TSHR
TSAb	Thyroid stimulating antibody
VNTR	Variable number of tandem repeats

Evidence That GD is an Autoimmune Disease

In 1835, Robert Graves described six pregnant women with diffuse goiter and hyperthyroidism [1]. Based on his paper, this condition is called "Graves' disease" in the UK and the US. Until 1956, the hyperthyroidism was believed to be of pituitary origin, presumably caused by thyrotropin (TSH). In that year, Adams and Purves reported that sera of Graves' patients contained a thyroid stimulating factor with a duration of action more prolonged than TSH, hence the term "long-acting thyroid stimulator" (LATS) [2]. The identification in 1964 that LATS was an immunoglobulin G molecule [3, 4] introduced the radical concept that autoimmunity can stimulate as well as destroy a target organ. Discovery of the TSH receptor (TSHR) in 1966 [5] was followed by the observations in 1970 and 1974 that LATS, like TSH, activated thyrocyte adenylyl cyclase and competed for TSH binding to the TSHR (reviewed in [6]). In addition to thyroid stimulating autoantibodies (TSAb), TSHR autoantibodies lacking agonist activity but capable of competing for TSH binding were found to be responsible for rare cases of autoimmune hypothyroidism (reviewed in [6]).

The role of TSHR antibodies in causing Graves' disease satisfied two of the Witebsky and Rose postulates for autoimmunity, namely the "direct demonstration of free circulating antibodies active at body temperature" and "recognition of the specific antigen (for this antibody)" [7]. Maternal transfer of TSHR antibodies leading to neonatal hyperthyroidism [8] provided powerful confirmation of the part played by TSHR autoantibodies. The other two requirements postulated by these eminent immunologists, involving immunization in animals, proved more difficult to fulfill. Unlike many autoantigens, only very small amounts of TSHR protein are present in the thyroid, precluding purification for use in immunization. Following its cloning in 1989 [9–11], recombinant TSHR protein was used to generate "antibodies against same antigen in experimental animals" (reviewed in [12]). However, TSHR antibodies induced by conventional immunization did not fulfill the final postulate, namely that the "experimental animal demonstrates same tissue changes in human."

In 1996, stimulatory TSHR antibodies and hyperthyroidism were induced in mice by injecting intact eukaryotic cells expressing the TSHR [13]. Building on this novel immunization approach, plasmid or adenoviral vectors were subsequently used to express the TSHR in vivo and induce TSAb and Graves'-like hyperthyroidism in mice or hamsters (reviewed in [14, 15]). These studies complement investigations in humans of Graves' disease, the commonest organ-specific autoimmune condition, with a prevalence of ~1 % [16].

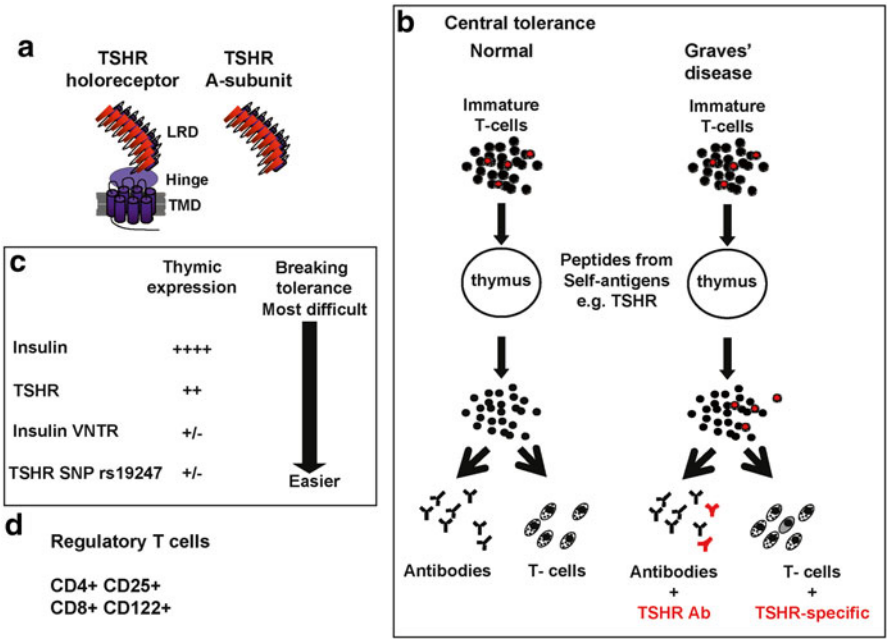

Fig. 2.1 (**a**) Schematic representation of the TSH holoreceptor including its transmembrane domain (*left*) and the TSHR A-subunit (*right*). (**b**) Central tolerance in a normal individual versus a patient with Graves' disease. (**c**) Relationship between thymic expression of insulin and the TSHR (and genetic variants) in relation to expectations for breaking self-tolerance. Insulin VNTR [29]; TSHR SNP rs19247 [30]. (**d**) Regulatory T cells; markers for subsets

Why Do TSHR Antibodies Develop?

TSHR antibodies develop in genetically susceptible individuals because of a breakdown in self tolerance to the TSHR, probably in association with environmental factors. Self-tolerance is a complex process. In addition, the characteristics of the TSHR itself play a role in the development of thyroid autoimmunity.

Characteristics of the TSHR: The TSHR, a member of the group A rhodopsin-like family, is a G-protein coupled receptor with seven membrane spanning domains. The extracellular portion, or domain (ECD) comprises a leucine-rich repeat domain (LRD) linked by a hinge region to the transmembrane domain (TMD). After synthesis and trafficking to the thyrocyte surface, some of the single polypeptide chain TSHR undergo intramolecular cleavage at two or more sites within the hinge region resulting in the loss of a C-peptide component. This posttranslational modification results in a two subunit structure with an extracellular A-subunit linked by disulfide bonds to a B-subunit comprising the remaining portion of the hinge region linked to the TMD (Fig. 2.1a, left panel).

In recent years, the molecular structures of the different TSHR components have been determined by X-ray crystallography or have been deduced by molecular modeling based on related molecules whose structures are known. Thus, the crystal structure of the TSHR LRD reveals it to comprise a slightly curved, oval-shaped tube with α-helix/β-strand repeats [17]. A fairly accurate structure for the TMD can be deduced by modeling [18] on the crystal structure of a related molecule, rhodopsin [19]. Until recently, the structure of the hinge region has been enigmatic. However, solving the crystal structure of the entire ECD (LRD plus hinge region) of the closely related FSH receptor [20] has enabled modeling of much of the TSHR hinge region [21, 22]. Because a portion of the TSHR hinge region comprises a poorly delineated "insertion" of approximately 50 amino acid residues relative to the gonadotropin receptors, this region cannot be modeled on the FSHR.

The loss of the C-peptide region during intramolecular cleavage of the TSH holoreceptor into disulfide-linked A and B subunits does not affect receptor function, either in its basal state or in response to ligand stimulation [23, 24]. However, disruption of the disulfide linkage, either by a specific enzyme or by continued proteolysis following intramolecular cleavage, leads to shedding of the TSHR A-subunit. There is strong evidence that the shed TSHR A-subunit rather than the membrane-bound holoreceptor (Fig. 2.1) is the autoantigen that induces the generation of the pathogenic autoantibodies that lead to hyperthyroidism in Graves' disease (reviewed in [25]). It is noteworthy that the other closely related members of the glycoprotein hormone receptor family, the luteinizing hormone- and follicle stimulating hormone receptors (LHR and FSHR, respectively), do not undergo intramolecular cleavage and shedding of a portion of their ectodomains. Unlike the TSHR, these gonadotropin receptors do not induce autoimmune responses in humans. The TSHR A-subunit is a heavily glycosylated soluble protein with a molecular weight of about 60 kDa. Perhaps unexpectedly in view of its central role in Graves' disease, the TSHR A-subunit is the least abundant of the three major thyroid autoantigens, the others being thyroglobulin and thyroid peroxidase.

Central tolerance: Central tolerance is based on negative selection of autoreactive T-cells in the thymus [26]. Immature T-cells generated in the bone marrow enter the thymus where they undergo processes of negative and positive selection (Fig. 2.1b). Stromal thymic medullary epithelial cells "ectopically" express a spectrum of peptides from self-proteins [27] and, in cooperation with dendritic cells, present them to immature T-cells (reviewed in [28]). T-cells that recognize self-peptides with high affinity are deleted from the repertoire [26]. In this "education" process, T-cells with moderate affinities for self-peptides are positively selected to undergo further differentiation and leave the thymus to become mature T-cells. In contrast, T- and B-cells with specificity for the TSHR may not be deleted in individuals subsequently susceptible to Graves' disease.

The degree of self-tolerance is related to the amount of autoantigen expressed in the thymus. Insulin, for example, is highly expressed in the thymus (Fig. 2.1c). A type I diabetes susceptibility locus in humans maps to a variable number of tandem repeats (VNTR) upstream of the insulin gene. This VNTR locus controls the level of intrathymic insulin expression and, by maintaining tolerance to insulin, is protective of disease [29].

Individuals homozygous or heterozygous for TSHR single nucleotide polymorphism (SNP) 179247, that is associated with Graves' disease, have significantly fewer thymic TSHR mRNA transcripts than individuals homozygous for the protective allele [30]. Thus, as for the insulin VNTR locus, lower intrathymic expression of the TSHR is likely to decrease central tolerance. As a result, T cells specific for the TSHR will not be deleted in the thymus (Fig. 2.1b, right). Persistence of these cells in the periphery, together with TSHR-specific B cells, will enhance the possibility of a triggering event leading to their activation and the generation of TSHR antibodies.

Autoimmune regulator (*Aire*): Intrathymic expression of a number of autoantigens is controlled by Aire and autoimmunity develops spontaneously in its absence (reviewed in [31]). In mice lacking one or both Aire alleles, thymic expression of insulin is reduced or absent [32, 33] but other autoantigens such as glutamic acid decarboxylase and α-fodrin in diabetes mellitus type 1 are unaffected by the absence of Aire [34, 35].

Patients with autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED) or autoimmune polyendocrine syndrome type 1 (APS-1) have mutations in Aire. In contrast, Aire mutations are not by themselves susceptibility genes for autoimmune thyroid disease (for example [36, 37]). Fifty percent of APECED patients in southern Italy had antibodies to thyroglobulin and thyroid peroxidase, as well as hypothyroidism in some patients [38]. However, Graves' disease has not been reported in APECED/APS-1 patients.

Regulatory T-cells: Deletion of auto-reactive T cells by central tolerance may not eliminate all self-reactive cells. Another potent mechanism for self-tolerance involves regulatory T cells (Treg) (Fig. 2.1d). Treg may be "natural" (constitutive) or inducible (involved in the adaptive immune response). Natural Treg develop in the thymus [39]. Both natural and inducible Treg are characterized by the expression of CD4, CD25 (the interleukin-2 receptor α chain) and the transcription factor Foxp3 (forkhead box P3 protein) (reviewed in [40]). Cell deletion studies showed that natural CD4+ CD25+ Treg regulate (for example) the development of autoimmune gastritis in BALB/c mice [41]. Another subset of Treg that express CD8 and CD122 (interleukin-2 receptor β chain) also controls auto-reactive effector T-cells in the periphery [42, 43].

Cytokines are involved in the effector mechanisms of Treg. For example, tumor necrosis factor or antibody to tumor necrosis factor regulate CD4+ CD25+ T-cells in Non-Obese diabetic mice [44]. In addition, CD8, CD122 expressing Treg generate interleukin 10 which suppresses production of interferon -γ as well as the proliferation of CD8 positive T cells [45].

B-cell tolerance: Immunoglobulin molecules expressed on the B-cell surface function as antigen receptors. If the rearranged immunoglobulin variable region genes have specificity for an autoantigen, B-cells can "edit" and replace their receptors with different antibody gene arrangements (for example [46]). Self-antigen-specific B-cells can be tolerized by other mechanisms including clonal deletion, anergy (functional inactivation) and perhaps competition for B cell growth factors.

Because T cells are required to stimulate B cells to proliferate and secrete IgG antibodies, tolerance mechanisms in B cells may be regarded as a secondary, or "fail-safe," mechanism. However, the increasingly recognized role of B cells as professional antigen presenting cells emphasizes the importance of silencing B cell autoreactivity even when the major players are T cells.

Tolerogenic dendritic cells: Plasmacytoid dendritic cells generate type 1 interferon in response to viral RNA or DNA. Their activities are complex: on the one hand, plasmacytoid dendritic cells are immunogenic because they have the ability to present antigens and induce naive T cells to differentiate. On the other hand, plasmacytoid dendritic cells can be tolerogenic by inducing deletion of CD8 positive cells and effector CD4 positive T cells. These cells contribute to both innate and adaptive immunity and should be considered as likely contributors to autoimmunity (reviewed in [47]).

TSHR Antibodies: Immunological Markers of Graves' Disease

T cells specific for the TSHR, their cytokine responses and relationship to MHC antigens, have been described [48–50]. Autoantigen-specific T cells are, of course, critical for the generation of IgG class autoantibodies. However, TSHR antibodies, the direct cause of hyperthyroidism, are the indisputable immunological markers of Graves' disease.

Unlike autoantibodies to other autoantigens that are measured by ELISA or Western blots, TSHR autoantibodies cannot be measured by such assays with sufficient sensitivity or specificity for clinical use. Instead, assays for TSHR autoantibodies can be separated into two types: assays involving competition for ligand binding to the TSHR and bioassays using intact cells in tissue culture. Beginning approximately 40 years ago, each type of assay has undergone extensive modifications (Table 2.1).

Competition assays: The "first generation" of competition assays involved inhibition by TSHR autoantibodies for radiolabeled TSH binding to porcine thyroid membranes or membrane extracts [51, 52]. Second generation assays included the use of porcine TSHR or recombinant human TSHR in solid phase rather than in solution and TSH ligand [53, 54]. In the "third generation" assay, a tagged human monoclonal TSHR autoantibody replaced TSH [55]. Both second and third generation assays provide comparable excellent sensitivity and specificity [56].

Bioassays: Bioassays for TSHR stimulating antibodies (TSAb) measure the ability of TSHR antibodies or TSH to increase intracellular cAMP levels in thyroid cell monolayers, initially using human thyroid cells [57, 58]. Subsequent assays employed a rat thyroid cell line [59] porcine thyroid cells [60] and, more recently, Chinese hamster ovary (CHO) cells expressing the recombinant human TSHR [61]. The sensitivity of the cultured thyroid cells assays was increased by using IgG or serum diluted in hypotonic medium [62] or in medium containing polyethylene glycol [63]. In some assays cAMP is detected indirectly by means of a light generating reporter molecule [64].

Table 2.1 Development since 1974 of assays for TSHR autoantibodies

Competition for ligand binding to the TSHR (TBI)				
Species	*TSHR source*	*Ligand*	*Format*	*References*
Porcine	Membranes	TSH	Suspension	[51]
	Membrane extracts	TSH	Suspension	[52]
Porcine	Membrane extracts	TSH	Solid phase	[53]
Human	Recombinant	TSH	Solid phase	[54]
Porcine	Recombinant	M22	Solid phase	[55]
Bioassays for TSHR stimulating antibodies (TSAb)				
Species	*Source/type*	*Serum/IgG*	*Signal*	*References*
Human	Thyroid monolayers	Serum/IgG	cAMP	[57, 58]
Rat	Thyroid cell line	Serum/IgG	cAMP	[59]
Porcine	Thyroid monolayers	IgG	cAMP	[60]
Human	CHO cell monolayer	Serum/IgG	cAMP	[61]
		Serum	Light[a]	[64]
Human-rat	CHO cell monolayer	Serum/IgG	Light[a]	[65]
TSHR-LHR				
Bioassays for TSH blocking antibodies (TBAb)				
Similar to TSAb but performed without and with a standard low TSH concentration				

[a]cAMP-dependent luciferase reporter gene
CHO chinese hamster ovary cells

Because both TSH blocking antibodies (TBAb) and TSAb will be positive in the TBI assay, only the bioassay can be used to specifically detect the former type of autoantibody. The recent use of a bioassay with CHO cells expressing a chimeric (TSH-LH) recombinant receptor to specifically detect TSAb and exclude TBAb [65] does not have a theoretical basis for such a property [66, 67], as confirmed in practice [68].

Nomenclature: The competition assays are most simply described as "TSH binding inhibition (TBI)" assays. TBII (TSH binding inhibitory immunoglobulin) is unnecessarily complex and TRAb (TSHR antibody) does not distinguish the competition assays from the bioassays. Although TSH is no longer used in some TBI assays, the term TBI can still describe competition for a TSHR autoantibody. Regarding the bioassays, TSAb (thyroid stimulating antibody) rather than the older term TSI (thyroid stimulating immunoglobulin) is preferable for consistency with TBAb (TSH blocking antibodies). The commonly used term TSBAb (TSH or thyroid stimulating blocking antibody), a tongue twister, is redundant because TSH is inherently a stimulator.

Characteristics of TSHR Antibodies

TSHR antibodies that stimulate the receptor (TSAb) are present at very low concentrations in serum [69–71]. In contrast, TSH blocking antibodies (TBAb) are present at much higher concentrations [71, 72]. The immunological properties of TSHR

antibodies are summarized in Table 2.2. The data include observations for serum TSHR antibodies as well as for human monoclonal TSHR antibodies [73–75]. TSHR antibodies are predominantly IgG although although IgA- and IgE-class TSHR antibodies have been observed by flow cytometry [76]. It should be noted that TSHR antibodies in sera as well as human monoclonals have extremely high affinities, as would be expected for antibodies that compete with TSH for binding to its receptor.

TSHR Autoantibody Epitopes

Features of TSHR autoantibody epitopes: Given the complexity of the TSHR structure, it is not surprising that defining the binding sites (epitopes) of autoantibodies to the TSHR has been a difficult task. The crowning achievements in this endeavor have been the recent determinations of the crystal structures of an human TSAb (M22) [17] and an human TBAb (K1-70) [77] in complex with the LRD component of the TSHR ECD (see above). These breakthroughs were facilitated by the cloning of monoclonal human TSAb and TBAb from the B-cells of patients with Graves' disease [73–75]. This information supports the deduction from earlier studies involving chimeric substitutions between the receptors for TSH and luteinizing hormone (LH) that human TSHR autoantibodies in humans, like most antibodies to complex globular proteins [78], do not recognize "linear" epitopes, but rather conformational epitopes formed by discontinuous segments in the amino acid sequence [66, 79]. Unlike human TSHR autoantibodies, some monoclonal TSHR antibodies generated by immunizing mice with TSHR protein do recognize linear epitopes, but these lack biological activity. Consistent with human autoantibodies, monoclonal mouse TSAb such as KSAb1 and KSAb2 [80] do not recognize linear epitopes.

Determination by X-ray crystallography of the molecular interactions between a human TSAb and human TBAb with the TSHR LRD also puts to rest one of the long standing mantras in the field that TSAb recognize the N-terminus and TBAb the C-terminus of the TSHR ECD. This view was generally held despite contrary evidence from chimeric receptor studies [66]. Indeed, the crystallography data (albeit from single TSAb and TBAb) reveal that the TSAb and TBAb epitopes largely overlap and that the TBAb epitope is actually situated more towards the TSHR N-terminus than the TSAb. Moreover, this information invalidates the theoretical basis for a new TSHR antibody bioassay originally purported to distinguish between TSAb and TBAb (see above). Of course, structural data from single human monoclonal TSAb and TBAb do not exclude the possibility that other TSHR autoantibodies have nonidentical epitopes. The view we favor, based on experimental evidence [67], is that the TSAb epitope(s) is more restricted to a "sweet spot" on the receptor that leads to receptor activation, whereas TBAb epitopes are more diverse. In order to block TSH binding by steric hindrance, an antibody can bind to a wide range of sites that overlap only partially with the TSH binding site.

Table 2.2 Characteristics of human TSHR antibodies

Serum or MAb	Concentration in serum	Affinity (Kd)	IgG subclass	Light chain	References
TSAb (common; characteristic of Graves' disease)					
Serum	50–500 ng/ml	$1.5–3.3\times10^{-11}$ M	IgG1, IgG4	Kappa, lambda	[71, 95, 96]
M22	–	2.0×10^{-11} M	IgG1	Lambda	[73]
K1-18		2.5×10^{-11} M	IgG1	Kappa	[75]
TBAb (in rare hypothyroid patients)					
Serum	1.7–27 μg/ml	$1.4–3.3\times10^{-11}$ M	IgG1, IgG2, IgG3	Kappa, lambda	[71, 97]
5C9	–	2.5×10^{-11} M	IgG1	Kappa	[74]
K1-70	–		IgG1	lambda	[75]

It should be emphasized that determining the precise amino acids comprising the epitope in the TSHR LRD of a monoclonal TSAb does not explain how TSAb activate the TSHR. This understanding will require knowledge of the three-dimensional structure of the entire TSHR, including the orientation of its individual components and, perhaps, its quaternary structure. The TSHR is known to multimerize [81, 82] but the number and arrangement of the protomers in this complex are unclear. It is known that there is partial steric hindrance to TSAb interaction with the TSH holoreceptor on the cell surface [72, 83]. High-affinity interactions between antibodies such as TSAb and the TSHR are largely determined by antigen-driven affinity maturation (mutagenesis) in the complementarity determining regions of the heavy and light chains. However, other regions of TSAb (such as the framework region) may also impinge on the TSHR, and not only at LRD residues revealed by the crystal structure but also further downstream in the hinge region [66, 84]. On the basis of the foregoing information, we propose that TSAb activation of the TSHR occurs because of partial steric hindrance to its primary binding site at other regions of the receptor protomer or multimer.

Switching from Hyper- to Hypothyroidism (or Vice Versa)

Switching between predominant TBAb to TSAb activities (or vice-versa) occurs in unusual patients after thyroxine (L-T4) therapy for hypothyroidism or anti-thyroid drug treatment for Graves' disease. TBAb-induced hypothyroidism must be distinguished from Hashimoto's thyroiditis (even more common than Graves' disease) in which massive lymphocytic infiltration and fibrosis overwhelms the TSH-driven regenerative capacity of the thyroid gland for example [85, 86].

Examination of case reports has provided insight into the basis for "switching" (reviewed in [87]) (summarized in Table 2.3). TSHR Ab switching involves differences in TSAb versus TBAb concentrations, affinities and/or potencies in individual patients. Thus, anti-thyroid drugs or suppression/hemodilution in pregnancy reduce initially low TSAb levels even further and lead to TBAb dominance. In contrast, emergence of TSAb following L-T4 administration may be sufficient to counteract

Table 2.3 Insight into the basis for "switching" between TSAb and TBAb (or vice versa) based on case reports (reviewed in [87])

	Factors that may impact the shift
(a)	L-T4 treatment, usually associated with decreased thyroid autoantibodies, occasionally induces or enhances thyroid autoantibody levels
(b)	Antithyroid drug treatment decreases thyroid autoantibody levels
(c)	Hyperthyroidism polarizes antigen presenting cells leading to impaired development of regulatory T cells
(d)	Immune suppression/hemodilution reduces thyroid autoantibodies during pregnancy with a rebound postpartum
(e)	Maternally transferred IgG transiently impacts thyroid function in neonates

TBAb inhibition, if present. Of interest, a model of Graves' disease involving immunizing TSHR "knockout mice" with mouse TSHR-adenovirus and transfer of TSHR antibody secreting splenocytes to athymic mice demonstrates the TSAb to TBAb shift, paralleling the outcome of maternally transferred "term limited" TSHR antibodies in neonates.

Why Measure TSHR Antibodies?

The occurrence of "switching" from TBAb To TSAb (or vice versa) emphasizes the need for careful patient monitoring and management, including measuring TSHR antibodies in selected individuals. In addition, there are other situations where measurement of TSHR antibodies is important:

Pregnancy. TSHR antibodies cross the placenta. In women with Graves' disease previously treated with ^{131}I, especially with a history of ophthalmopathy or dermopathy, TSHR antibody levels can be high and can persist through parturition, though generally declining during the third trimester. The fetal thyroid is fully functional at the end of the first trimester. Therefore, performing a TBI or TSAb test during the first trimester is of value. Even though the mother may be euthyroid or hypothyroid on thyroid hormone replacement, high TSAb levels may cause fetal hyperthyroidism.

If antithyroid drugs are required to treat maternal hyperthyroidism during pregnancy, both methimazole and propylthiouracil cross the placenta and can counteract the effect of TSAb on the fetal thyroid. However, after parturition, neonatal clearance of these drugs is much more rapid than that of TSAb, which can persist for weeks. Therefore, in women with Graves' disease being treated with anti-thyroid drugs, it is of value to determine maternal TSAb in late pregnancy.

High TSHR antibody levels transferred to the fetus can persist unopposed for many weeks and the baby can develop hyperthyroidism even after uneventful delivery and initial home care [8].

Prediction of remission: TSHR Ab levels are higher in Graves' patients that relapse after anti-thyroid drugs than in those that remain in remission (for example [88]). The predictive value is not absolute but provides some insight for physician and patient as to chances of remission if anti-thyroid drug therapy is contemplated. Unlike in Europe and in Asia, this prediction may not be a major issue in the USA where radio-iodine therapy is most commonly the primary choice [89]. However, the situation may be changing with the decrease of the use of radio-iodine therapy in the USA [89] and the very large increase in the number of prescriptions dispensed for methimazole between 1991 and 2008 [90].

Guidance for management of Graves' ophthalmopthy and dermopathy: As will be discussed later (Chap. 13), there is a strong relationship between TSHR autoantibodies and the extra-thyroidal manifestation of Graves' disease. In brief, the TSH

receptor is expressed in orbital tissue and the prevalence of ophthalmopathy in untreated Graves' patients is positively correlated with the levels of TSH receptor autoantibodies [91, 92]. The aggravating effect of radio-iodine therapy (unlike surgery and anti-thyroid drugs) on Graves' ophthalmopathy [93] is associated with an increase in TSHR antibody levels [94]. TBI levels decreased to baseline within one and a half years after medication or surgery but persist above base line levels 5 years after radioiodine [94]. Patients treated with medication or surgery have high numbers of individuals that become TBI negative. In contrast, three years after radio-iodine, only 50 % of patients are TBI negative [94]. In summary, the close relationship between TSHR autoantibodies and Graves' ophthalmopathy provides important insight into the optimal means of treating this distressing condition.

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Chapter 3
Epidemiology and Genetic Factors in Graves' Disease and Graves' Ophthalmopathy

Sara Salehi Hammerstad and Yaron Tomer

Introduction

Graves' disease (GD) is an organ-specific autoimmune disease, characterized by the production of antibodies (Abs) to the TSH receptor (TRAb) that bind to the TSH receptor [1] activating it and resulting in the clinical manifestations of hyperthyroidism. One of the most serious complications of GD is Graves' ophthalmopathy (GO), a complex chronic autoimmune inflammation affecting the orbital and retro-orbital tissues. GO is the most common extra-thyroidal manifestation of GD: GO reduces significantly the health-related quality of life (HRQL) of GD patients and it may persist years after the diagnosis and treatment of GD [8]. GO is associated with Graves' hyperthyroidism in most cases (90 %); however, it can exceptionally occur in patients with hypothyroidism or euthyroid subjects [9–13]. Since GO and thyroid diseases occur concurrently [14], it is highly likely that these two conditions share common etiology.

While significant progress has been made in our understanding of the pathophysiology of GD, the underlying causes are still not fully elucidated. GD is a complex disease which means that it is caused by a combination of predisposing genetic factors

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and environmental triggers. GO is still considered a mystery in thyroidology and its treatment is still nonspecific and challenging [15]. In this chapter we review the epidemiological evidence for genetic involvement in development of GD and GO and summarize recent findings on the genetic contribution to the etiology of GD.

Epidemiology of GD and GO

Epidemiology of Graves' Disease (GD)

Estimated Prevalence and Incidence

The prevalence of hyperthyroidism is reported to be 0.5–2.5 in women and 1:4 to 1:10 of that in men [16–20]. From these data the prevalence of GD can be estimated since GD accounts for approximately 70–80 % of cases of hyperthyroidism in iodine-sufficient geographic regions [21], such as the USA. In a longitudinal epidemiological study performed at the Mayo Clinic, the average annual incidence of GD was 36.8 and 8.3 per 100,000 in females and males, respectively, for a period of 33 years (1935–1967) [22]. Looking into subgroups, there was no indication that the incidence of GD has changed during these three decades. In contrast, the same group found a tenfold increase in the incidence of Hashimoto's thyroiditis during the same period [22]. Longitudinal surveys can give an indication on the relative importance of genetic and environmental factors in the etiology of a disease; in general a constant incidence indicates strong genetic involvement since the environmental influences are expected to change over 20–30 years. A Danish study reported similar incidence rates of thyrotoxicosis during a 3-year survey (1972–1974), 46.5/100,000 in women and 8.7/100,000 in men [23].

Epidemiological studies in Sweden, which is also an iodine-sufficient country, analyzed the trends during the last four decades. The annual incidence of GD was relatively constant—17.7/100,000 (1970–1974) and 22.3/100,000 (1988–1990)—in Malmo, Sweden [24, 25]. A significant increase in incidence was only observed in women aged <50 [25]. A new evaluation for the period 2003–2005 in the same region showed an increase in incidence to 29.6/100,000 [26]. However, the annual incidence was higher in inhabitants born outside Sweden and up to the age of 69 [26], compared to the incidence in the general population in Sweden which was reported to be 21.5/100,000 [27]. Similarly, Bodansky et al. reported an increase in incidence of T1D in offspring of Asian immigrants, approaching that of the indigenous population [28].

The level of dietary iodine was clearly shown to affect the incidence of thyrotoxicosis of various etiologies. While the incidence of hyperthyroidism is increased in iodine-deficient regions, the incidence of GD tends to be lower in these areas, suggesting that other forms of thyrotoxicosis are increased by iodine insufficiency. The annual incidence of thyrotoxicosis in Iceland (1980–1982), an iodine-sufficient country, was reported to be 23/100,000, whereas GD accounted for 83 % of cases [29]. Intriguingly, Iceland has shown to have one of the lowest incidence rates for some

autoimmune diseases such as type 1 diabetes compared to related ethnic countries [30]. In contrast, a high incidence of thyrotoxicosis (47/100,000) was reported in a region of Denmark with low average iodine intake, but the incidence of GD was low in this region (14.8/100,000) and lower than that in Iceland [31]. It is possible that mild iodine deficiency protects against autoimmune thyroid diseases [18]. Similar incidence rates were reported in other iodine-sufficient countries such as New Zealand (15/100,000) [32]. These results suggest that in addition to genetic susceptibility, environmental factors also play a role in the development of GD.

Age, Gender, Ethnicity

The peak incidence of GD was reported to be in women at ages 20–39 [22]. Other studies report that the highest risk of onset of GD is in the age group of 40–60 years old [23, 33, 34]. However, these data should be reviewed with caution since most epidemiological studies only looked at the incidence of thyrotoxicosis and not GD. Like many other autoimmune diseases, GD occurs more frequently in women. The female/male (F/M) ratio is reported to be 4:1 to 10:1 [16–20]. GD occurs in all ethnic groups including Caucasians, Asians, and Africans. The prevalence is reported to be lowest in Africans [35]. Surprisingly, a recent study including all US active duty military aged 20–54 showed a higher incidence of GD in Blacks and Asians/Pacific Islanders compared to Caucasians [36]. This study, however, confirmed that Hashimoto's thyroiditis is less prevalent in Asians and Blacks compared to Whites [36]. The geographical distribution showed a significantly higher incidence in urban populations compared to rural populations [23]. However, other studies in iodine-sufficient region could not confirm these findings [32].

Epidemiology of Graves' Ophthalmopathy (GO)

The clinical classification of GO has evolved during the last two decades [9], and standardized assessment for the activity and severity of the disease is now much better defined. Based on a questionnaire-based survey in Europe, it is commonly reported that approximately 50 % of GD patients have ocular involvement [37]; however, the frequency of severe GO is probably much lower and closer to 5 %. The estimated prevalence of GO depends on the methodology used to identify GO. For example, using CT scan to diagnose GO results in higher estimated rates of ophthalmopathy [38].

Estimated Prevalence and Incidence of GO

Limited epidemiological data are available on GO. Most studies included small numbers of patients and reported results are confounded by the variable clinical presentation of GO and diagnostic criteria. Ethnicity is also important in the assessment of

orbitopathy, as the anatomy of orbita may differ (e.g., between Caucasian and Asian patients) [39]. There are anecdotal reports on the declining incidence of GO [11], which is assumed to be mainly due to the decreased prevalence of smoking [33]. However, this observation requires further confirmation.

In a longitudinal study in the USA, the age-adjusted incidence of GO was found to be 16/100,000/year in women and 2.7/100,000/year in men (Olmsted County, Minnesota; 1976–1990). There was a trend for decreased incidence over the years; however, this trend was not statistically significant [9]. Another review of clinical reports from 1960 to 1990 showed a general decline in the prevalence of GO [40]. Using the standard criteria in a series of 346 patients, Tanda et al. reported that 20 % of patients with GD had mild GO, 6 % had moderate to severe GO, and 0.3 % had sight-threatening GO [40]. A national survey in Denmark (1992–2009) reported a lower incidence rate of GO of 16.1/million (women 26.7, men 5.4); in this study the incidence of GO was approximately 1/5 that of GD [33]. Here also, only 6 % of GO patients presented with moderate to severe GO. Similar results were reported in another population-based study [41].

Age and Gender

In general GO may occur at any age; however, the risk is higher in patients aged 40–60 [33, 42]. The onset peaks in a bimodal fashion in the fifth and seventh decades of life and differs between women and men (age groups 40–44 years and 60–64 years in women and 45–49 years and 65–69 years in men) [9]. Children and adolescents can also develop GO; however, severe forms are very rare in these age groups. In addition, the involvement of the eyes is usually transient and disappears when euthyroidism is restored [43].

In general, the female/male (F/M) ratio for GO is reported to be similar to the F/M ratio for GD [9, 33, 42]. The F/M ratio in GO was reported to be lower in a study of Asian patients [44]. However, the percentage of males who smoked was relatively high in this study. Another study from Japan reported an F/M ratio for GO of 1.3 [45]. In addition, the F/M ratio of GO tends to decrease with increased severity of the disease [42, 45]. Hence, older men are especially at a high risk to develop severe GO. Whether this is related to smoking needs further investigations.

RAI has also been implicated in the worsening and de novo development of GO in patients treated for thyrotoxicosis [6], and some of the differences in the incidence of GO might reflect the frequency of using RAI ablation in different subsets of GD patients.

Ethnicity

The literature on ethnic differences in the incidence of GO is sparse. One study from the UK reported significant ethnic differences in the prevalence of GO. The prevalence was higher in Caucasian than in Asian GD patients (42 % and 7.7 %,

respectively) [46]. This difference was only partly related to different prevalence of smoking [46]. However, another group that analyzed GO in patients from several Asian populations (Chinese, Malays, and Indian) could not confirm ethnic differences in the frequency of GO. Using standardized criteria, the prevalence of GO in GD patients was 35 %, which is fairly similar to the frequency reported in Caucasians [44]. There is some evidence that the manifestations of GO may differ between Asian and Caucasian patients [47]; however, this observation needs further investigation. It should be noted that the adequate adjustment of normal values of exophthalmus according to individual and ethnic differences is important for the diagnosis of orbital morbidity and for the management of thyroid-associated orbitopathy [39].

Genetic Susceptibility in Graves' Disease

An unexplained trend showing an increased incidence of several autoimmune diseases over the past several decades has been reported. This trend suggests changing environmental influences. Interestingly this trend does not apply to GD, suggesting a strong genetic influence on GD etiology. Indeed, family and twin studies also support a strong genetic contribution to the etiology of GD (reviewed in [48]).

The familial occurrence of AITD is well known to clinicians caring for GD patients and has been reported by many groups [49, 50]. There is a significant clustering of GD in families resulting in a sibling risk (λs) that is >10, suggesting a strong genetic susceptibility [51]. The strongest evidence for genetic involvement in the development of GD comes from twin studies. Danish twin studies reported a significantly higher concordance rate of GD in monozygotic than dizygotic twins (0.36 and 0, respectively) [52]. Interestingly, the concordance rates were similar in the young cohort [52] and after 25 years of observation [53]. Similar results were also reported by a study from California [54]. Based on these observations, it was concluded that 75 % of the risk for autoimmune thyroid diseases is hereditary [55]. Nevertheless, the lack of complete concordance of GD in MZ twins points to the importance of environmental and epigenetic factors in the etiology of GD.

Immune System Genes

Human Leukocyte Antigen (HLA)

The MHC region on chromosome 6p21 encodes the HLA glycoproteins and various additional proteins, most of which are associated with immune response [56]. HLA molecules recognize antigens and present them to T cells. The current paradigm is that HLA alleles create pockets with different affinities for peptides from autoantigens (e.g., thyroid proteins). Therefore, some HLA alleles will be able to present

self-antigens more efficiently to self-reactive T cell receptors on T cells that have escaped tolerance [57]. Thus, HLA alleles that create peptide-binding pockets that can bind and present autoantigenic peptides to self-reactive T cells will be associated with autoimmunity [58].

The HLA gene complex was the first to be tested for association with GD. Early studies showed the association of GD with HLA-B8 in Caucasians [59, 60], but later a stronger association was found with HLA-DR3, which is now recognized to be in linkage disequilibrium with HLA-DR8. Studies in non-Caucasian GD patients identified other HLA association; for example, HLA-B25 and HLA-Bw46 are associated with GD, respectively, in Japanese and Chinese patients (reviewed in [2]). HLA-DPB1*0501 and HLA-A*02 are also associated with GD in Japanese [61]. Recently, we were able to delineate the mechanism by which HLA-DR3 predisposes to GD. Sequencing analyses demonstrated that the specific HLA-DR pocket amino acid that was key for the development of GD was arginine at position 74 of the HLA-DR beta chain (HLA-DRb1-Arg74) [62]. Moreover, through molecular dynamic simulations, we were able to show that the presence of arginine at position 74 of the HLA-DR beta chain conferred a unique structure to the peptide-binding pocket of HLA-DR that likely predisposed to disease by enabling the presentation of pathogenic peptides [63].

CD40

We have shown that the CD40 gene locus (chromosome 20q11) was linked and associated with GD [4, 64]. Sequencing analysis demonstrated the association of GD with a C/T polymorphism at the 5′ untranslated region (UTR) of the CD40 gene [4]. The association showed recessive inheritance with the C/C genotype of this SNP associated with GD, while the presence of one or two copies of the T allele was protective. These results have been replicated in many other datasets from different ethnic groups including Caucasians [65], Japanese [66], and Koreans [67].

CD40 is a member of the TNF-receptor superfamily [68]. CD40 is expressed on the surface of different cells including B cells, macrophages, dendritic cells, and endothelial and epithelial cells. Ligation with its ligand, CD40L (CD154) on stimulated T cells, induces B cell proliferation, antibody secretion, and generation of memory cells. Thus, CD40 is a key player in both the innate and adaptive immune responses. We have demonstrated that the C allele caused an increase in CD40 protein expression compared to T allele [69]. Moreover, we have further shown that the upregulation of CD40 accelerated the disease in a mouse model of GD through activation of IL-6 in the thyroid [70]. In fact, blocking IL-6 completely suppressed the experimental autoimmune GD in mice [70]. If this mechanism operates in human GD, it may imply that anti-IL-6 therapy can be effective in human GD.

The enhanced expression of CD40 may contribute to the development of autoimmunity in general. Indeed, CD40 has been implicated in the etiology of a variety of autoimmune diseases such as rheumatoid arthritis, asthma, type 1 diabetes, and multiple sclerosis [71–74].

FOXP3

Regulatory T cells (Treg) have an important role in the modulation of T cell response with an essential function to suppress immune responses (reviewed in [75]). Natural Treg cells (CD^{4+} CD^{25+} Treg cells) express FOXP3, a transcription factor that has become a signature gene expressed in Treg cells that is key to the differentiation of T cells into Tregs [76].

Two whole genome scans have shown evidence for the linkage of GD with putative X-chromosome loci, Xq21 and Xp11 [77, 78]. Intriguingly, the FOXP3 gene is located within the Xp11-linked locus, and in view of its fundamental role in regulating the immune response it was an obvious positional candidate gene for GD. Moreover, knockout mutations in the FOXP3 gene cause severe systemic autoimmune disease (reviewed in [79]). Therefore, the FOXP3 gene was analyzed for the association with several autoimmune diseases including GD. A study from the UK reported that a FOXP3 haplotype was associated with GD; however, this was a suggestive association because it was significant only before correction for multiple testing [80]. We have also examined the contribution of the FOXP3 gene to the genetic susceptibility to GD, testing for association in two ethnic groups [81]. The results showed an association between FOXP3 variants and GD in Caucasians but not in Japanese [81]. This study, however, cannot rule out an association in the Japanese as it is plausible that other FOXP3 polymorphisms, not examined in our study, are associated with GD in other ethnic groups. In another study, we demonstrated the linkage of FOXP3 with the phenotype of AITD + type 1 diabetes, known as a variant of the terminology autoimmune polyglandular syndrom 3 (APS3) [82].

These data suggest that inherited defects in Treg's function may be a major mechanism predisposing to AITD. FOXP3 was also reported to be associated with type 1 diabetes, but these results are inconsistent and require further confirmation [83, 84].

Other Immune System Genes

Other immune regulatory genes have also been tested for association with GD. The most important non-HLA immune regulatory gene conferring susceptibility to GD is CTLA-4 [85]. Similar to FOXP3, CTLA-4 is an important gene for suppressing immune responses, and variants of CTLA-4 that are associated with GD have been shown to reduce its expression and/or function [86]. Other important immune regulatory genes that have been shown to be associated with GD include PTPN22 [87], an important susceptibility gene in many autoimmune diseases, and CD25 [88].

Thyroid-Specific Genes

The hallmark of GD is the presence of TSH receptor antibodies, and therefore the TSH receptor presents a logical candidate gene. Furthermore, 30–85 % of GD patients also present thyroglobulin autoantibodies (Tg Abs) and/or thyroid peroxidase (TPO Abs) [89, 90]. Hence, these proteins may present potential autoantigen.

TSHR

Previously we identified a locus on chromosome 14q that was linked with GD [91]. The TSHR gene is located on chromosome 14q and it was found to be strongly associated with GD [92]. Later, we confirmed that the 14q locus we identified as linked with GD was indeed the TSHR gene locus [93]. The causative variant was fine-mapped to a relatively narrow region in intron 1 of the TSHR gene. Since the TSHR is the target of the immune response in GD, it is possible that the TSHR gene variants that are associated with GD help target the immune response to the TSHR. However, functional studies on the intron 1 variants are still lacking.

Thyroglobulin

We mapped a locus on chromosome 8q24 that was linked with AITD [91, 94]. The same locus was found to be linked with AITD in a Japanese study [95]. This locus contains thyroglobulin gene, one of the major autoantigens in autoimmune thyroid diseases [96]. Therefore, we and others tested the thyroglobulin (Tg) gene for association with both GD and HT. Our family linkage studies showed an association of AITD with two microsatellite markers, D8S284 and Tgms2 [94]. Another group from UK found a significant association of a rare allele of Tgms2 with AITD [97]. The same group could not show an association with four other SNPs of Tg gene in UK Caucasian GD [98].

In contrast, most other studies showed significant associations of variants in Tg with AITD. A case-control study from Japan showed a significant association between 5 out of 25 examined SNPs in Tg and GD [99]. The two SNPs with strongest association (rs2256366 and rs2687836) were located in intron 4 [99]. Sequencing of all 48 exons of Tg gene identified 14 exonic SNPs [100], and a case-control association study revealed that an exon 10–12 SNP cluster and an exon 33 SNP were significantly associated with AITD [100].

Moreover, we have discovered an interaction (synergism) between the exon 33 SNP in Tg and HLA-DRβ1-Arg74 in predisposing to GD [101]. Inheriting both the exon 33 susceptible (CC) genotype and HLA-DRβ1-Arg74 resulted in a very high odds ratio for developing GD [100, 101]. These findings suggest that gene-gene interactions may be necessary to develop thyroid autoimmunity.

More recently, we identified a SNP in the Tg promoter (−1623A→G) that was strongly associated with AITD in Caucasians [5]. We, furthermore, demonstrated that the disease-associated allele modified a binding site for an interferon-induced transcription factor (IRF-1), and this binding was marked by enrichment of monomethylated LYS-4 residue of histone H3 and was associated with increased Tg promoter activity [5]. Furthermore, treatment with interferon-α, a known trigger of thyroid autoimmunity, increased Tg promoter activity through binding of IRF-1 to the Tg promoter in the presence of the disease-associated variant [5]. This study points to a novel mechanism of gene-environment interaction and epigenetic modifications in thyroid autoimmunity.

Genetics of Graves' Ophthalmopathy

Graves' ophthalmopathy is believed to be an autoimmune affection of orbital tissues that is triggered by the immune response to the TSHR in GD. There are few family studies but no twin studies that assessed the role of genetic factors in GO. We performed a family study in 114 patients with severe GO and found no evidence for familial segregation of GO [51]. Only 3/114 GO patients had a family history of GO, and in all three patients the affected family members were second-degree relatives.

Clinical symptoms of GO may occur before, simultaneously, or after the onset of GD [14], which demonstrates that these diseases may share a common etiology. Researchers have therefore focused mostly on the same genes that have been found to be associated with GD. So far, most of the genetic studies in GO have been inconclusive.

Both HLA classes I and II have been studied for association with GO; however, the results were mixed. For example, one early study failed to confirm a previously reported association between GO and HLA-DR3 [102] which was shown to be strongly associated with GD [103, 104]. Moreover, a meta-analysis of studies of HLA-DR3, HLA-DR4, and HLA-DR7 could not find any significant association with GO [105]. Since CTLA-4 is strongly associated with GD, several studies have also investigated the association of CTLA-4 gene polymorphisms with GO, in Caucasian and Asian population. Few studies have shown an association [106]; however, overall, no significant association was confirmed [105, 107–110].

In vitro and in vivo studies have shown expression of TSHR in orbital adipocytes [109, 111], suggesting a role in the etiology of GO. One group reported TSHR expression on fibrocytes and suggested a role in the etiology of GO [112]. Therefore, TSHR may also be the target antigen in GO. Intriguingly, Yin et al. could not find evidence that TSHR gene polymorphism adds to the risk of developing GO beyond the risk they confer for GD [113]. Furthermore, as phonotypic variation of GO may be related to genetic predisposition, the same group investigated gene polymorphism in groups of patients with different degrees of eye affection. Here again, TSHR gene polymorphism was not more prevalent in patients with GD and GO compared to GD alone, and no significant difference was found between the severe and mild forms of GO [113]. The same group reported that two additional GD genes, HLA-DR3 and CTLA-4, were not specifically associated with GO [113].

Cytokines have a central role in the development and progression of GO (for review see [114]). Several cytokines and growth factors capable of stimulation of in vitro proliferation of fibroblasts derived from retro-ocular connective tissue or extraocular muscle have been studied [115]. IL-1α has shown to be specific for fibroblasts in GO [116]. IL-1 gene polymorphisms have therefore been studied for association with GO, mostly in Asian countries. However, these studies have not been consistent [116–119]. In addition, the results are difficult to compare as different criteria for the diagnosis of GO were used in each of these studies. Our own group has previously shown that genotypic variants of the IL-23 receptor gene were significantly associated with GO compared to controls [120]. However, these results have not been replicated by others [113]. Another interesting study showed associations of

polymorphisms in anti-inflammatory cytokine genes (IL-4, IL-10, and TGF-β) with GO [121].

Alleles of two SNPs in the TLR-9 gene showed significant associations with GO in male patients [122]. The criteria for the diagnosis of GO were not given in this study; also there was a significant difference in smoking habits between women and men. In a Polish-Japanese cohort, only in Japanese GD an NFkβ1 polymorphism was significantly associated with the severity of GO [123]. In a study from the UK, comparing FOXP3 polymorphisms in GD patients with GO vs. controls showed no significant difference in allele frequency [80].

Other researchers could not demonstrate an association between CD40 [124], PTPN22 [125], and IL-13 [126] gene polymorphisms and GO. Other cytokines and receptors have also been investigated in GO (for review see [105]). Nevertheless, further studies on larger cohorts are required in order to dissect the unsolved genetics of GO.

Epigenetics

For many years, the nature of the interaction between susceptibility genes and environmental triggers was unclear. One emerging mechanism for the gene-environment interaction in complex diseases is through epigenetic modulation. Epigenetic effects are long-term effects (sometimes heritable) on gene expression that are not encoded in the DNA. The most important epigenetic modifications of DNA include: (1) DNA methylation which usually downregulates gene expression if occurring in the promoter regions of genes; (2) modification of histones, a cluster of protein at the core of the nucleosomes that regulate the activity of chromatin and gene transcription; and (3) regulation of microRNAs, short non-coding RNAs that regulate the expression of coding RNAs through binding to the 3′ UTR [127]. We have recently shown that a genetic-epigenetic interaction upregulates thyroglobulin (Tg) gene expression [5]. How the upregulation of Tg gene expression trigger AITD is unclear, but it may be through misfolding or alterations in post-translational modifications that lead to the degradation of Tg and production of immunogenic peptides.

One likely environmental factor that interacts epigenetically with AITD susceptibility genes is infection [128]. Indeed, there is growing evidence, however indirect, that the development of autoimmune thyroid diseases maybe associated with a variety of infectious diseases. While the mechanisms by which infectious agents induce AITD are not known, one attractive hypothesis is of bystander activation. According to this hypothesis, a viral infection of the thyroid can trigger local inflammation that in susceptible individuals will lead to AITD. Indeed, our group has shown that the hepatitis C virus (HCV) can infect human thyroid cells in vitro [129] and that the HCV receptor, CD81, is expressed on thyrocytes and can bind the HCV envelope protein E2, inducing cytokine production [130]. Enteroviruses were also implicated in triggering AITD. One study reported that enteroviruses were present significantly more frequently in thyroid tissues of GD patients compared to controls [131], with

high expression of MxA1, a surrogate marker for the in situ production of interferon [89]. Other infectious agents have also been implicated in the development of AITD (reviewed in [132, 133]).

Conclusion and Further Directions

GD is a common autoimmune disease and its etiology is slowly being deciphered. One of the most serious complications of GD is GO. While much is known on the genetic susceptibility to GD, much less is known on the genetic susceptibility to GO. It is now being realized that genetic variants that predispose to disease interact with environmental factors, such as infections, through epigenetic modifications. Epigenetic modifications amplify the risk conferred by susceptibility genes until a threshold is crossed and disease develops. As we learn more about genetic-epigenetic interactions that trigger GD and GO, new therapeutic targets will emerge.

Conflicts of Interest The authors have no potential conflicts of interest to declare.

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Chapter 4
Laboratory and Clinical Assessment of Hyperthyroidism

M. Regina Castro

Clinical Case

A 35-year-old woman presents for evaluation of a thyroid nodule and abnormal thyroid function tests. Eight months after delivering her baby, she noted a lump on the left side of her neck. She has also complained of feeling more tired and anxious, but she has not been sleeping well at night since her baby was born. She is no longer breast-feeding. She has never been exposed to radiation to her head or neck. Her weight has remained stable. She denies compressive symptoms such as dysphagia or breathing difficulties related to this nodule. Her grandmother had thyroidectomy years ago for thyroid cancer but is doing well without recurrence. Thyroid function tests obtained at her primary doctor's office show TSH of 0.03 mIU/L, free thyroxine of 2.2 ng/dL (normal 0.8–1.8 ng/dL), and total T3 of 264 ng/dL (normal 80–190 ng/dL).

Examination shows a slightly anxious woman, with a blood pressure of 126/60 mmHg and pulse of 110 bpm.

Eyes: Positive stare and lid lag; no conjunctival injection, chemosis, or proptosis; and extraocular movements are normal. Neck exam shows an enlarged left lobe with a palpable 3.5 cm firm nodule that moves freely with swallowing. Right lobe is mildly enlarged, but without discreet nodules. There is no palpable neck lymphadenopathy. There is a very slight tremor of her extended fingers. No clubbing. Her deep tendon reflexes are normal. Remainder of her exam is noncontributory.

What is the next best step in the evaluation of this patient's complaints?

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Introduction

"Hyperthyroidism" and "thyrotoxicosis" are terms that are often used interchangeably. However, strictly speaking, the term "thyrotoxicosis" refers to any condition caused by excess circulating levels of thyroid hormones, thyroxine (T4) and triiodothyronine (T3) or both, regardless of their source, whereas "hyperthyroidism," the most common cause of thyrotoxicosis, is due to excessive synthesis and secretion of thyroid hormones and is most commonly due to Graves' disease (autoimmune hyperthyroidism). Hence, although most thyrotoxic patients have hyperthyroidism, some patients may have other conditions that result in elevated thyroid hormone levels but are not due to increased synthesis of thyroid hormone. In addition to the elevated serum thyroid hormone levels, suppressed serum TSH concentration is also seen in patients with thyrotoxicosis.

Etiology

Thyrotoxicosis may be due to hyperthyroidism or occur in the absence of increased synthesis and secretion of thyroid hormones. Typically, most causes of hyperthyroidism are associated with normal or increased radioiodine (RAI) uptake. Graves' disease is the most common cause of hyperthyroidism in the United States (up to 80 % of cases of hyperthyroidism) [1] with an estimated prevalence of 1.2 % [2] and is more common in women than men (5:1 ratio) and in areas with iodine deficiency [2, 3]. Its peak incidence occurs between the ages of 40 and 60 years [1, 4]. Graves' disease is an autoimmune disorder in which antibodies directed against the thyrotropin (TSH) receptor (TRAb or TSI) bind to and stimulate these receptor leading to excess synthesis and secretion of thyroid hormones (T4 and T3). Other causes of hyperthyroidism include autonomous production of thyroid hormones by toxic multinodular goiter (Plummer's disease) and toxic adenomas, which are due to activating mutations of the TSH receptor [5]. The frequency of nodular thyroid disease increases with advancing age and is more common in areas of iodine deficiency, where they can account for up to 50 % of cases of hyperthyroidism [6]. Pituitary TSH-producing adenomas represent a very rare cause of hyperthyroidism, accounting for <2 % of all pituitary tumors [7]. Other uncommon causes of hyperthyroidism include human chorionic gonadotropin (hCG)-secreting tumors, hyperemesis gravidarum, and, rarely, functional metastatic thyroid carcinomas.

Conditions associated with thyrotoxicosis without increased thyroid hormone secretion usually demonstrate low RAI uptake. Such conditions include subacute thyroiditis, exogenous thyrotoxicosis (iatrogenic or factitious), and radiation-induced thyroiditis. In addition, certain drugs (such as amiodarone and α-interferon) can cause thyrotoxicosis by their cytotoxic effect on thyroid cells, causing release of preformed thyroid hormones. Table 4.1 summarizes the most common causes of thyrotoxicosis.

Table 4.1 Evaluation of causes of hyperthyroidism

Etiology	Thyroid function tests		Radioiodine uptake/ scintigraphy	Additional helpful tests	Comments
	TSH	FT4 and Total T3			
High radioiodine uptake					
Graves' disease	↓↓	↑↑	↑ or N, homogeneous	TRAb, TSI	Usually + family history
Hashitoxicosis	↓	↑↑	↑ or N, homogeneous	TPO	Rare. Initially thyrotoxic, hypothyroidism later
Toxic adenoma	↓	N or ↑	↑ Focal uptake. Rest of gland may have suppressed uptake	Ultrasound	
Toxic MNG	↓	N or ↑	↑ or N, heterogeneous	Ultrasound, CT or MRI	CT or MRI to assess relation to other neck structures
Pituitary TSH-producing adenoma	N or ↓	↑	↑ Homogeneous	Pituitary MRI; alpha-subunit	
Low radioiodine uptake in the neck					
Subacute, painless, postpartum, and radiation- or amiodarone-induced thyroiditis	↓	↑	↓↓RAI uptake	Erythrocyte sedimentation rate (ESR)	Thyroglobulin (Tg) high from release of preformed thyroid hormone
Surreptitious thyroid hormone ingestion; over-replacement or suppressive therapy	↓	↑	↓↓RAI uptake	Thyroglobulin	Thyroglobulin usually low (suppressed)
Iodine induced (includes IV dye, amiodarone)	↓	↑	↓↓RAI uptake	Urinary iodine excretion	
Struma ovarii	↓	↑	↓RAI uptake (neck) ↑RAI uptake (pelvis)	Whole-body scan, pelvic ultrasound	Pain or pelvic mass common

Major causes of hyperthyroidism according to the presence of a high or low radioiodine uptake. High uptake indicates increased new hormone synthesis by the thyroid, whereas low uptake indicates release of preformed hormone, exogenous ingestion, or extrathyroidal hormone synthesis

Clinical Presentation

The clinical manifestations of thyrotoxicosis are generally independent of the source of thyroid hormone excess and include tremor, weight loss which often occurs despite increased appetite, tachycardia, nervousness or anxiety, insomnia, heat intolerance, diaphoresis, fatigue, weakness, increased frequency of bowel movements, and, in women, irregular menses. The severity of the symptoms does not always correlate well with the magnitude of thyroid hormone levels in serum, but in one study of 25 GD patients, it was found to be inversely correlated with age [8]. Elderly thyrotoxic patients often present with more subtle and milder symptoms (apathetic hyperthyroidism), which may also be less typical, such as fatigue, weakness, depression, or atrial fibrillation [9–11]. Reduced libido and painful gynecomastia can occur in men [12]. Other features, such as thyroid tenderness and pain, may be seen in specific conditions such as in subacute thyroiditis, also known as de Quervain's thyroiditis, or in postradiation thyroiditis.

In subclinical hyperthyroidism, which is defined as suppressed serum TSH (<0.5 mU/L) with normal free thyroxine (T4) and T3 levels, patients may have no clinical symptoms of hyperthyroidism or, if present, symptoms are usually mild and nonspecific and the diagnosis is usually made by routine screening. Elderly patients with subclinical hyperthyroidism may present with tachycardia or new-onset atrial fibrillation [9, 13].

Thyroid storm is a severe form of hyperthyroidism, which may be life-threatening, in which patients present with severe tachycardia (>140 beats per minute), atrial fibrillation, congestive heart failure, fever, agitation, and psychosis or coma [4, 14]. Most commonly, this syndrome is precipitated by a stressful event such as trauma, childbirth, infection, or surgery in a known hyperthyroid patient but may also occur in a previously undiagnosed patient [4]. Therefore, thyrotoxicosis should be included in the differential diagnosis of any patient presenting with fever and altered mental status [4].

Physical Examination

Common findings on physical examination include stare (lid retraction) and lid lag. Patients are usually restless and may have rapid speech. Skin is usually moist and warm. Tachycardia is one of the most common findings in thyrotoxic patients, and in those with atrial fibrillation, the pulse may be rapid and irregular. Tremor, hyperreflexia, and proximal muscle weakness are also common manifestations of thyrotoxicosis.

Thyroid examination may reveal the presence of a goiter, which may range from small to very large, in patients with GD or toxic MNG or in the much more rare cases of TSH-induced hyperthyroidism in patients with a TSH-producing adenoma. A single palpable nodule may be noted, indicating a possible autonomously functioning toxic adenoma. A painful, tender gland suggests subacute (de Quervain) thyroiditis.

Finally, a small or non-enlarged thyroid gland may be seen in patients with exogenous hyperthyroidism (iatrogenic or surreptitious) and more rarely in struma ovarii.

In patients with Graves' disease, signs and symptoms of ophthalmopathy are common and may be present in up to 50 % of affected patients. In most cases, signs of ophthalmopathy are mild and generally include conjunctival irritation or injection, lid retraction, and mild periorbital soft-tissue swelling. Severe Graves' ophthalmopathy (GO) is much less common, occurring in approximately 3–5 % of such patients and presenting with chemosis, inflammation, corneal ulcers, proptosis, extraocular muscle dysfunction that may lead to diplopia, and optic neuropathy due to optic nerve compression [15, 16]. A more rare physical finding in patients with GD is pretibial myxedema or dermopathy, which occurs in 1–2 % of patients, presenting as indurated areas of non-pitting edema, most commonly seen in the pretibial region, the feet, or other areas of trauma [17] (Fig. 4.1). Acropachy (clubbing of the fingers) is rare, occurring in less than 1 in 1,000 patients with GD (Fig. 4.2).

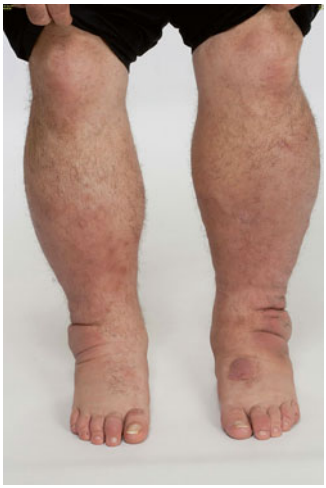

Fig. 4.1 Graves' dermopathy, pretibial myxedema. Note areas of thickened, indurated, non-pitting edema, in the pretibial region, and the feet

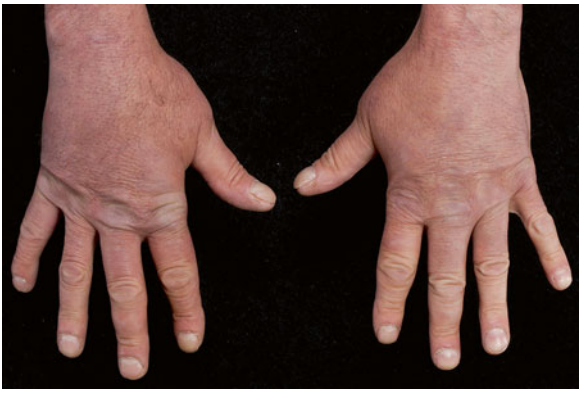

Fig. 4.2 Acropachy (clubbing of the fingers)

Laboratory Assessment

Most patients with overt thyrotoxicosis have elevated serum levels of the thyroid hormones free thyroxine (FT4) and triiodothyronine (T3), while thyrotropin (TSH) levels are suppressed and often undetectable. Serum TSH is the most sensitive test for evaluation of thyroid hormone excess [18]. In patients with milder (or subclinical) hyperthyroidism, serum T4, FT4, and T3 are usually normal while serum TSH is suppressed or, in cases of "T3-toxicosis," only T3 (and not FT4) will be elevated while TSH is suppressed or undetectable (<0.001) [19].

With the rare exception of patients with pituitary TSH-producing adenomas or those with thyroid hormone resistance (both uncommon conditions), a normal serum TSH essentially excludes hyperthyroidism. "Euthyroid hyperthyroxinemia" is a term that describes various conditions, most of them related to thyroid hormone-binding protein disorders in which serum total (but not free) T4 and T3 concentrations are elevated in the absence of hyperthyroidism [20]. Among these conditions, there are elevations in thyroxine-binding globulin (TBG) or transthyretin (TTR), familial hyperthyroxinemic dysalbuminemia (caused by an abnormal albumin with high binding T4 capacity), abnormal TTR and occasional TBG excess associated with pregnancy or estrogen administration, hepatitis, or drugs such as narcotics, amiodarone [21], and high-dose propranolol [19]. TSH-mediated hyperthyroidism, although very rare, should be considered in patients with normal or mildly elevated TSH and elevated serum levels of thyroid hormones (FT4 and T3) after exclusion of "euthyroid hyperthyroxinemia." In these patients, a high serum level of alpha-subunit and a pituitary adenoma on MRI support the diagnosis of a pituitary TSH-oma [22, 23]. Patients with thyroid hormone resistance syndrome, on the other hand, often have a family history of similar laboratory abnormalities and positive genetic test results identifying a mutation in the thyroid hormone receptor [24].

Thyrotropin receptor antibodies (TRAb) are present in more than 90 % of patients with GD, but determination of these antibodies is rarely needed, since the clinical diagnosis is usually obvious, particularly if thyroid uptake has been done and found to be elevated or high normal. However, measurement of these antibodies is helpful in pregnant or lactating women or in those situations when thyroid uptake and scan are contraindicated or unavailable, and the etiology of hyperthyroidism is not clear on clinical grounds. Current methods of determination of antibodies that bind to the thyrotropin receptor (TRAb) use recombinant human thyrotropin receptor and are more sensitive than first-generation assays [25]. Measurement of these antibodies is also helpful in the differential diagnosis of patients presenting with proptosis but without biochemical evidence of hyperthyroidism, since 10 % of such patients may have GD [4, 26]. Certain bioassays measure the ability of antibodies in the patient's serum to stimulate the production of cyclic adenosine monophosphate (cAMP) in cultured cells. Such antibodies measured by this assay are called thyroid receptor-stimulating immunoglobulins (TSIs) and are positive in 94 % of patients with untreated Graves' disease [27].

Imaging Modalities Helpful in the Assessment of Hyperthyroidism

RAI Uptake

The thyroid radioiodine uptake (RAIU) is the measurement of the proportion of an administered dose of radioactive iodine that accumulates in the thyroid at selected times following ingestion [28]. This study is indicated when the etiology of hyperthyroidism is not clear (except during pregnancy), and it helps to distinguish between causes of thyrotoxicosis with normal or elevated uptake in the thyroid gland and those with very low uptake [19].

Thyroid uptake reflects a combination of iodine transport into the thyroid follicular cells, its oxidation and organification, and its release from the thyroid. In general, conditions in which there is increased synthesis and secretion of thyroid hormone will demonstrate elevated thyroid uptake (GD, single toxic adenomas or toxic multinodular goiter [TMNG]). In GD the pattern of RAIU is generally diffuse, while in patients with single toxic adenoma, the uptake is focal, with suppressed uptake in the surrounding and contralateral thyroid tissue. In patients with TMNG, multiple areas of focal increased and suppressed uptake are seen [29]. On the contrary, the RAIU will be near zero in patients with thyrotoxicosis due to painless, postpartum, or subacute thyroiditis, in those with factitious ingestion of thyroid hormone, or in those with recent excess iodine exposure, as seen with patients taking amiodarone or in those recently exposed to intravenous iodinated contrast.

Scintigraphy

Thyroid scintigraphy with either ^{99m}technetium pertechnetate or I^{123} should be performed in patients presenting with hyperthyroidism and thyroid nodularity [19, 30] to document whether the nodule is hyperfunctioning (i.e., greater tracer uptake than surrounding normal thyroid), isofunctioning or "warm" (i.e., equal tracer uptake as surrounding thyroid), or nonfunctioning (i.e., uptake is lower than the surrounding thyroid tissue) [30]. Since hyperfunctioning nodules are rarely malignant, no cytologic evaluation of such nodules is necessary [30].

Whenever available, I^{123} is preferred. Most benign nodules and virtually all malignant nodules are hypofunctioning, but up to 5 % of thyroid cancers may concentrate ^{99m}Tc but not RAI [31]. Patients with GD may also present with concomitant nonfunctioning thyroid nodules (Fig. 4.3), which would warrant further investigation with FNA biopsy.

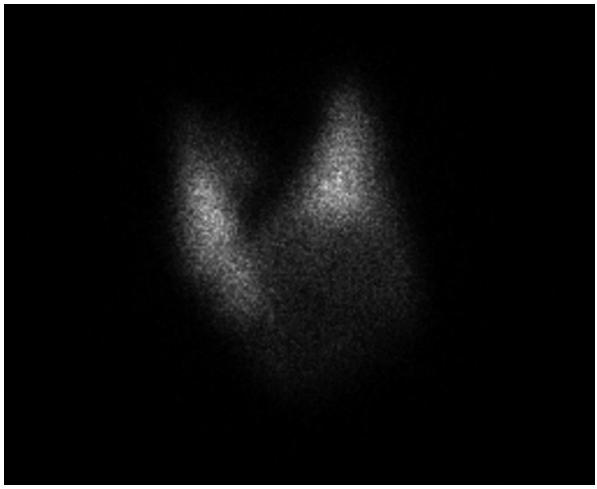

Fig. 4.3 I^{123} scintigraphy of patient with GD and nonfunctioning thyroid nodule. Note area of reduced uptake in left mid and lower thyroid lobe. This area corresponds to a palpable thyroid nodule

Ultrasonography

Ultrasound is generally not necessary in most patients with GD. However, it is essential in the assessment of patients with hyperthyroidism and palpable nodularity, particularly if such nodule(s) appears to be hypofunctioning on thyroid scintigraphy, since ultrasound-guided FNA is indicated in their evaluation. Also, sonographic assessment of blood flow may help to distinguish Graves' hyperthyroidism from painless thyroiditis [32].

Differential Diagnosis

Several conditions may result in an incorrect diagnosis of hyperthyroidism as they may present with thyroid function test abnormalities that resemble those seen in hyperthyroidism. Such conditions include the following:

Euthyroid Hyperthyroxinemia

Several conditions exist in which normal serum TSH concentrations are seen in association with elevated serum levels of total thyroxine (T4) and triiodothyronine (T3), without symptoms or signs of thyrotoxicosis. This pattern of thyroid function test abnormalities is known as "euthyroid hyperthyroxinemia." In this setting, however, free T4 concentration is generally normal. When this pattern is seen in a patient without clinical signs or symptoms of thyroid dysfunction, various thyroid-binding

protein abnormalities should be considered. The most common cause of these binding abnormalities is due to acquired thyroxine-binding globulin (TBG) excess. Physiologic increases of TBG may be seen in pregnancy, due to estrogen-induced TBG production by the liver, and may also be seen during exogenous estrogen administration (as with the use of oral contraceptives, postmenopausal estrogen replacement therapy, etc.). In these patients, a proportional increase in serum levels of total T4 and T3 concentrations is seen, but free T4 and T3 levels remain normal. Non-thyroidal illnesses, such as various forms of hepatitis, and primary biliary cirrhosis may also lead to hyperthyroxinemia due to TBG excess [33]. Other drugs that may be inconsistently associated with this pattern include narcotics (heroin and methadone), clofibrate, and the antimetabolite 5-fluorouracil [33].

In addition, several inherited abnormalities of serum thyroxine binding resulting in a similar pattern of abnormal thyroid function tests have been recognized. Familial dysalbuminemic hyperthyroxinemia (FDH) is an autosomal dominant disorder, in which there is an abnormal albumin molecule with increased affinity for T4, but not T3 [20, 33]. Affected patients have high serum total T4 but normal T3 serum levels, are euthyroid, and have normal serum TSH concentrations. Similarly, euthyroid hyperthyroxinemia may also be seen in patients with hereditary increased serum levels of thyroxine-binding prealbumin (TBPA). Thyroid-binding protein electrophoresis performed in the presence of radiolabeled T4 may be used to confirm these diagnoses.

In some patients, the presence of antibodies that bind T4 can lead to elevated serum levels of thyroxine, when T4 is measured by radioimmunoassays, because they bind to radiolabeled T4, but not T3, and patients are euthyroid because enough serum T4 remains unbound to maintain normal thyroid function. The presence of these antibodies can be confirmed by adding radiolabeled T4 to the patient's serum and precipitating the immunoglobulin fraction by the addition of polyethylene glycol [34].

Another rare cause of euthyroid hyperthyroxinemia is the syndrome of generalized resistance to thyroid hormone (GRTH), an autosomal dominantly inherited disorder, in which high serum T4 concentrations are associated with normal or slightly elevated serum TSH concentrations, due to reduced sensitivity of peripheral tissues to thyroid hormone action. These patients are often euthyroid, but some may have clinical manifestations of hypothyroidism or even hyperthyroidism, because the receptor defect can vary in different organs.

Central Hypothyroidism

Patients with central (hypothalamic or pituitary) hypothyroidism have serum FT4 levels that are low or low-normal, with serum TSH values that are usually low, but may also be inappropriately normal or rarely mildly elevated (up to 10 mIU/L). Normal or high serum TSH concentration in these patients is due to the secretion of an abnormally glycosylated form of TSH which is less biologically active, but has normal immunoreactivity [35, 36]. These patients usually have symptoms that are

similar to, but less severe than, those with primary hypothyroidism (fatigue, cold intolerance, weight gain), but a goiter is typically absent, and there is often a history of pituitary disease or evidence of other hormonal deficiencies.

Recovery from Hyperthyroidism

Patients who have been treated for hyperthyroidism and are in the recovery phase may show persistently suppressed serum TSH concentrations for several months, even when thyroid hormone (FT4, T3) levels have normalized. Also, patients recovering from thyrotoxicosis caused by thyroiditis may show similar pattern of thyroid function tests.

Non-thyroidal Illness

Euthyroid hospitalized patients with non-thyroidal illness, especially those in intensive care units and those receiving high-dose glucocorticoids or dopamine, may have suppressed serum TSH levels, with low or low-normal free T4 and very low serum T3 concentrations. These abnormalities often resolve after recovery from their non-thyroidal illness. Because of this, it is recommended that thyroid function not be evaluated in seriously ill patients unless there is a strong suspicion of thyroid dysfunction. In the majority of these patients with non-thyroidal illness, TSH is mildly suppressed, but usually not undetectable. The low serum T4 levels are generally due to reduced concentration of one or more of the thyroid hormone-binding proteins or due to the production of an abnormally glycosylated TBG that binds poorly to T4.

Back to Our Patient

This patient has evidence of thyrotoxicosis and a palpable thyroid nodule. Differential diagnosis should include Graves' disease with a nonfunctioning thyroid nodule or alternatively a hyperfunctioning thyroid nodule as the cause of the hyperthyroidism. Distinguishing between these two scenarios is important as it would have relevance for the management.

In this case, a thyroid uptake with scintigraphy would be most helpful given the presence of the thyroid nodule. This study demonstrated increased 4.5 h thyroid uptake of 45 % (6 h normal is 3–16 %), consistent with Graves' disease, and a focal area of decreased uptake in the left inferior thyroid lobe, consistent with a "cold" nodule (Fig. 4.3). A thyroid ultrasound showed a 2.2×2.9×3.7 cm lobulated solid mass with increased vascularity, occupying the inferior aspect of the left thyroid lobe (Fig. 4.4). An ultrasound-guided FNA biopsy of this nodule was performed and

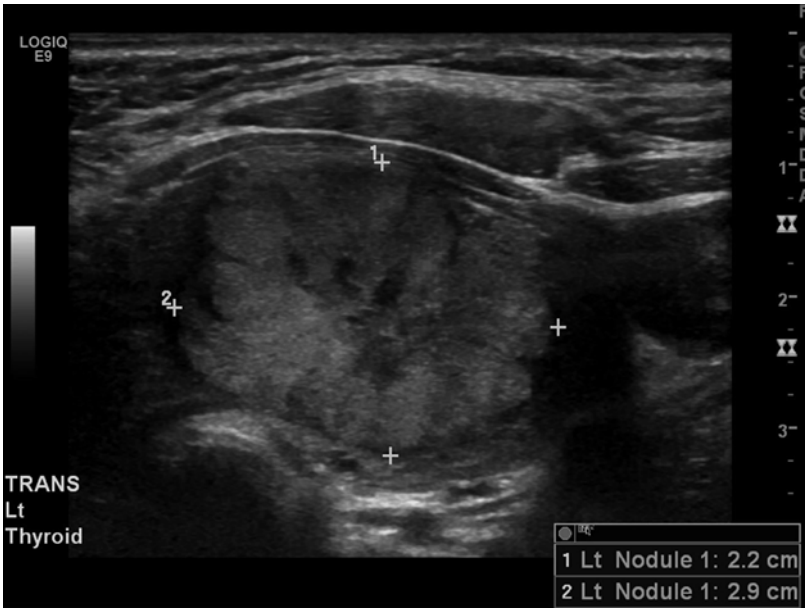

Fig. 4.4 Thyroid ultrasound of patient in Fig. 4.3 demonstrates a 2.2×2.9×3.7 cm lobulated solid mass in the left lobe of the thyroid corresponding to the hypofunctioning area seen on scintigraphy

cytology was read as "Suspicious, with cytologic features suggestive of a follicular neoplasm." The patient underwent a near-total thyroidectomy. The final histopathology revealed a minimally invasive follicular carcinoma (6×3.5×3.5 cm) grade 2 of 4, with focal capsular but no vascular invasion. The contralateral lobe showed benign thyroid parenchyma with hyperplastic changes.

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Chapter 5
Evidence-Based Discussion of Treatment Options for Graves' Disease

Juan P. Brito and Victor M. Montori

In the last 2 months, Jessica, a 24-year-old student and part-time worker, has lost her hair and has been unable to sleep. She has become increasingly anxious, irritable, and fatigued. By the time she sought care, she had lost 20 pounds and had to stop work due to fatigue. She is now sitting in the office with an endocrinologist who has confirmed the diagnosis of Graves' disease (GD). How should they discuss treatment options from an evidence-based medicine perspective? How should they select the best approach in a patient-centered way, i.e., the best treatment for this patient at this time? In this chapter, we will discuss the principles of evidence-based medicine and illustrate their application to making treatment decisions in patients with GD.

Evidence-Based Medicine

Evidence-based medicine (EBM) is an approach for the scientific practice of medicine [1]. The first principle of EBM is that more confident decisions result from having better research evidence. This principle hints at the notion of a hierarchy of evidence, in that some evidence is better able to support the decision maker's task of choosing the best course of action for a particular patient [2]. Clinicians addressing the concerns of patients with GD should understand that all evidence has limitations and that these limitations change the confidence we have in the evidence when using it to make decisions.

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Randomized clinical trials (RCTs) are frequently located on the top of this hierarchy of evidence, as they can, as a result of randomization, provide the greatest protection against some forms of bias, such as error introduced by selecting participants to receive certain treatments and not others (selection bias) by which we attribute to the treatments what is in fact a difference in the prognosis of patients who chose to receive such treatments. An example of highly reliable evidence can be found in an RCT that compared the three available treatments for GD [3]. This study demonstrated a high frequency of relapse with ATD compared to surgery or radioactive iodine. Randomized trials, particularly those that enroll few participants and follow them for brief periods, often provide accurate yet imprecise estimates about the effect of treatments on uncommon beneficial or harmful effects. Adverse effects are usually elucidated through larger observational studies that followed patients for longer periods. Such studies have their own set of limitations, such as a limited ability to control for selection bias despite ever more sophisticated forms of statistical adjustment.

A key second principle of EBM is that the best available evidence for a particular outcome is not informed solely by any single study, but rather by the accumulated evidence of all pertinent studies [2]. Using the whole body of evidence has significant advantages over using single studies even when those studies are well conducted and of high quality [4]. The assessment of the whole body of evidence rather than isolated studies brings other issues to consider the reliability of this evidence not available for inspection of each study [5]. For example, when the evidence offers a consistent answer across studies, the user gains confidence in the reliability of this estimate. When estimates from different studies are statistically pooled, the precision of the estimates is improved in a manner that also enhances their reliability (by reducing random error). Directness refers to the extent to which a study directly addresses the issues of salience in discussing treatment options with our patient. Across studies with consistent answers, we may find a range of patients, interventions, and outcomes that together give us more confidence to apply this evidence to the clinical conundrum before us.

These factors (risk of bias, consistency, directness, precision) will determine how confident the clinician is in the estimate of effect across the outcomes that matter most to the patient. When the available evidence is comprised of consistent and highly reliable studies of direct relevance to our clinical dilemma that yields precise pooled estimates for these outcomes, the clinician can have high confidence in that evidence, and this in turn can lead to confident decision making. If the confidence in the estimate is high, it implies that further research is very unlikely to change the estimate of effect. When our confidence in the evidence is low, the estimates of effect should be considered uncertain, and this likely will reduce the confidence clinicians should have in making decisions based on this evidence [1].

An important aspect of directness relates to the use of patient important outcomes rather that surrogate endpoints. Surrogate endpoints are markers of effect intended to substitute for a clinical endpoint and expected to predict clinical benefit (or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidences [6].

Surrogate endpoints are frequently seen in trials as they may change faster and to a greater extent than patient important outcomes and thus reduce the time and cost required to detect an effect from intervention. However, surrogates not always capture the effect of treatment on outcomes, especially if the disease process and treatment mechanism are poorly understood. Furthermore, surrogate markers are rarely connected with patient important outcomes [7]. An example of a surrogate marker in GD is the change in thyroid antibody titers. While this marker is useful to diagnose GD, following the titer during therapy provides little information about resolution of GD symptoms or quality of life.

For GD, the only systematic review (SR) of studies of the comparative effectiveness of GD treatments summarized 8 studies of 1,402 patients from 5 continents [8]. Table 5.1 presents the evidence table for the effectiveness of each option, and Table 5.2 presents the estimates for other patient important outcomes. The risk of bias of the included studies reduces our confidence in this evidence. Among the comparisons between treatment options, a higher relapse rate was found with ATDs than RAI [odds ratio (OR) = 6.25; 95 % confidence interval (95 % CI), 2.40–16.67] and with ATDs than surgery [OR = 9.09; 95 % CI, 4.65–19.23]. These large pooled estimates may enable us to conclude with low-to-moderate confidence that patients treated with ATD vs. RAI or surgeries have at least a threefold higher risk of relapse; more imprecise results still from studies not properly protected from bias yield only low confidence that surgery is superior to RAI. If we consider this SR a good representation of the body of evidence for the comparative effectiveness of treatments for GD, we could, for instance, state that we are somewhat confident that patients who receive RAI or surgery relapse less (~10 out of 100 patients) than patients who receive ATD (~50 out of 100 patients).

Based on this evidence, and following the first two principles of EBM, one might deduce that all patients should receive the most effective therapies, i.e., RAI or surgery. There is however a third principle of EBM, one that is often forgotten, that is very pertinent for patients like Jessica. This principle of EBM states that when making decisions, the evidence about the relative benefits and harms of the available options is necessary but not sufficient to make a clinical decision. EBM requires that the patients' perspectives, beliefs, expectations, goals for life and health, values, preferences, and contexts be considered [1].

The Treatment Options

There are three widely accepted treatments for GD: antithyroid drugs (ATD), radioactive iodine ablation (RAI), and surgery. They differ greatly in their mechanism to induce euthyroidism, as well as in their efficacy, safety, convenience, and cost [9]. Each one offers favorable and unfavorable features, such that none emerges as the best choice for all patients. Indeed, patients like Jessica, if given the choice, would face the daunting task of considering which option is the best for them:

Table 5.1 Summary of the evidence

Quality assessment						Summary of finding							
						No. of patients			Odds ratio (95 % CI)	Absolute risk for relapse			Quality
Outcome: risk of relapse	Risk of bias	Inconsistency	Indirectness	Imprecision	Magnitude of effect	ATD	RAI	Surgery		ATD	RAI	Surgery	
RAI <ATD	(1 RCT, 6 Obs.) Significant limitations	Significant inconsistency ($I^2 = 81$ %)	No serious indirectness	Moderate imprecision (wide CI)	Large, OR > 5	393/694	90/846	•	7.22 (3.26–15.98)	52 out of 100	11 out of 100	•	Moderate quality because of magnitude of effect
Surgery <ATD	(1 RCT, 7 Obs.) Significant limitations	No serious inconsistency	No serious indirectness	Moderate imprecision (wide CI)	Large, OR > 5	407/766	•	38/247	10.3 (5.2–20.2)	53 out of 100	•	15 out of 100	Moderate quality because of magnitude of effect
Surgery <RAI	(1 RCT, 7 Obs.) Significant limitations	No serious inconsistency	No serious indirectness	Moderate imprecision (wide CI includes benefit for both interventions)	Small	•	91/858	41/405	1.66 W(0.75–3.67)	•	11 out of 100	10 out of 100	Low quality because of risk of bias and imprecision

Risk of bias: refers to study limitations. For the randomized clinical trial (RCT), lack of blinding, not analyzed using intention to treat analysis, but allocation was reported appropriately. For observational studies, (Obs), limitations for ascertainment of exposure, outcomes, and comparability of the cohorts. Inconsistency: may arise from differences in the studies' designs, populations, interventions, comparisons, or outcomes. It is measured quantitatively through the I^2 statistic. The higher the I^2 statistic, the more inconsistent the body of evidence. Imprecision: refers to the width of the confidence interval around the pooled point estimate. A wide confidence interval consistent with both harm and benefit decreases our confidence in the estimate. Indirectness: refers to the idea that the evidence being evaluated is not directly applicable to the clinical scenario in any of several dimensions, including population, intervention, comparison, and outcome. When indirectness occurs, confidence in the evidence is decreased. Large magnitude of effect, the larger the magnitude of effect, the stronger the evidence for the association between intervention (or comparison) and outcome, thus increasing confidence in the evidence

Table 5.2 Summary of evidence for patient important outcomes

	Cure rate	Cost	Adverse effects	Need for lifelong thyroid replacement	Speed of recovery	Frequency of follow-up (first year)	Mild eye disease
ATD	50–60 %	$300–400	One in four patients will drop treatment due to side effects (nausea, skin rash, pruritus)	0 %	4–8 weeks	4–8 per year	Unchange
RAI	90 %	$4,000–5,000	New eye disease (15 %) Minor risk for malignancy Impair male fertility (4–6 months) Avoid pregnancy (6 months)	90 %	12–18 weeks	2–3 per year	May Worsen
SURGERY	95 %	$30,000–40,000	Permanent scar (1–2 in.) Temporal hoarseness (4 %) Permanent hoarseness (<1 %) Need for calcium pills for lifetime (1 %)	100 %	Immediately	1–2 year	Unchange

- Antithyroid drugs inhibit the synthesis of thyroid hormones. Patients take 1–3 pills daily for 1 or 2 years and see their doctor periodically to titrate the medicine and monitor for adverse effects such as elevated liver enzymes, pruritus, and low white cell count. About half of the patients after 2 years of treatment will see GD symptoms return and will need another treatment.
- Radioactive iodine destroys the thyroid gland within 6–8 weeks. Patients experience hypothyroidism and require lifelong therapy with thyroid hormone replacement. Some patients may need a second dose of treatment. This treatment could worsen eye symptoms in patients with Graves' eye involvement. The long-term safety of this treatment is not clear.
- Surgery removes the thyroid gland causing an immediate and definitive cure. Lifelong thyroid hormone replacement is needed. Between 2 and 10 % of patients may suffer severe surgical complications, such us permanent hypocalcemia and vocal cord injury.

Clinicians need to compare and contrast the benefits and disadvantages of each of the three therapies in the context of having this discussion with patients. This task is made possible by careful application of the first principles of EBM. But, as we discussed above, evidence considerations are not sufficient. Consideration of patient values, preferences, and context requires patient involvement, as patients are the only reliable experts in these matters. In fact, current guidelines for hyperthyroidism advocate for patient involvement in GD treatment decisions. The Guidelines for Hyperthyroidism of the American Thyroid Association and American Association of Clinical Endocrinologists [9], published in 2011, stated that "Once the diagnosis has been made, the treating physician and patient should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and cost."

However, this discussion may not always take place in the clinical encounter. The three treatment options offer a particular balance of preference-sensitive features, such that none emerges as the best choice for all patients. Even if we were to focus on the two options that the evidence suggests are superior on one of the outcomes (but not in other outcomes of importance to patients), relapse, we see that the path to treatment selection indicates a road less traveled: 60 % of physicians in the United States treat GD with RAI and less than 1 % treat GD with surgery [10]. The causes of this lopsided distribution are not fully known, but may reflect an unwarranted consensus, a style or standard of practice (blind to variation in informed patient preferences such as cost of treatment, side effects, and frequency of follow-up), or may reflect the distribution of preferences for treatment among patients with GD. The latter seems unlikely given that observational studies suggest that this pattern reflects clinician preferences [11]. If true, the adoption of a dominant approach prevents patient access to care options that may have represented a better fit. If true, the treatment given would have been the wrong treatment, a patient safety issue resulting from the misdiagnosis of patient preferences [12]. Thus, the goal for evidence-based care for patients with GD facing treatment options, like Jessica, is to ensure the patients and clinicians make informed decisions consistent with the

body of best available evidence (first two principles of EBM) and with the values and preferences of the informed patient (third principle of EBM). The latter task can be accomplished by the implementation of shared decision making.

How to Make Evidence-Based Decisions with Patients

The clinical encounter includes two experts: one is the clinician (expert in medical science and in the body of pertinent evidence) and the other is the patient (expert in their values, preferences, and context). A decision made by one without the other is not a quality decision and is certainly not consistent with the practice of EBM. In contrast, high-quality decision making occurs when the endocrinologist and the patient relate to and influence each other as they collaborate in making decisions [13], a process also known as shared decision making (SDM). This approach encourages the adequate and understandable delivery of information to patients and cooperative involvement of both patients and clinicians in the process of deliberation about care. SDM can result in decisions that are more congruent with patient values, preferences, and context, which in turn increase quality of life and improve the likelihood of achieving health goals [14].

It is our thesis that SDM is essential for the evidence-based treatment of GD. The fact that RAI and surgery are definitive (irreversible) and invasive makes the treatment decision a critical event. These sorts of decisions require patient engagement to ensure that the patient understands the ramifications of the decision and the fact that the consequences cannot be revised. It is important to prevent a misdiagnosis of the patient preference that could lead to the selection of the wrong treatment with consequent loss of care quality.

To ensure that high-quality, evidence-based SDM is achieved in GD, a structured approach is required. SDM, in the context of GD, must include several steps [15]: (1) uncertainty, explaining to the patient that there is no best choice and that a decision or choice has to be made; (2) sharing information, clinician provides information about the harms and benefits of each option and patients share pertinent knowledge about themselves; (3) deliberation, in light of what has been shared, a process by which true and informed patient values and preferences form; and (4) consensus about the best approach for the patient and a plan for implementation. At the end of the process, patients should be clear that a decision is necessary and that finding the best option is not a technical process, but rather one that is value-laden. They should become aware of the options; the important benefits, harms, and inconveniences of each one; and their relative likelihood. This awareness is supported by the use of decision aids (DAs). DAs are designed to help patients participate in making specific choices among healthcare interventions [16].

Many patients with GD will face limitations in understanding important medical information to make informed medical decisions. It has been estimated that the average American reads at about the eighth-grade reading level [17] and about 20 % of those that are college educated are unable to determine which risk, 1 % or

5 %, is higher [18]. It is possible, therefore, that when patients are presented with information such as *the relapse rate for GD among patients taking ATD is about 60 %*, they cannot use it to make an informed decision. Likewise, patients with GD are often told phrases like *the risk of GD relapse with ATD is high and for RAI is low*. The interpretation of high and low for the patients and physician is highly variable; for instance, a relapse of 10 % for RAI (low for the physician) may be high for a patient. Therefore, DAs help clinicians and patients by improving risk communication through the use of pictograms. Pictograms present probabilistic information in a graphical and numerical format.

DAs help elicit patients' values, preferences, and context within the decision-making process. A SR of RCTs by The Cochrane Collaboration has evaluated the efficacy of DAs [16]. Its latest update includes 115 trials and concludes that DAs increase knowledge, risk perceptions, satisfaction with the decision, and the number of patients achieving decisions that were informed and consistent with their values. For instance, a trial of a DA, *Statin Choice* [19], for patients facing the decision of whether or not to take a statin to reduce cardiovascular risk found that patients in the DA group had more participation and were more satisfied with the decision-making process. Patients also showed better understanding of the information and had a calibrated sense of their baseline risk and of their risk reduction with statins. Likewise, *Osteoporosis Choice* [20] trial tested a DA to help patients at risk of osteoporotic fractures and their clinicians discuss bisphosphonate treatment. It was shown to improve knowledge, enhance patient involvement in the decision-making process and decisional quality, and improve patient adherence to therapy at 6 months. Patients and clinicians who used the DA found it helpful. A DA for patients with GD would help patients making decisions about treatment align the decision to their values; for instance, a young woman with GD, recently married, might not choose RAI because of potential short-term impairment in fertility; a middle-aged farmer, with GD with limited access to healthcare, may want surgery because it is the option that requires the least frequent follow-up; a poorly compliant middle-aged executive may opt for RAI as opposed to daily ATD.

Despite the evidence in favor of SDM and DAs, these tools are rarely used in clinical practice, in part due to limited interest from clinicians, lack of financial incentives for use, and concerns about their effects on the length of the consultation [21]. It has also been suggested that informed patients may make decisions with negative financial impact to healthcare institutions when they choose less expensive interventions. Additionally, SDM might not always be needed in the encounter; patients sometimes want the physician to make decisions on their behalf. Others might want to make the decision without involvement of the physician [22]. Often, options for therapy include a purely technical discussion (e.g., type of stent during endovascular procedures) not amenable for SDM [13]. While noting these limitations and exceptions, SDM is undoubtedly the right path to improve patient-centered and evidence-based practice for the majority of our patients. For GD, a DA is under development by our group (Fig. 5.1 depicts the prototype of a decision aid for treatment options for patients with GD.)

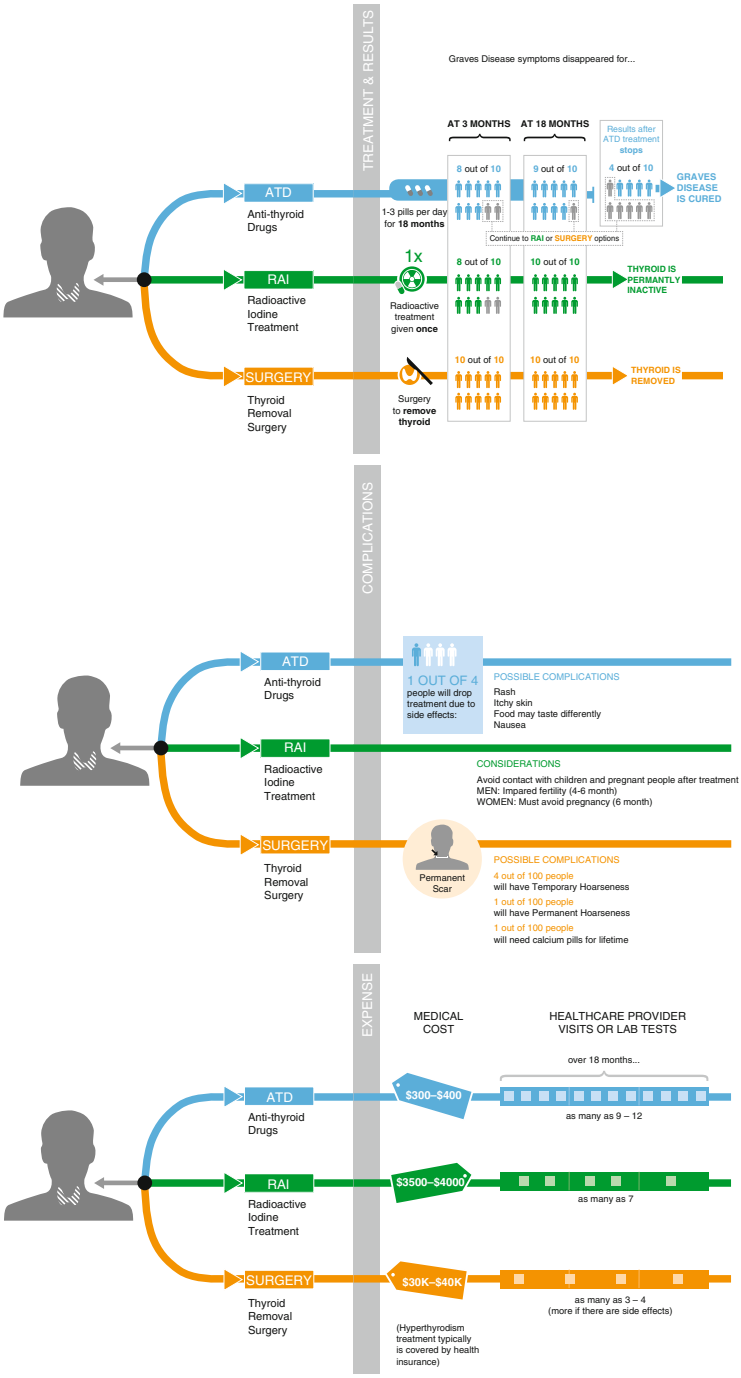

Fig. 5.1 Prototype of a decision aid for treatment options for patients with Graves' disease

Back to Jessica

The final treatment for Jessica will depend on which approach the clinician implements.

Unidirectional Approach

The clinician discusses with Jessica the three available options. He explains that surgery is an aggressive approach, and that is the reason why he does not recommend it. ATD, on the other hand, is an option he has used, but, based on his experience, a significant number of patients switched to another treatment due to the side effects. Consequently, he recommends to Jessica that she be treated with RAI as it is a definitive treatment with no significant side effects. The clinician also recognizes that Jessica is pursing pregnancy and prescribes her oral contraceptive. For Jessica, this sounds like a good idea and she proceeds with the therapy.

EBM-Informed and Shared Decision-Making Approach

The clinician explains to Jessica that there is no best choice and a decision has to be made. Using a DA, he shows Jessica the different characteristics of each treatment: failure rate, cost, adverse effects, need for lifelong thyroid replacement, speed of recovery, frequency of follow-up, and concerns with eye disease. Jessica states that she is interested in knowing more about the failure rate and the adverse effects. After hearing information about failure rates, she chooses RAI; then, the clinician describes the adverse effects, including the fact that pregnancy should be avoided for the next 6 months after receiving RAI. For Jessica, this is important as she is pursuing pregnancy. After some deliberation with her clinician, she chooses surgery. The clinician makes an appointment with surgery and decides to follow up with her after the operation.

The first approach, perhaps seen more often, completely dismisses the patient's values and only considers the clinician's input and experience. In the second approach, both experts, the clinician (the expert on the science) and Jessica (the expert on what she wants and on values), deliberate and reach a shared decision. The latter is a high-quality evidence-based decision-making process.

Conclusion: Toward Evidence-Based Endocrinology

Endocrinology is hindered by a lack of high-quality evidence, specifically high-quality evidence assessing patient important outcomes. This lack of high-quality evidence informed by patient important outcomes leaves endocrinologists and

patients facing tough decisions in which the trade-off between benefits and harms is unclear. This lack of clarity has typically been resolved using the endocrinologists' clinical acumen. While this approach is often useful, it may not be optimal as it may fail to explicitly consider patient's values, preferences, goals, and context. Without explicit consideration of these factors, endocrinology cannot claim to be patient centered or evidence based.

An evidence-based endocrinologist should be at the forefront of designing, along with patients, randomized clinical trials that assess outcomes that matter to patients. An evidence-based endocrinologist understands that the best available evidence for a particular outcome is not informed solely by any single study, but rather by the accumulated evidence of all pertinent studies. Finally, an evidence-based endocrinologist would recognize the uncertainty in the evidence and carefully assess patient's circumstances and elicit the patient's values and preferences and work together with the patient to make a decision that is informed by both the clinician's knowledge and the patient's preference.

These steps require a redesign of medical education with the integration of evidence-based medicine in the curricula as well as training in shared decision making and tools to implement it. Soon, patients with endocrine conditions such as GD will demand the care of evidence-based endocrinologists. We should be ready to response to this wonderful challenge.

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Chapter 6
Antithyroid Drug Therapy in Patients with Graves' Disease

Peter Laurberg and David S. Cooper

Abbreviations

ANCA	Anti-neutrophil cytoplasmic antibody
ATD	Antithyroid drug
CMZ	Carbimazole
MMI	Methimazole
PTU	Propylthiouracil
Tg	Thyroglobulin
TPO	Thyroid peroxidase
TRAb	TSH-receptor autoantibodies

Once the diagnosis of thyrotoxicosis has been made, the two most important considerations are the cause of the thyrotoxicosis and the choice of therapy. The differential diagnosis of thyrotoxicosis is discussed elsewhere [1]. If the condition is caused by Graves' disease, the three standard modalities of therapy are: antithyroid drugs (ATDs) for 12–18 months or long-term, radioiodine therapy (in some patients

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preceded and possibly also followed by ATD therapy for a period of time), and thyroid surgery (normally performed after ATD therapy has been given until the patient is euthyroid).

Patient and physician preferences among the three modalities vary, depending on the health care system, medical tradition, specialist availability, and population preference. Thus, exposure to radioactive substances is a major concern in some parts of the world, and less so in other countries. Radioiodine also may have adverse effects on thyroid eye disease. Surgery is associated with potential long-term complications and increased expense. On the other hand, only a minority of patients treated primarily with ATDs have a permanent remission, and this depends on a variety of factors including environmental iodine, genetics, underlying severity of disease, smoking, and other factors. Clearly, there is no treatment that is ideal for all patients, and individual patient preferences are of paramount importance. Primary ATD therapy given for a period of time is the first choice in many clinics around the world, especially in Europe, South America, and Asia, and this choice of therapy has also been on rise in the USA in recent years [2].

At the initial visit, ATDs, radioiodine, and surgical therapies for Graves' disease are discussed with the patient. Typically, primary Methimazole (MMI) therapy is recommended for most patients with a first episode of thyrotoxicosis and mild to moderate disease. Radioiodine therapy is typically recommended in patients with side effects to drugs or if hyperthyroidism relapses after discontinuation of ATD, and surgery is advised if there is concomitant hyperparathyroidism, if the thyroid gland contains suspicious nodules, is extremely large, or if ablative therapy is chosen and the patient suffers from moderate to severe Graves' orbitopathy. The aim of radioiodine and surgery is to ablate the thyroid, with the need for lifelong thyroid hormone replacement therapy. After 2 years of ATD therapy, the overall chance of a "remission" (normal thyroid function for >1 year off medication) will be in the order of 50 %, but is higher (70–80 %) in patients with milder biochemical disease, a small goiter, and unmeasurable serum TSH-receptor antibody (TRAb) at baseline, and much lower in patients with severe disease, large goiter, and very high TRAb levels.

Indications for ATD Therapy

The central indications for starting therapy with an ATD are that the patient is thyrotoxic (that is, the abnormal thyroid function tests are not caused by laboratory interferences or thyroid hormone resistance), that the thyrotoxicosis is caused by hyperthyroidism (that is, the patient suffers from thyroid gland hyperactivity and not from thyroiditis with passive release of hormones or excessive intake of thyroid hormone), that the patient is expected to tolerate the drug, and that the informed patient accepts the plan for therapy.

In patients with clinically and biochemically obvious hyperthyroidism caused by Graves' disease, therapy with an ATD is often initiated before results of all planned

investigations are achieved. If the patient has eye signs typical for Graves' disease, this is normally sufficient for diagnosing Graves' disease as the cause of the hyperthyroidism, and a clearly enlarged diffuse thyroid with a bruit from high blood flow also provides the correct diagnosis. Occasionally, the primary diagnosis of Graves' hyperthyroidism has to be changed to another cause of thyrotoxicosis and overall therapy plans changed, when all the results of diagnostic studies become available.

Contraindications to ATD Therapy

Previous severe side effects to the drugs, as discussed below, are absolute contraindications to their reuse. Moreover, Methimazole/Carbimazole (MMI/CMZ) should not be used in early pregnancy, as this may lead to birth defects in ~1/30 of exposed cases, and defects may be severe [3]. The use of Propylthiouracil (PTU) in early pregnancy may also be associated with an increase in risk (~1/40 may develop a birth defect), but defects tend to be less severe [4], and PTU use should be limited when possible. Suspicion of a nonhyperthyroid type of thyrotoxicosis, such as painless thyroiditis, is a relative contraindication, because the patient is exposed to the (limited) risk of side effects, and the drug will have no effect.

Mechanisms of Action

ATDs have been in use to treat hyperthyroidism for over half a century. Currently, MMI (or its derivative CMZ) is the drug of choice because of increased risks of hepatotoxicity and vasculitis from PTU. PTU is recommended in specific circumstances, described below.

The thionamide ATDs' primary mechanism of action is to inhibit the thyroid peroxidase (TPO)-mediated iodination of thyroglobulin (Tg), and thereby the synthesis of thyroid hormones, T4 and T3 (Fig. 6.1). The mechanism likely involves TPO-mediated iodination of the drugs themselves, with the drugs competing for oxidized iodine with the normal biosynthetic pathway, in which oxidized iodine is bound to tyrosine residues in Tg to form iodotyrosines. This could explain why ATDs are less effective in patients with high iodine intakes, and especially in patients having large amounts of intrathyroidal iodine (e.g., in type I amiodarone-induced thyrotoxicosis). There is also some evidence that the drugs inhibit the TPO-mediated intramolecular coupling reaction, whereby iodotyrosines are linked to form the iodothyronines T4 and T3.

In addition to this primary mechanism of action, PTU, but not MMI, decreases T4 to T3 conversion in peripheral tissues and in the thyroid gland itself, by inhibiting type I deiodinase [5, 6]. This effect may be important in the management of patients with "thyroid storm."

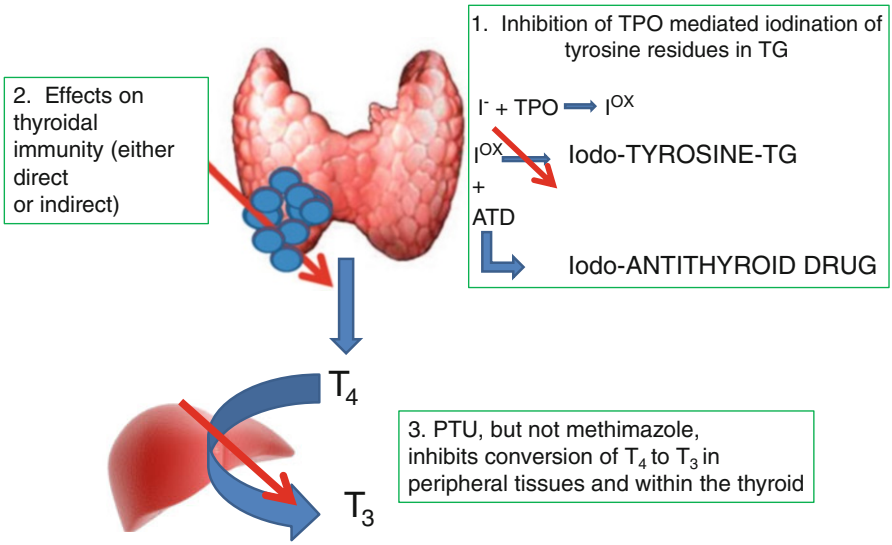

Fig. 6.1 Antithyroid drugs act in multiple ways. (1) After active transport into the thyroid, they block TPO-mediated iodination of tyrosine residues in thyroglobulin by diverting the oxidized iodine species (TPO-I ox) from the normal iodination pathway ("organification") by becoming iodinated themselves. They are not "inhibitors" of TPO in vivo. They may also inhibit the "coupling" reaction between iodotyrosines to form iodothyronines (T3 and T4) in an as yet unknown manner. (2) Antithyroid drug therapy is associated with a decline in thyroidal autoimmunity, either due to direct effects on immune cells and antigen presentation within the thyroid, or else by disrupting a dysfunctional immune system by rendering the patient euthyroid. (3) PTU, but not methimazole, inhibits T4 to T3 conversion in peripheral tissues and within the thyroid itself by inhibiting Type 1 deiodinase. It does not inhibit Type 2 deiodinase found in the brain and pituitary

Finally, ATD therapy may have immunosuppressive effects, either indirectly or directly. Some experts have proposed that the hyperthyroid state itself can perpetuate a dysregulated immune system, for example via induction of plasma cell differentiation [7] or affection of one or more among the many other mechanisms whereby thyroid hormones participate in immune system homeostasis [8]. In this construct, by making and keeping patients euthyroid, the immune system's normal tolerance to "self" is gradually restored [9]. On the other hand, there is also plentiful in vivo and in vitro evidence of multiple direct effects of ATDs on intrathyroidal immune modulatory cells [10], including effects to increase apoptosis of T lymphocytes [11] and effects on thyrocyte antigen presentation [12].

Irrespective of the mechanism, it is clear that ATD therapy is most often associated with a decline in thyroid-specific autoimmunity with a decline of circulating TRAb. Furthermore, ATD pretreatment prior to radioiodine therapy blunts the post-radioiodine rebound in circulating TRAb, thought to be responsible for worsening hyperthyroidism in the weeks and months after radioiodine treatment. This is discussed in detail later in this chapter.

Initial Doses of ATDs

The appropriate initial dose of ATD in Graves' disease depends on the biochemical and clinical severity of the disease. PTU has a less favorable pharmacokinetic profile and more side effects, and it should only be used in special situations (Table 6.1). When the difference in duration of action is taken into account, the relative activity of the two drugs is about 1:20, or in other words 5 mg MMI once daily has about the same effect as 50 mg PTU twice daily. CMZ is a pro-drug to MMI, and 10 mg of CMZ is converted in the body to yield 6 mg MMI [13]. Taking this into account, the two drugs are interchangeable.

A number of studies have addressed the effectiveness of various initial doses of MMI and PTU to normalize the thyroid function in patients with Graves' hyperthyroidism. ATDs are more effective in blocking thyroid hormone production when patients' iodine intake is low, and, conversely, the drugs' effectiveness is lower when dietary iodine is high [14]. Therefore, patients with lower iodine intakes and milder disease can quickly become hypothyroid if the dose of ATD is not tailored to the degree of biochemical disease. Based on this observation, patients with active Graves' hyperthyroidism should be advised not to take iodine containing supplements. In many populations, over the counter vitamin and mineral supplements are very popular, and GD patients should choose supplements without iodine, and they should not take supplements containing kelp.

In Europe, a multicentre study including 509 GD patients compared the effects of initial daily doses of 10 and 40 mg MMI [15]. Overall, the fraction of patients who had normalization of thyroid hormone levels at 3 weeks was 62 %, after taking 10 or 40 mg MMI per day respectively, and after 6 weeks it was 84 %. The superiority of a starting MMI dose of 40 mg per day was at the price of more patients experiencing side effects from the drug [16]. In a multivariate analysis, the time to normalization of serum T4 was shorter when patients were given 40 mg MMI, had a small or no goiter, had less elevated serum T3 at diagnosis, had no measurable TRAb, and lived in an area with a low iodine intake.

In Japan [17], a randomized prospective study comparing MMI 15 mg daily, MMI 15 mg twice a day, and PTU 100 mg three times a day concluded that MMI 15 mg daily was suitable for mild and moderate cases (Free T4 < 4.5 times above upper reference limit; 86 % had normal FT3 after 3 months), but MMI 15 mg × 2 per day was advisable for more severe cases of Graves' hyperthyroidism. PTU 100 mg three times a day was similar in effect to MMI 15 mg a day. PTU therapy resulted in more side effects than MMI, and MMI 30 mg per day was associated with more side effects than MMI 15 mg day.

Table 6.1 Indications for the use of propylthiouracil

Patient intolerant to methimazole/ carbimazole; refuses radioiodine or surgery
First trimester of pregnancy—to reduce the risk of severe birth defects
Thyrotoxic crisis to reduce T4 deiodination to T3 by deiodinase type 1

Thus, the recommended initial drug is MMI with few exceptions (Table 6.1), and the starting dose of MMI should be high enough to make patients euthyroid within a reasonable time limit (preferably 4–8 weeks); but not higher than necessary, in order to minimize the risk of iatrogenic hypothyroidism or side effects to the drug, which are dose related for MMI. The starting dose of MMI should be based on the biochemical severity; for example MMI 30 mg a day in patients with thyroid test results >2–3 times the upper reference limit, 20 mg a day if function tests are >1.5–≤2 times the upper reference limit, and 5–10 mg per day if test results are ≤1.5 times upper reference limit. No study clearly shows the superiority of splitting the initial MMI dose over the day in patients with more severe disease. On the one hand, studies on duration of TPO block suggest that a split dose may be more effective (see below); on the other hand, compliance with therapy will be better with a single daily dose regimen, and prolonged therapy with lower doses of MMI should always be given as a once daily dose.

Side Effects of Antithyroid Drugs

The vast majority of patients take ATDs without any problem. However, there are adverse reactions that can occur uncommonly, necessitating an alternate form of treatment. Most authorities divide ATD side effects into "minor" and "major" categories (Table 6.2). The minor side effects occur in 2–5 % patients, and include an itchy skin rash, GI distress, and arthralgias. Typically, these reactions occur within the first few weeks of beginning the medication. The pruritic papular skin eruption may be severe enough to require discontinuation of the drug, but in some cases it will resolve with concomitant use of antihistamines for 1–2 weeks. Switching from MMI to PTU is also a possibility, but cross-reactivity between the two drugs can occur in a minority of patients.

The "major" drug reactions are agranulocytosis, an anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis, and hepatotoxicity. It is thought that these reactions are generally mediated by immune mechanisms. Interestingly, a recent

Table 6.2 Antithyroid drug adverse reactions

	PTU	Methimazole
Minor reactions		
Fever, rash, GI distress	1–5 %	1–5 % (dose-related)
Major reactions		
Agranulocytosis	0.2–0.3 %	0.2–0.3 % (dose related)
ANCA positive vasculitis	<1 %, can occur after years of therapy. Predilection for Asians	Rare
Hepatotoxicity	1 % mild; ? 0.1–0.01 % potential life-threatening hepatocellular damage	Rare; primarily cholestatic

study suggested that patients with Graves' disease may be more susceptible to these "allergic" reactions than patients with nonimmune hyperthyroidism (e.g., toxic multinodular goiter), but this observation requires confirmation [18].

Agranulocytosis

Agranulocytosis is the most common of the major toxicities of ATDs. It is defined as an absolute granulocyte count of $<0.5 \times 10^9$/L, but most patients have extremely low counts, approaching zero. The frequency of agranulocytosis is in the range of 0.2–0.3 % and is similar for both MMI and PTU [19]. There is no dose relationship with PTU therapy, but there is a clear cut dose effect with MMI, so that this complication is extremely unusual with MMI doses in the 5–10 mg per day range [20]. Since many patients' thyrotoxicosis can be easily controlled with small doses of MMI, this should be the initial strategy for mild to moderate hyperthyroidism.

Agranulocytosis typically occurs within the first few months of initiating drug therapy, and may be more common in the elderly. It is important to recall that agranulocytosis can occur on a second exposure to the drug, typically after an interval of years, rather than weeks or months, between drug exposures [20, 21].

Some asymptomatic ATD-treated patients have been found on screening to have low white blood cell counts, suggesting that hematologic monitoring might be useful in identifying at risk patients. However, this has not been shown to be cost-effective, especially since agranulocytosis can occur quite precipitously. The typical presentation is a fulminant oropharyngeal infection with odynophagia, cervical lymphadenopathy, high fever, and malaise. Other infections, especially in the elderly, have been described including pneumonia, sepsis, and skin infections. Bone marrow examination may have predictive value, as complete absence of granulocytic precursors is associated with longer recovery times (i.e., 10–14 days).

The treatment of agranulocytosis is fairly straightforward: Immediate cessation of the ATD (and not using the other drug since cross reactivity has been described), hospitalization with broad-spectrum antibiotic coverage, and consideration of hematopoietic growth factor therapy (G-CSF or GM CSF), which has been shown to reduce the fatality rate and decrease the time of hematologic recovery [22]. Factors that predict worse outcome include older age (>65 years), lower granulocyte counts, and severe underlying comorbidities such as renal failure or cardiac or respiratory disease. Mortality rates in the 5–10 % range have been reported in recent series [23].

Vasculitis

The rheumatologic side effects of antithyroid drug therapy include both drug-induced lupus and PTU-induced vasculitis. Drug-induced lupus typically has more musculoskeletal involvement, serositis, and gastrointestinal abnormalities, whereas

vasculitis typically is associated with renal and pulmonary involvement. There is considerable overlap between these clinical syndromes, and both are associated with ANCA positivity [24]; however, pANCA (peri-nuclear ANCA) is found in both syndromes equally, while cANCA (cytoplasmic ANCA) is typically seen in patients with vasculitis. cANCA is also associated with Wegener's granulomatosis, while pANCA antibodies can be directed against a variety of proteins, typically myeloperoxidase, but also elastase, lactoferrin, and cathepsin. Cross-sectional studies have shown that 10–60 % of patients taking PTU have pANCA positivity [25, 26], but these are almost inevitably asymptomatic individuals, and the significance of this serologic finding therefore remains uncertain. Furthermore, one study showed that up to 67 % of patients with Graves' disease who had not been treated with an antithyroid drug were pANCA positive, but this antibody was directed against proteins other than myeloperoxidase [27], including cathepsin.

For unclear reasons, vasculitis is far more common with PTU therapy rather than with MMI treatment and Asian ethnicity seems to be a risk factor for its development. Interestingly, one study suggested that younger patients are more likely to develop drug-induced lupus, while older individuals may be more susceptible to drug-induced vasculitis [24]. ATD-related vasculitis typically occurs after several months of treatment, but has been reported to develop after years of treatment.

The typical presentation includes fever, polyarthritis, purpura of the acral parts of the body including the ear lobes, and, in the case of vasculitis, glomerulonephritis and/or pneumonitis (Fig. 6.2). For drug-induced lupus, recovery occurs after discontinuation of the drug, but some patients afflicted with vasculitis require glucocorticoids or other immunotherapies, including cyclophosphamide and plasmapheresis. However, in general, PTU-related vasculitis has a more benign course than idiopathic vasculitis [28].

Hepatotoxicity

It is been known for over six decades that PTU use can rarely be associated with fulminant hepatotoxicity. In contrast, MMI is rarely associated with cholestasis rather than hepatocellular dysfunction. With regard to PTU, the frequency of hepatotoxicity requiring liver transplant or resulting in death is probably in the 1/10,000 range, but milder degrees of hepatic involvement may occur as commonly as 1 % of treated patients. A recent literature review confirmed that PTU-induced hepatotoxicity occurred after a median of 120 days of drug exposure, and is not dose related [29]. Typical symptoms include malaise, nausea, jaundice, dark urine, and light-colored stools, and lethargy. Prompt recognition and discontinuation of the drug, and referral to a center capable of caring for patients with severe hepatic failure, including the availability of hepatic transplantation, is essential.

For MMI, the mean onset of hepatotoxicity in one review was 36 days [30]; once the drug is stopped, it can take many weeks for complete normalization of serum bilirubin and alkaline phosphatase levels. There have been no reported fatalities

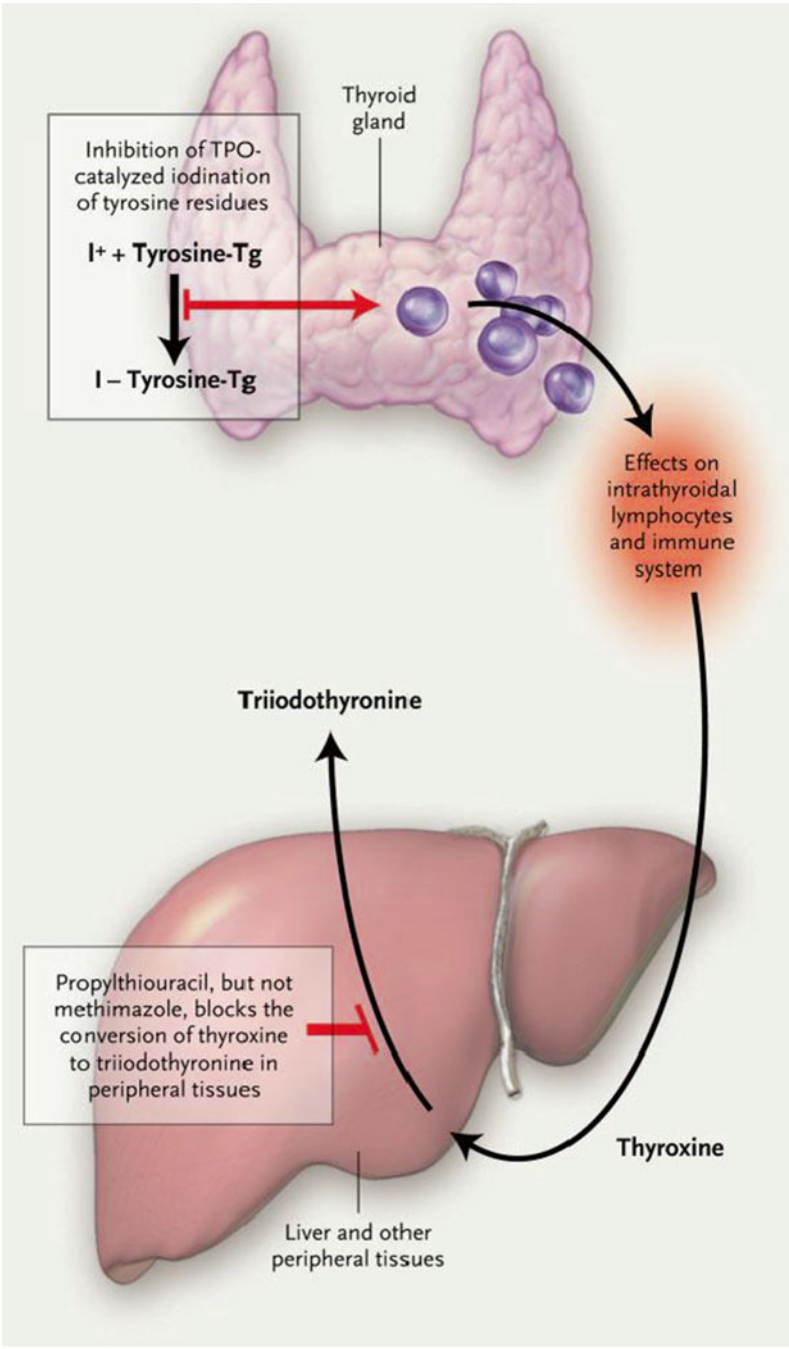

Fig. 6.2 (**a**) Multiple purpuric lesions on the face and ear. (**b**) Bilateral irregular purpuric areas on the lower legs. Lack of progression of the lesions beyond the demarcated borders illustrates their nonmigratory behavior. With permission: Chastain MA, Russo GG, Boh EE, Chastain JB, Falabella A, Millikan LE. Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. J Am Acad Dermatol. 1999;41:757–64 [68]

from MMI-related cholestasis. Treatment of the underlying hyperthyroidism in patients with ATD-related hepatotoxicity might include the use of the other drug, since the two drugs have very distinct hepatotoxicities.

Adjustment of ATD Dose During Therapy

The dose of drug should be gradually reduced as thyroid function tests normalize, and a "once a day" drug regimen should be adopted as soon as possible to improve overall compliance. MMI has a considerably longer duration of action than PTU and once daily dosing is clearly effective in nearly all patients during prolonged therapy. The reason that the dose of MMI may be split over the day in patients with severe hyperthyroidism is that MMI given once a day may not lead to effective TPO blockade for a full 24 h period. In a study of the duration of MMI's inhibition of iodine organification in the thyroid, the average percent of iodine not organified (a measure of TPO blockade) after a single 5 or 20 mg dose of MMI was after 2 h: 82 and 92 %; 6 h: 69 and 84 %; 13 h: 22 and 65 %; 25 h: 3 and 27 %, with considerable differences among patients [31]; similar results were reported in another study [32].

The adjustment of the ATD dose to give rapid normalization of thyroid function without inducing hypothyroidism requires frequent assessment of thyroid function. The frequency of thyroid function testing and ATD dose adjustment differs somewhat depending on the local organization of health care and the costs of testing. For example, in the Thyroid Clinic at The Johns Hopkins Hospital in Baltimore, USA, patients are requested to have thyroid function tests (Free T4, T3, TSH) 4–6 weeks after initiation of MMI therapy, and 4–6 weeks after any adjustment to their drug dose. Testing can be done at the hospital or at various commercial laboratories. Patients are typically seen in the clinic every 12 weeks, as dose adjustments can be made via phone calls and more recently, through electronic communication. After the first follow-up visit at 12 weeks, patients are not seen again for another 3–6 months, but laboratory testing is dose every 4–6 weeks until thyroid function is stable.

In Aalborg, Denmark follow-up would mostly be organized without seeing patients. Standard thyroid function tests (TSH, T3, and T4) would be ordered in the centralized laboratory database to be performed after 2–3 weeks of ATD therapy, and then again depending on the response to therapy. Blood sampling can be performed at all hospitals in the region or at local GPs according to the preference of patients. Results of tests will be seen by the responsible endocrinologist, and forwarded by mail to the patient with information on the ATD dose and the new approximate date of testing. The first follow-up visit after initiation of therapy will be after 2–6 months, depending on the judgement of the physician at the initial visit. In both Baltimore and Aalborg, if patients experience side effects or other problems, they can contact the clinic and be seen promptly.

The standard duration of ATD therapy at the Johns Hopkins and Aalborg clinics is 18–24 months, but patients with moderate or severe Graves' orbitopathy are offered prolonged low-dose ATD therapy [33]. All patients are instructed about pos-

sible side effects of therapy and are given written information about adverse reactions, and women of childbearing age are informed about the association between use of ATD in early pregnancy and birth defects [34].

Titration Versus Block + Replacement Therapy

When patients become euthyroid during ATD therapy, the general recommendation is that the dose of the ATD should be gradually adjusted to the lowest dose that keeps the patient euthyroid (titration therapy) [35]. A different approach is to keep the initial high dose of the ATD and to add Levothyroxine (L-T4) therapy to maintain the patient in a euthyroid state (block + replacement therapy) [36]. Theoretically, this strategy could make it easier to keep the patient euthyroid during prolonged therapy, because the high dose of ATD will prevent excess thyroid hormone secretion in the event of worsening of disease activity. Also, the risk of overtreatment leading to hypothyroidism will be lower, because of the replacement therapy that is being given. However, this regimen is not recommended [35], because the higher ATD dose increases the risk of side effects.

Even if the dose of ATD should be kept low when possible, a more cautious "partial block + replacement" is used by some physicians in an attempt to stabilize thyroid function and prevent episodes of hyper- and hypothyroidism, especially in patients with moderate to severe Graves' disease, and in those patients whose thyroid function is difficult to control on MMI alone, with episodes of both hyperthyroidism and hypothyroidism. This type of therapy implies drug titration with reduction of the MMI dose to ~5–10 mg daily, and then a gradual addition of L-T4 to keep the serum TSH around 1 mU/L [33].

ATD Withdrawal and Remission of Graves' Disease During ATD Therapy

Over a 12–24 month period of ATD therapy, the majority of patients experience some degree of resolution of the autoimmune abnormality. As noted above, it is uncertain whether this phenomenon is caused by a restoration of the euthyroid state, because hyperthyroidism itself is causing or perpetuating the disordered immune function, or if it is a direct effect of the drugs to impair organ-specific autoimmunity.

In many patients thyroid function can be kept stable using a small dose of MMI (2.5–10 mg given once daily). At that point, assuming that the TRAb has become normal, the ATD is withdrawn with the hope for a prolonged remission with no need of medication. Several studies have investigated the association between the duration of therapy and the risk of relapse after ATD withdrawal [36]. These studies have shown that a shortening of therapy duration below 1 year increases the risk of relapse, but there is no evidence that prolonging therapy to longer than 18 months will reduce the risk. Notably, a major advantage of more prolonged therapy is that the majority

of patients stay euthyroid on such therapy, even if the dose of ATD is low [33]. Accordingly, several investigators have suggested the possibility of prolonged, possibly life-long ATD therapy to patients with a high risk of relapse, and who reject ablative therapy followed by lifelong hormone replacement therapy [37, 38].

Withdrawal of ATD therapy is most commonly done by simply stopping the medication, but some clinicians gradually withdraw the medication, guided by thyroid function testing [39]. The decision to withdraw or taper medication is based on the preference of the patient after being informed about the risk of relapse, that, among other factors will depend on the length of time that the patient has been on therapy (typically 12–24 months), and also on the TRAb level (see below). In patients who are offered more prolonged ATD therapy, the dose should be kept low, to minimize the risk of ATD side effects. Moreover, because of the risk of ANCA positive vasculitis during prolonged administration, and also the small risk of severe liver failure, PTU is not suitable for prolonged ATD therapy.

Relapse of Hyperthyroidism After ATD Withdrawal

The risk of relapse differs substantially among patients depending on a number of factors (Table 6.3). Relapse risk may be as low as 10 % in patients who initially had no goiter [40], no eye signs [41], mild hyperthyroidism [42], and who had very low or unmeasurable TRAb values at the time of diagnosis [43]. On the other hand, the risk of relapse may be ~90 % if the drug is withdrawn after 1 year of therapy in patients with active moderate to severe Graves' eye disease [44], and it is also high in patients who remain TRAb positive and who had a large goiter at diagnosis [45], in patients who smoke cigarettes [46], and in children [47].

The predictive value of the patient becoming TRAb negative during therapy has been much discussed, but most recent studies have shown a clear predictive value. A typical result was obtained in a prospective Swedish study where ATD was given for 18 months, and follow-up was 3.5 years [48]. Among patients who had become TRAB negative, 29 % had relapse of hyperthyroidism, whereas the risk of relapse was 89 % in patients who were still TRAb positive at the time of ATD withdrawal

Table 6.3 Factors that increase the risk of relapse after withdrawal of ATD therapy

Childhood
Large goiter
Severe thyroid dysfunction at diagnosis
Short duration of ATD therapy
Active orbitopathy at time of ATD withdrawal
Presence of TSH-receptor antibodies at time of withdrawal
Active smoker
High iodine intake
Postpartum period

[49]. Typically, relapses tend to occur within the first 6 months after drug discontinuation, but patients can relapse at any time. The postpartum period is a time when relapse is especially common [50].

After a relapse, ATD therapy may be initiated again following the principles discussed above, or the patient may desire radioiodine therapy or surgery. As noted above, patients may develop antithyroid drug side effects, including agranulocytosis, after resuming a drug that previously had been taken without incident months or even years earlier [21]. Thus, patients should be reeducated about drug adverse reactions whenever the ATD is restarted.

A Syndrome of Persistent Thyroid Drive

A small fraction of patients treated with ATD do relatively poorly, with difficulty controlling thyroid function even if high doses of ATD are given. The clinical picture of this "syndrome of persistent thyroid drive" [51] was described in the early 1980s [52–54] and it consists typically of an increase in goiter size (with a bruit), high levels of TRAb, a relatively high serum T3 compared to the serum Free T4 level, and a clinically unstable condition.

In a prospective Swedish study, four out of 71 patients initially randomized to be treated with ATD developed this syndrome and finally underwent surgery [49]. If only serum FT4 and TSH but neither serum T3 nor TRAb are measured during ATD therapy it may be difficult to recognize such patients, and noncompliance with therapy may be erroneously suspected. The recommended therapy in such patients is surgical thyroidectomy [55] preceded by high-dose ATD plus potassium iodide therapy, or radioiodine if the patient rejects surgery. Radioiodine may be less effective in patients with severe disease [56].

Antithyroid Drug Therapy Prior to Radioiodine Treatment

Theoretically, it would be reasonable to obtain a euthyroid state prior to the administration of radioactive iodine, especially in elderly patients or in those with underlying cardiovascular disease. This is because radioiodine treatment has been associated with an exacerbation of thyrotoxicosis in the days, weeks, and months following its administration [57, 58], likely related to acute inflammation early on, and to an increase in TRAb levels weeks to months later [59].

In one meta-analysis, there was a suggestion that pretreatment with ATDs led to better outcomes, including fewer instances of atrial fibrillation and fewer fatalities, but the number of events was very small [60]. In a randomized controlled trial, in which patients received either MMI therapy to normalize thyroid function prior to radioiodine treatment or were simply given radioiodine without ATD pretreatment, patients in the pretreatment group had more stable and normal thyroid function, with

less of a tendency to have marked increases in thyroid hormone levels following radioiodine therapy [61]. In another similarly designed study, thyroid hormone levels rose after MMI was stopped, but they were always lower than the thyroid hormone levels in the non-pretreated group, and pretreated patients had better symptom scores than the non-pretreated group for the month following radioiodine treatment [62]. The lower thyroid hormone levels following radioiodine treatment in the MMI pretreated patients may be related to the observation that ATD pretreatment prevents or attenuates the rise of TRAb levels following radioiodine treatment [63].

There is some evidence to support restarting ATDs 7 days after radioiodine administration in patients considered to be at risk for cardiovascular complications, owing to the fact that thyroid hormone levels may be more stable with ATD treatment both before and after radioiodine administration [64]. Since ATDs interfere with iodine utilization by the thyroid gland, the drug must be stopped for about 3 days prior to radioiodine administration; stopping it for longer than 3 days is not necessary [65].

Based on this evidence, the American Thyroid Association recommended that ATD pretreatment should be considered for patients undergoing radioiodine therapy who are extremely symptomatic, had free T4 levels >2–3 times the upper limit of reference range, or were elderly, had underlying cardiovascular disease or other comorbidities (e.g., atrial fibrillation, heart failure, pulmonary hypertension, and those with renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease) [35]. While some studies have suggested that ATDs can interfere with the efficacy of radioiodine treatment, this may be less of a problem with MMI than with PTU [66, 67], and increasing the radioiodine administered activity by 10–15 % likely would negate this effect [60].

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Chapter 7
Radioiodine Treatment in Patients with Graves' Disease

Douglas S. Ross

History of Radioiodine

Controversy surrounds the discovery and initial use of radioiodine to treat Graves' hyperthyroidism [1]. Two Massachusetts General Hospital (MGH) physicians, Saul Hertz and J. Howard Means, collaborated with two Massachusetts Institute of Technology physicists, Robley Evans and Arthur Roberts, and were the first to study radioiodine (128-I, half-life 25 min) in animal models. Using the Berkeley, California cyclotron in 1939, Joseph Hamilton, Mayo Soley, and Ernest Lawrence made 130-I (half-life 12 h) and 131-I (half-life 8 days) and used these isotopes to study physiology in humans. Hertz and Roberts in Boston during March 1941 and Hamilton and Lawrence in Berkeley during October 1941 both treated hyperthyroid patients with radioiodine, initially with the short-lived isotope, and both reported their preliminary data at a national meeting in 1942. The Second World War interrupted Hertz' studies, and Earl Chapman took over his practice at MGH. Since non-radioactive iodine ameliorates Graves' hyperthyroidism, Hertz had initially treated his patients with radioiodine followed a few days later by supersaturated potassium iodine (SSKI). Chapman used radioiodine alone to avoid any ambiguity regarding its beneficial effect [2]. After the war, Hertz was not allowed to return to MGH. In May 1946, the Journal of the American Medical Association published two papers on the use of radioiodine to treat hyperthyroidism, one authored by Hertz and Roberts, the second by Chapman and Evans.

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Mechanism of Action

Sodium 131-I can be obtained in capsule form or in solution for administration to patients. The isotope is rapidly absorbed and transported from the blood into thyroid follicular cells, where it is organified to tyrosyl residues on thyroglobulin. Beta emissions from the isotope have a path length of 1–3 mm and result in cell damage and necrosis [3]. After an interval of approximately 8–16 weeks, most thyroid glands have been effectively ablated and can no longer produce normal amounts of thyroid hormone.

Choice of Therapy

In a survey of endocrinologists who are members of the American Thyroid Association, The Endocrine Society, or the American Association of Clinical Endocrinologists, 54 % would recommend antithyroid drugs, 45 % radioiodine, and 1 % thyroidectomy for a typical patient with uncomplicated Graves' hyperthyroidism [4]. Endocrinologists from the United States were more likely to choose radioiodine (60 %), compared to their European colleagues (13 %). Since all three options for treatment are effective, however, the choice of therapy importantly needs to incorporate the values of the patient; e.g., some patients may fear radioiodine, and others may fear surgery or side effects from antithyroid drug. The choice of therapy is discussed in detail in Chap. 5.

Contraindications

Pregnancy and nursing are absolute contraindications to the use of radioiodine. Fetal thyroid tissue is present by 10–12 weeks of gestation and would concentrate and would be destroyed by radioiodine. Cretinism or developmental abnormalities could potentially occur in such infants. Guidelines suggest that all women of childbearing age have a pregnancy test before receiving radioiodine [5]. A survey of the outcome after radioiodine was inadvertently administered to 237 pregnant women (55 of whom had therapeutic abortions) reported 6 hypothyroid infants, of whom 4 had mental deficiencies [6]. In order to limit radiation exposure to breast tissue, radioiodine should be delayed until production of breast milk ceases, usually about 6 weeks after weaning.

Use in Patients with Ophthalmopathy

Many studies including a randomized controlled trial of the three treatment options for Graves' hyperthyroidism [7] suggest that radioiodine is more likely than antithyroid drugs or surgery to be associated with new onset or worsening ophthalmopathy.

The mechanism may be transiently higher levels of thyrotropin receptor antibody following radioiodine [8]. The concurrent use of corticosteroids may prevent worsening ophthalmopathy [9]. There is not uniform agreement among experts regarding the use of radioiodine in patients with moderate or severe ophthalmopathy. Radioiodine alone, as initial therapy in patients with ophthalmopathy, was recommended by only 2 % of endocrinologists, while radioiodine with corticosteroids was recommended by 17 % of specialists [4]. The 2011 American Thyroid Association guidelines for the treatment of hyperthyroidism suggested the concomitant use of corticosteroids in patients with mild ophthalmopathy and in smokers and advised against using radioiodine in patients with moderate or severe ophthalmopathy [5]. This topic is discussed in detail in Chap. 16.

Pretreatment with Antithyroid Drugs

Radioiodine administration as initial therapy for treatment of Graves' hyperthyroidism is generally safe. The concomitant use of beta-adrenergic blocking agents helps to control symptoms and tachycardia.

There are several reasons why pretreatment with antithyroid drugs prior to radioiodine administration may be desirable. Thyroid function becomes normal on average 5.7 weeks after methimazole treatment [10], and 97 % of patients are euthyroid by 12 weeks [11]. In contrast, radioiodine takes on average 8–16 weeks before a euthyroid state is obtained, and 14 % of patients fail to respond to the initial dose and require a second treatment [12]. Therefore, hyperthyroid symptoms and the risk for hyperthyroid complications (e.g., atrial fibrillation) are ameliorated more rapidly when patients are rendered euthyroid with methimazole prior to radioiodine administration.

Additionally, chemical hyperthyroidism and hyperthyroid symptoms may transiently worsen shortly after radioiodine administration, and this can be prevented by pretreatment with antithyroid drugs [13–15]. Rarely, thyroid storm has been reported shortly after radioiodine administration, although reported episodes may be due to prolonged omission of antithyroid drug therapy prior to radioiodine [16].

The 2011 American Thyroid Association guidelines recommended pretreatment with antithyroid drugs only in elderly patients, patients who were poorly tolerating hyperthyroid symptoms, and patients whose free T4 concentrations are two to three times higher than the upper limit of normal [5]. In contrast, most patients in the United Kingdom are pretreated with antithyroid drugs [17].

Resistance to Radioiodine Caused by Antithyroid Drugs

There is controversy regarding whether the use of antithyroid drugs, specifically PTU, prior to radioiodine administration, reduces the effectiveness of radioiodine. Two retrospective studies have concluded that the use of PTU within 55 days [18] or 15 days [19] of radioiodine administration, compared to patients using

methimazole or no antithyroid drug pretreatment, reduced cure rates from 61–66 % to 24 % and from 73–78 % to 32 %, respectively. However, a meta-analysis limited to randomized trials did not include these retrospective reports and concluded that the risk of treatment failure was increased and the risk of hypothyroidism decreased, after antithyroid drug pretreatment, and that there was no difference between PTU and methimazole [20]. Regardless, higher cure rates can be achieved by administering higher doses of radioiodine [20].

Stopping Antithyroid Drugs Before Giving Radioiodine

Since antithyroid drugs prevent organification of iodine (and therefore radioiodine) to proteins in the thyroid follicular cells, they should be stopped prior to radioiodine administration. Surprisingly, radioiodine may still be partially effective even when antithyroid drugs are continued. In one study, treatment was successful in 61 % of patients in whom methimazole was stopped 8 days prior to radioiodine and in 44 % of patients who did not stop the methimazole [21]. For the majority of patients, the optimal time to stop methimazole is 2–3 days before radioiodine administration. An analysis of patients who did not receive pretreatment or who had antithyroid drugs stopped for 1 or 2 days before radioiodine administration demonstrated that uptake, uptake curves, and isotope half-life were restored to normal 2 days after discontinuing methimazole and that 87 % of patients receiving radioiodine 2 days after discontinuing methimazole were cured [22].

Discontinuing antithyroid drugs more than 2–3 days before radioiodine treatment defeats one of the reasons for pretreatment—avoiding the increase in thyroid hormone levels that can occur following radioiodine administration. In one study comparing patients whose antithyroid drug was stopped 7 days or 2 days before radioiodine, free T4 levels were increased during the week off antithyroid drugs, but not after stopping antithyroid drugs for only 2 days, while the 24-h radioiodine uptake and the outcome at 6 months and 2 years were identical in the two groups [23]. In another study, thyroid hormone levels did not increase after radioiodine when antithyroid drugs were held for 3 days prior to treatment [24].

Resuming Antithyroid Drugs After Radioiodine

While some do not resume antithyroid drugs once radioiodine is administered, because of the 6–18-week delay for radioiodine to become effective, it is common to resume antithyroid drugs 3–7 days after radioiodine treatment, to avoid exacerbation of chemical and clinical hyperthyroidism in the few weeks between administering radioiodine and before it becomes effective. In one study, patients who resumed methimazole 7 days after radioiodine treatment had free T4 index values after 3 weeks that were 6 % lower than the values at the time of radioiodine treatment, compared to patients who did not restart methimazole, whose values were 36 % higher than those at the time of radioiodine treatment [25].

Radioiodine Dose and Outcome

Low Versus High

When radioiodine was first used to treat Graves' hyperthyroidism, it was hoped that a dose could be selected that would destroy enough tissue to render the patient euthyroid, but leave enough tissue to avoid hypothyroidism. Despite the use of complex formulas [26], this hope was never realized. Low doses, especially repetitive low doses, will prolong the duration of overt or subclinical hyperthyroidism and increase complications such as reduced bone density or atrial fibrillation. Patients who initially appeared to be euthyroid after radioiodine treatment might subsequently develop recurrent hyperthyroidism or insidiously become hypothyroid. Additionally, especially in children, there is evidence that neoplasia could develop in the remaining irradiated remnant [27]. Therefore, most experts and the American Thyroid Association guidelines recommend the use of a dose of radioiodine, especially in children, that results in near complete ablation of the gland and permanent hypothyroidism [5, 28]. After higher doses of radioiodine, most patients require thyroid hormone replacement within 3 months of treatment.

Fixed Versus Calculated

There are multiple factors that can influence the effectiveness of the ablative dose of radioiodine including gland size, radioiodine uptake, the degree of hyperthyroidism (which is associated with the turnover of thyroid hormone and iodine and therefore the duration of radioiodine retention in the gland), age and renal function, and dietary iodine intake, as well as the prior use of antithyroid drugs. While some models have used elaborate dosimetry to calculate ablative doses, most centers either use a fixed dose or adjust the dose based on only two variables—gland size and the radioiodine uptake.

Calculated dose regimens use 100–200 μCi/g of thyroid tissue adjusted by the radioiodine uptake, for example:

$$150\ \upsilon\text{Ci/g of tissue} \times 45\ \text{g thyroid / uptake of } 55\ \% = 12.3\ \text{mCi}.$$

In one study using 128–155 υCi/g of tissue, 90 % of patients were cured, and 80 % became hypothyroid [12].

Low fixed doses are not as effective as higher fixed doses. Five mCi resulted in only a 67 % cure rate and 41 % permanent hypothyroidism, while 10 mCi cured 85 % and made 61 % hypothyroid [29]. In theory, fixed dose regimens would undertreat patients with low radioiodine uptake or large glands. Studies have demonstrated the dependence of successful treatment on gland size when using fixed dose regimens [30]: ablation was successful in all patients with glands less than 15 g, but success was attained in only 25 % of patients whose glands exceeded 75 g. A variable fixed dose regimen—5 mCi for small glands, 10 mCi for medium glands, and 15 mCi for large glands—compares favorably to a standard calculated dose regimen [31].

Additionally, a randomized controlled trial of a higher fixed dose (15 mCi) versus a calculated dose regimen failed to show superiority of the calculated dose regimen [30].

Radioiodine-Resistant Graves' Hyperthyroidism: High Turnover

Some patients fail repetitive radioiodine treatments because of rapid turnover of iodine and thyroid hormone. In addition to the dose administered and the size of the gland, the duration of the retention of radioiodine within the gland is an important determinate of absorbed radiation dose. The ratio of the 4- to 6-h radioiodine uptake to the 24-h radioiodine uptake has been used as a surrogate marker for radioiodine turnover. In one study, this ratio was the most important determinate of radioiodine efficacy with a 48 % failure rate if the ratio exceeded 1.0 compared to an 11 % failure rate for a ratio less than or equal to 1.0 [32]. In another study, patients with a 5- to 24-h uptake ratio greater than or equal to 0.8 had a 34 % rate of treatment failure, compared to 16 % if the ratio was less than 0.8 [33]. The authors of that study utilized "double doses" of radioiodine (200 υCi/g instead of 100 υCi/g) in patients with high turnover and demonstrated a reduction in the failure rate. Another suggested approach is to use lithium in these patients to reduce turnover [34]. Patients with large isoechoic glands also have higher radioiodine failure rates compared to patients with hypoechoic glands, 22 % versus 7 %, respectively [35].

Dosing in Patients with Renal Failure

Because radioiodine is cleared by the kidneys, the use of high-dose radioiodine in treating patients with thyroid cancer is problematic, since lethal bone marrow exposure could occur with standard dose regimes. Fortunately, the doses used to treat hyperthyroidism do not approach maximal permissible exposures to bone marrow and other organs [36] and do not require adjustment. However, since iodine is concentrated in the dialysate, for patients receiving hemodialysis, radioiodine administration should be administered a minimum of 10 h before a dialysis treatment and is usually given shortly after a dialysis session, 24–48 h prior to the next session.

Treatment Failure: Repeat Treatment with Radioiodine

Failure of the first dose of radioiodine to achieve either a euthyroid or hypothyroid state occurs in 14 % of patients [12]. There is no fixed rule for when a second treatment should be administered. In one study utilizing a fixed dose of 11.8 mCi of radioiodine (not all patients had Graves' disease), hypothyroidism occurred before 8 weeks in 16 % of patients, after 8 and before 16 weeks in 46 % of patients, after 16 and before 24 weeks in 24 % of patients, and after 24 weeks in 14 % of patients

[37]. In addition to assessing thyroid hormone levels, the extent to which the goiter has regressed also correlates with a successful ablation. For example, a patient who remains chemically hyperthyroid 3 months after radioiodine, and whose gland has not regressed, might be retreated early, while a patient who remains mildly hyperthyroid 3 months after radioiodine, but whose gland has reduced to a normal or subnormal size, should be followed for another 4–8 weeks, as the success of the ablation may be delayed. Most of the patients who fail the first dose respond to a second dose of radioiodine, but rare patients may require 3 or more doses. One should question patients regarding iodine ingestion and iodine exposures (if using a fixed dose) and consider the possibility of rapid turnover in patients who fail one or more radioiodine treatments. An occasional patient who remains minimally hyperthyroid following radioiodine may be treated with nonradioactive iodine (e.g., SSKI) to avoid a second radiation exposure (see below).

Adjunctive Use of Beta-Adrenergic Blocking Agents

In patients who are not pretreated with antithyroid drugs, radioiodine may have little effect on thyroid hormone levels for the first 4–8 weeks or longer. During that time, chemical hyperthyroidism and/or hyperthyroid symptoms may transiently worsen before getting better. Unless there are contraindications, the use of beta-adrenergic blocking drugs should be administered to reduce symptoms and prevent complications [38].

Adjunctive Use of Lithium

Lithium prolongs the retention of radioiodine in thyroid tissue and in theory could increase the effectiveness of radioiodine or permit the use of lower doses. Several studies have reported higher cure rates and shorter duration to cure, when lithium at 800–900 mg per day was given with or before radioiodine administration [39, 40]. Additionally, lithium prevents the rise in free T4 when antithyroid drugs are discontinued prior to radioiodine administration [41]. However, a large randomized controlled trial failed to show a benefit of adjunctive lithium [42]. And 10 % of patients treated with lithium may experience adverse side effects including nausea, vomiting, or diarrhea [42].

Adjunctive Use of Iodine

Uptake of iodine into thyroid follicular cells is normally autoregulated: high intracellular levels reduce further transport of iodine uptake into follicular cells. Iodine ameliorates Graves' hyperthyroidism by interfering with its own uptake as well as inhibiting release of thyroid hormone. In selected patients who might have been

good candidates for pretreatment with antithyroid drugs had they not had contraindications, the use of supersaturated potassium iodine (SSKI) commencing 1 week after radioiodine administration shortens the interval before achieving a euthyroid state by several weeks [43].

The inhibitory effect of iodine on thyroid hormone synthesis and release is increased after radioiodine exposure [44]. In patients who remain minimally hyperthyroid following a first dose of radioiodine, the hyperthyroidism may be ameliorated by a drop or two of SSKI daily for as long as several years, and the patient may be able to avoid a second radiation exposure.

Low Iodine Diet

When radioiodine is used to treat patients with thyroid cancer, patients are instructed in a low iodine diet, since remnant radioiodine uptake is usually quite low. In contrast, patients with Graves' hyperthyroidism generally have high radioiodine uptake, and the use of low iodine diets is unnecessary. It is prudent, however, to question patients regarding the use of seaweeds, kelp, or other iodine-containing supplements (which may have been recommended by alternative healthcare practitioners), topical iodophors including iodine-containing douches, or recent iodinated radiocontrast exposures, since these and other high iodine exposures may reduce the radioiodine uptake and result in treatment failure. Similarly, recent radiocontrast may significantly lower the radioiodine uptake for up to several weeks. In such patients, using a calculated dose regimen rather than a fixed dose regimen may be preferable.

Patient Management After Radioiodine

Monitoring After Radioiodine

Patients require close monitoring of thyroid function following radioiodine administration, since they might develop transient exacerbation of hyperthyroidism, they usually develop hypothyroidism over the following 6–18 weeks, they occasionally develop transient euthyroidism or even hypothyroidism followed by recurrent hyperthyroidism, and they may have persistent hyperthyroidism (treatment failure). Patients are usually reassessed at 4–8-week intervals until chemically stable.

Hyperthyroidism results in suppression of the pituitary-thyroid axis, and once suppressed, pituitary TSH production may remain subnormal for up to 2 months or occasionally longer [45, 46]. It is therefore critical to assess patients with serum free T4 measurements in the weeks following radioiodine administration, since the TSH level may well remain subnormal, even though the patient is chemically and symptomatically hypothyroid with low free T4 concentrations [46]. Serum T3 levels may also be useful in a patient with low or normal free T4 and low TSH to distinguish between persistent T3 toxicosis and transient "central hypothyroidism" after

radioiodine. Since these patients are all known to be recently hyperthyroid, once hypothyroidism is diagnosed, treatment with a full replacement dose based on body weight is appropriate, but close monitoring remains essential since a rare patient will develop recurrent hyperthyroidism.

Long-Term Outcomes and Patient Satisfaction

Even patients who receive low-dose radioiodine treatment and achieve euthyroidism subsequently become hypothyroid at a rate of 2–3 % a year [47]. Once patients have achieved a stable TSH level on a stable dose of thyroid hormone, monitoring can be reduced to every 6–12 months. In the randomized trial of radioiodine, surgery, or antithyroid drugs for the treatment of Graves' hyperthyroidism, patients were equally satisfied with their outcomes shortly after treatment, as well as 14–21 years later [48].

Radiation Precautions

Patients who receive radioiodine may expose household and workplace contacts to radiation, as well as the general public, due to radiation in their saliva or urine or emitting directly from their bodies. Recommendations for minimizing harm to contacts have been inconsistent and have varied among states and countries. In 2011, the American Thyroid Association published recommendations based primarily on calculation of exposures and dose limits established by the Nuclear Regulatory Commission [49]. For example, patients are instructed to sleep alone for 3 days after 10 mCi or 6 days after 15 mCi; this is increased to 15 and 18 days, respectively, if sleeping with a pregnant woman or a child. The limit for sitting next to a nonpregnant adult (e.g., on a bus, on an airplane, or in the workplace) is 5.9 and 3.9 h on the day of treatment after 10 or 15 mCi, respectively, and increases to 9.2 and 6.1 h on the first day after treatment and 13.0 and 8.7 h on the second day after treatment with 10 or 15 mCi, respectively.

In Europe, the recommended exposure limits are tenfold lower than in the United States. As a result, precautions are recommended for approximately 1, 2, and 3 weeks after 5, 10, or 15 mCi of radioiodine [50], and some countries require that the patients be admitted to the hospital because of public safety concerns.

Pregnancy After Radioiodine

An arbitrary recommendation to delay pregnancy for 4–6 months after radioiodine is not supported by data, and probably one menstrual cycle is sufficient to allay any concern regarding the radiation exposure to the eggs. However, it usually takes 4–6

months after radioiodine therapy to ascertain that the hyperthyroidism is cured and the hypothyroidism is adequately treated and that serum levels of thyroid hormone are stable and optimal for a pregnancy. The dose to the ovary after radioiodine treatment for hyperthyroidism is about 3 rads, similar to that received from a hysterosalpingogram or a barium enema [51]. Birth defects are not more common in the offspring of children and adolescent who received radioiodine [52]. Theoretical risks of genetic damage suggest a risk of 0.005 %, which compares to the spontaneous risk of 0.8 % [53].

Gonadal Function in Men

Transient reductions in serum testosterone concentrations are seen after radioiodine, but no change in FSH. Sperm motility is impaired in hyperthyroid men and improves after radioiodine; there is no change in sperm concentration or morphology [54]. It is prudent for men to wait at least 3 months after receiving radioiodine before trying to impregnate their partner, thus allowing for complete turnover of the sperm exposed to the radioiodine.

Cost

While the average dose of radioiodine costs approximately $ 400–$ 800, facility charges for a nuclear pharmacy and radiation safety programs add considerably to the total costs. In an analysis that took into account laboratory tests, office visits, imaging, and complications, the cost of treating a patient with radioiodine for Graves' disease based on 2007 Medicare reimbursement rates was 23,610 compared to $33,195 for a thyroidectomy [55]. This does not include the costs of missed work or childcare, which might be necessary to comply with radiation safety requirements.

Adverse Effects

Radiation Thyroiditis and Thyroid Storm

One percent or fewer patients who receive radioiodine develop a radiation thyroiditis. This results in severe thyroid pain, which can be associated with dysphagia, and may last as long as 3 weeks. Transient recurrent laryngeal nerve dysfunction and hypoparathyroidism have also been described after radioiodine [53]. Nonsteroidal anti-inflammatory drugs usually provide adequate pain control, but some patients require corticosteroids.

Radiation thyroiditis might also be associated with exacerbation of thyrotoxicosis, especially if thyroid hormone stores were not first depleted by pretreatment with antithyroid drugs. Treatment with prednisone may limit the exacerbation of chemical hyperthyroidism.

Increase in Thyrotropin Receptor Antibodies

Thyrotropin receptor antibodies (TRAb) may increase after the administration of radioiodine, while they tend to fall after surgery and during the administration of antithyroid drugs [56]. It is likely that this is the mechanism for initiation or exacerbation of ophthalmopathy after radioiodine therapy. While fetal hyperthyroidism from transplacental passage of TRAb is rare, in theory this might occur with increased frequency in women who become pregnant within a few months of radioiodine treatment [57].

Cardiovascular Events and Mortality

Several studies suggest that radioiodine therapy is associated with increased cardiovascular events and mortality; however, it is difficult to ascertain whether the adverse outcomes are attributable to the radioiodine treatment or the underlying hyperthyroidism. Three studies from the same group of investigators have reported excess mortality in patients receiving radioiodine. In their first study, the standardized mortality ratio (SMR) was 1.1 (95 % confidence interval 1.1–1.2), but most of the excess deaths occurred in the first year following treatment [58]. In another study, the increased mortality occurred only in patients who did not become hypothyroid or in patients prior to thyroid hormone therapy [59]. In their third study, the SMR was 1.30 (95 % confidence interval 1.05–1.61) during treatment with antithyroid drugs and 1.24 (1.04–1.46) prior to thyroid hormone replacement therapy, but it was no longer increased once the patient was treated with thyroid hormone replacement [60]. While these data suggest that the excess mortality after radioiodine is related to hyperthyroidism per se, another study found higher rates of hospitalization for atrial fibrillation, cerebrovascular disease, hypertension, and heart failure after radioiodine, and these rates remained elevated for 35 years after radioiodine treatment [61].

Carcinogenesis

In the United States, the Cooperative Thyrotoxicosis Therapy Follow-up Study has followed 35,593 patients from 26 centers with a mean follow-up of 21 years. There has been no increase in overall cancer mortality [62, 63]. A small increase in thyroid

cancer was observed in patients who received radioiodine for toxic nodular goiter. It is uncertain whether this is due to the radioiodine or the known increased risk of thyroid cancer in nodular thyroids.

In the United Kingdom, despite no overall increased cancer mortality among 7,417 patients, there was an increased incidence of thyroid cancer and cancer of the small bowel [64]. A small study from Finland of 2,793 patients found an increased risk of breast, stomach, and kidney cancer [65].

Use in Children and Adolescents

The use of radioiodine in adolescents generally parallels treatment considerations in adults. Children with Graves' disease present additional considerations. It is well established that low levels of radiation exposure predispose to thyroid neoplasia in children through age 20 [66]. However, the risk appears to be greatest for exposures from the thyroid equivalent dose of 30 υCi/g of tissue or less and not the ablative doses used to treat Graves' hyperthyroidism [5, 67]. In the Cooperative Thyrotoxicosis Therapy Follow-up Study, there was no increase in thyroid neoplasia in adults with Graves' disease treated with radioiodine [27]. However, almost 30 % of children who received 50 υCi of radioiodine per gram of thyroid tissue developed thyroid adenomas, but children who received 100–200 υCi/g did not have an increased risk of neoplasia [67]. Thus, it is particularly important in children to use higher ablative doses of radioiodine to prevent thyroid neoplasia.

Whole body radiation exposure is also a concern in children. Using phantom modeling, the estimated whole body radiation exposure was 0.85 rem/mCi for adults, 0.9 rem/mCi for adolescents aged 15, and 1.45 and 2.4 rem/mCi for children aged 10 and 5 years, respectively [5]. The corresponding estimated relative lifetime cancer risk for a 15 mCi dose was 1.02 for adults, 1.04 for adolescents, and 1.08 and 1.16 for children aged 10 and 5 years, respectively. Small long-term studies have failed to show an increased risk in children treated with radioiodine [68]. Nonetheless, based on the above theoretical concerns, radioiodine was not recommended by the American Thyroid Association for children under age 5 and was felt to be an acceptable treatment for children between age 5 and 10 only if the calculated fully ablative dose was under 10 mCi [5]. In the United Kingdom, the use of radioiodine among those under age 21 has increased from 0.2 to 1.5 % of all treatments between 1990 and 2008 [69].

Conclusions

Radioiodine has been used successfully to treat Graves' hyperthyroidism for almost seven decades. Its safety has been well established, but its use in the United States has fallen slightly, likely because of the possibility that it will exacerbate

ophthalmopathy. Radiation precautions and childcare issues also provide obstacles to its use. Until we have an effective treatment that reverses the underlying pathophysiology of Graves' disease, radioiodine will remain one of the three mainstays of treatment, all of which are effective, none of which are ideal.

Checklist for Radioiodine Therapy for Hyperthyroidism

Pretreatment
Beta-blockers for most patients
Antithyroid drugs for patients at increased risk of hyperthyroid complications
Elderly, severe symptoms, free T4 more than 2–3 times upper normal
Stop antithyroid drugs 2–3 days before treatment
Pregnancy test when appropriate
Patient not lactating
Measure radioiodine uptake in a patient with recent or ongoing iodine exposure
Patient can comply with radiation safety precautions
Ask about young children or pregnant women in the home
Ask about proximity to co-workers
Ask about urinary incontinence
Restart antithyroid drugs 3–7 days after treatment in most pretreated patients
Consider prophylactic steroid coverage in patients with ophthalmopathy
Especially smokers
Monitor free T4 and TSH every 4–8 weeks until "cured" and stable
Antithyroid drugs can usually be stopped between 8 and 16 weeks after radioiodine
Levothyroxine is started when free T4 becomes subnormal (TSH may still be low)
Watch for occasional patients who are transiently eu- or hypothyroid, then relapse
Retreat by 12–18 weeks if goiter and moderately severe hyperthyroidism persist
Consider measurement of the 6-h/24-h radioiodine uptake ratio

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Chapter 8
Thyroidectomy in Patients with Graves' Disease

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Introduction

Thyroid surgery has a long, rich, and colorful history; it began as a highly mortal operation, but with the development of surgical science, including instrumentation, anatomy, anesthesia, antisepsis, and ultimately experience, it has evolved into a commonly performed procedure that is safe when performed by an experienced operator. Thyroidectomy was first described as early as the twelfth and thirteenth centuries AD, with descriptions of the use of setons, hot irons, and caustic powders, often with fatal results. As late as 1886, the American surgeon Samuel Gross wrote "…can the thyroid gland…be removed with a reasonable hope of saving the patient? …every stroke of a knife will be followed by a torrent of blood…no honest and sensible surgeon would ever engage in it…" [1]. Theodor Billroth, the premier surgeon of the nineteenth century, had a mortality rate of 40 % while performing his first 20 thyroidectomies, leading him to abandon the practice; when he resumed performing thyroid surgery after substantial improvements had been made in surgical instrumentation, antiseptics, and anesthesia, he was able to reduce his mortality

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rate to 8.3 %. He subsequently became one of the most experienced thyroid surgeons in the world. Theodor Kocher, known as the "Father of Thyroid Surgery," became the first surgeon to win the Nobel Prize in Medicine for his work in the "physiology, pathology, and surgery on the thyroid gland." He had an initial mortality rate of 12.8 % after his first 101 thyroidectomies; at the time of his death in 1917, he had performed approximately 5,000 thyroidectomies, with a reported mortality rate of just 0.5 % [2].

The American surgeon William Stewart Halsted visited Kocher at the Bern clinic in Switzerland in 1899 and implemented many of his techniques for thyroidectomy upon his return to the United States. By 1907, Halsted had performed 90 operations for Graves' disease, with a mortality rate of approximately 2 %. Charles Mayo reported his series of 234 patients with thyrotoxicosis in 1908; like Halsted, he incorporated techniques of thyroidectomy from Kocher, including unilateral or bilateral thyroid pole vascular pedicle ligation as a preliminary step to thyroidectomy in patients with severe thyrotoxicosis. In collaboration with Henry Plummer, his endocrinology counterpart on the Mayo Clinic thyroid team, Mayo began to use iodine in the preoperative preparation of patients with hyperthyroidism, resulting in a decrease in operative mortality to <1 % and a decrease in the incidence of multistage operations from over 50 % to 2 % [1].

In addition to the achievements of Plummer and Mayo in lowering the incidence of multistage thyroidectomy, the extent of thyroid surgery also evolved in the late nineteenth and early twentieth centuries. Anton Wolfler, who was Billroth's first assistant, detailed the effects of damage to the recurrent laryngeal nerve and of the postoperative effects of tetany; in 1891, Eugene Gley first reported that tetany was due to the (inadvertent) removal of the parathyroid glands or interference with their blood supply. Jan Mikulicz, a Polish surgeon, first described a "partial resection" of the thyroid to avoid injury to the recurrent laryngeal nerve, writing "I extirpated… the second lobe, only in part, resecting in such a manner that a portion of the lobe remained in the neighborhood of the inferior thyroid artery…I ventured to do this because I had observed that [it]…could be accomplished without evil consequence" [1]. In doing so, Mikulicz demonstrated the technical feasibility of a partial or subtotal thyroidectomy. The works of these early pioneers in thyroid surgery have laid the foundation for contemporary thyroid surgery and the surgical management of patients with Graves' disease.

Indications for Surgery in Patients with Graves' Disease

The principle treatment options for Graves' disease include antithyroid medications (including beta blockers, for the management of cardiovascular sequelae of hyperthyroidism), radioactive iodine (RAI) therapy, and surgery (thyroidectomy). The goal of antithyroid medications, such as methimazole, propylthiouracil, or carbimazole, is to restore euthyroidism while awaiting resolution of the

autoimmune process and remission of the hyperthyroid state. In contrast, the goal of RAI and thyroidectomy is to induce a state of hypothyroidism, to be followed by thyroid hormone replacement. Each of these options has been shown to be an effective treatment strategy, and the decision to proceed with one modality over another is often the result of geographic location, cultural considerations, patient preference, and the general feasibility (risks, benefits, and logistics, including access to experienced surgical care) of the different treatment options [3–6]. For example, in one survey of members of the American Thyroid Association (ATA), European Thyroid Association (ETA), and Japan Thyroid Association (JTA), RAI was the first-line treatment modality for the majority of ATA respondents (69 %), compared to 22 and 11 % of respondents from the ETA and JTA, respectively; similarly, while 77 and 88 % of ETA and JTA respondents chose antithyroid medications as the first-line therapy, only 31 % of ATA respondents did [3]. A more recent survey of members of the Endocrine Society (TES), ATA, and the American Association of Clinical Endocrinologists (AACE) has shown that antithyroid medications are the preferred mode of therapy for patients with uncomplicated Graves' disease, chosen by 53.9 % of respondents, compared to RAI (45.0 %) or thyroidectomy (0.7 %) [4].

Guidelines for the management of patients with hyperthyroidism and other forms of thyrotoxicosis were issued by the ATA and AACE in 2011. They state that "patients with overt Graves" hyperthyroidism should be treated with any of the following modalities: ^{131}I therapy, antithyroid medication, or thyroidectomy (recommended rating: strong, with moderate quality of evidence) [7]. However, there are certain circumstances that may warrant preference for surgery rather than use of antithyroid medications or RAI. If surgery is chosen, thyroidectomy by a high-volume thyroid surgeon is recommended [7]. Absolute indications for surgery include patients with thyroid nodules that are suspicious/diagnostic of malignancy, large goiters causing symptomatic compression, coexisting hyperparathyroidism requiring surgery, females planning pregnancy in <4–6 months, and persistent disease despite previous treatment with antithyroid medications and/or RAI. Surgery is also suggested for those patients who may prefer or require rapid control of symptoms; this includes patients for whom antithyroid medications are not effective, who have a contraindication to antithyroid medications, and in whom a persistent, prolonged hyperthyroid state is not desirable, such as those with significant cardiac comorbidities [7, 8].

Relative indications for surgery in patients with Graves' disease include patients with a large goiter (without significant compressive symptoms) and/or concomitant thyroid nodules with benign cytology, patients with moderate-severe Graves' ophthalmopathy, those who are poorly compliant with antithyroid medications or who have a fear of radiation exposure with RAI, and children with Graves' disease. Absolute contraindications to surgery include severe patient comorbidities, such as cardiopulmonary disease, end-stage cancer, or other disorders that may shorten the patient's life expectancy and/or place the patient at risk for increased operative morbidity and mortality [7].

Surgery for Graves' Disease in Pregnancy

Pregnancy is a relative contraindication to elective surgical procedures; when necessary, surgery is optimally performed in the latter portion of the second trimester, given the teratogenic effects of anesthesia and increased risk of fetal distress or loss in the first trimester and the increased risk of preterm labor/delivery in the third trimester. However, for pregnant patients in whom rapid control of hyperthyroidism is desired and in whom antithyroid medications are not effective and/or cannot be used, surgery should be performed [7, 9, 10]. It is recommended that TSH receptor antibody titers be obtained at the time of surgery to assess the potential risk of fetal hyperthyroidism and that patients be given beta blockers and iodine solution preoperatively [10].

Surgery for Graves' Disease in Children

Pediatric Graves' disease accounts for 10–15 % of pediatric thyroid disease, with an overall incidence of 0.1–3 per 100,000 children and a peak incidence at 10–15 years [11]. The treatment modality of choice in children diagnosed with Graves' disease remains antithyroid medications, preferably methimazole. However, if euthyroidism is not established within 18–24 months of initiating therapy, there is a lower likelihood of remission and decreased compliance with medications with longer periods of watchful waiting; as a result, debate has centered around the use of RAI or surgery for definitive management, with the ultimate goal of achieving hypothyroidism [11]. Concerns regarding the use of RAI include potential long-term risks of developing a secondary malignancy (thyroid and other locations, such as brain, renal, stomach, and soft tissue) and hyperparathyroidism, as well as higher risks of recurrent hyperthyroidism compared to patients undergoing total thyroidectomy [11, 12]. Surgery affords the opportunity for definitive therapy with rapid resolution of hyperthyroidism and extremely low risk of recurrent disease. Given the small size of the parathyroid glands and recurrent laryngeal nerve in children, pediatric thyroidectomy can be associated with a greater risk of endocrine-specific complications such as recurrent laryngeal nerve injury or permanent hypoparathyroidism, with significantly more devastating effects on development and quality of life; however, in the hands of experienced thyroid surgeons, these risks are minimized [12–15].

Current ATA/AACE guidelines recommend consideration of RAI or thyroidectomy in pediatric patients with Graves' disease who are not in remission after 1–2 years of therapy with methimazole. Thyroidectomy is recommended in patients <5 years and should be considered more strongly in those with larger thyroid glands. If thyroidectomy is chosen, total thyroidectomy should be performed by high-volume thyroid surgeons; referral should be made to a high-volume thyroid surgery center if local pediatric thyroid expertise is not available [7].

Surgery as First-Line Treatment for Patients with Graves' Disease

To date, there have been no randomized, clinical studies that indicate that one treatment modality (antithyroid medications, RAI, or surgery) is superior to others. Thyroidectomy can be an effective treatment modality for patients with Graves' disease, however, because of the rapid correction of the hyperthyroid state (2–4 weeks, compared to the 6 weeks to 6 months required for both antithyroid medications and RAI to reach maximal effect), low risk of recurrence, and acceptably low rates of morbidity and mortality when performed in experienced hands [12, 13, 16–23].

A recent, retrospective, single institution study examined 56 patients with Graves' disease who underwent 58 thyroid procedures, including 32 (55 %) patients who underwent total thyroidectomy, 24 (41 %) patients who underwent subtotal thyroidectomy or thyroid lobectomy, and 2 (3 %) patients who underwent completion thyroidectomy. Of these, thyroidectomy was performed for persistent disease despite medical therapy in 47 % of patients and failed RAI in 16 % of patients. Overall, there was no difference in postoperative complication rates between patients who underwent total or subtotal thyroidectomy. Transient symptomatic hypocalcemia occurred in 6 (11 %) patients; only 1 (2 %) patient had hypocalcemia lasting >6 months. No patient had a permanent recurrent laryngeal nerve injury. The median follow-up was 9 months (range 1–96), and four patients developed recurrent hyperthyroidism; all four (6 %) patients were in the group that had subtotal thyroidectomy [16]. Phitayakorn et al. reviewed a 25-year history of surgery for Graves' disease at a single institution; of 300 patients who underwent surgery, total thyroidectomy was performed in 210 (70 %) patients; the remaining patients underwent subtotal thyroidectomy. The authors, similar to Liu et al., showed no differences in surgical morbidity between the two groups (hematoma, readmission, infection/seroma, or temporary or permanent rates of recurrent laryngeal nerve injury or hypoparathyroidism) [24].

Several recent meta-analyses and systematic reviews have been performed to examine the outcomes among the different treatment options for Graves' disease. Through a systematic review and network meta-analysis, Sundaresh et al. sought to identify relapse rates of the different treatment options and included eight studies with 1,402 patients from five continents [25]. Mean follow-up was 57 months in patients treated with antithyroid medications, 64 months for RAI, and 59 months following surgery. Overall, despite a moderate-high risk of bias noted in the analysis, patients treated with antithyroid medications had higher relapse rates (52.7 %; 352 of 667) than those undergoing RAI (15 %, 46 of 304; odds ratio [OR] = 6.25, 95 % confidence interval [CI], 2.40–16.67) or surgery (10 %, 39 of 387; OR = 9.90, 95 % CI, 4.65–19.23) (Fig. 8.1). There was no difference in relapse rates between RAI and surgery in this review, although the surgical studies included patients undergoing both subtotal and total thyroidectomy [25].

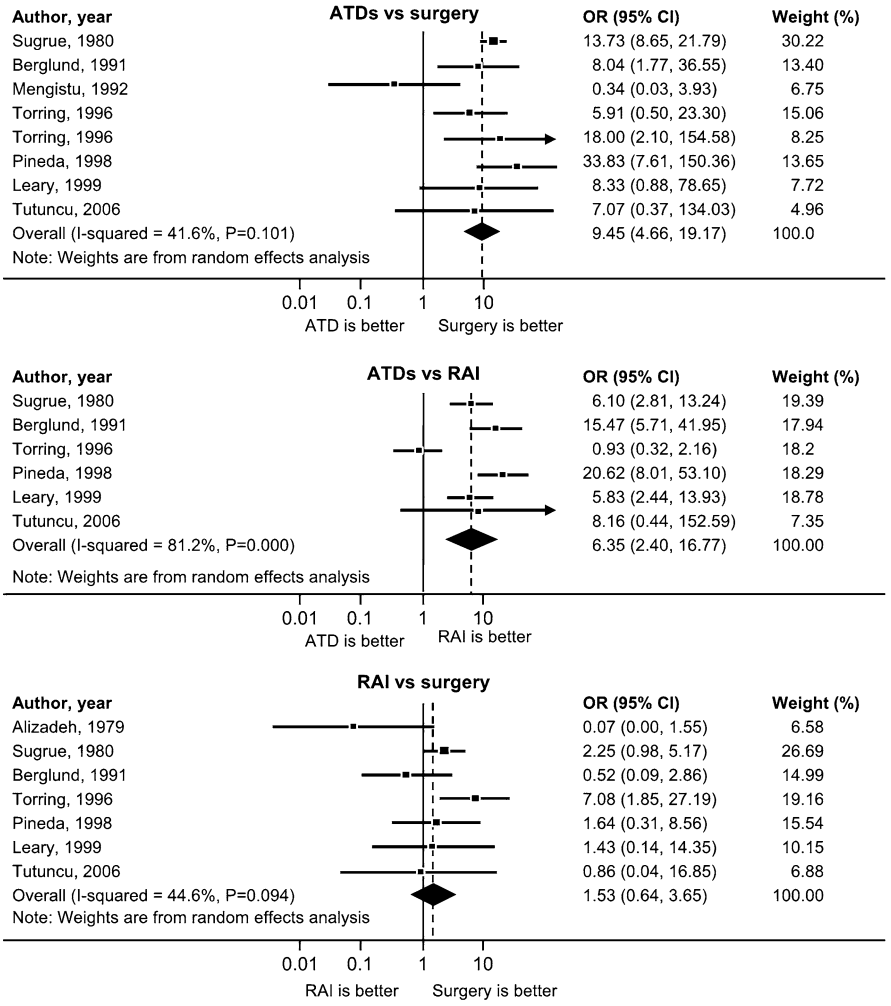

Fig. 8.1 Random effect meta-analysis of the included studies comparing risk relapse rates among the three interventions. *Vertical lines* indicate no risk difference; *squares* and *horizontal lines* indicate OR and associated 95 % CI for each study; *diamonds* indicate pooled OR. (Reprinted with kind permission from Sundaresh V, Brito JP, Wang Z, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2013 Sep;98(9):3671–7)

In a single systematic review of the literature between 2001 and 2011, Genovese et al. examined the outcomes of 14,245 patients who underwent either surgery (including subtotal or total thyroidectomy) or RAI for Graves' disease. The majority (9,699; 68 %) of patients had RAI; of the remaining patients, 3,158 (22 %) patients underwent subtotal thyroidectomy, and 1,388 (10 %) patients underwent total thyroidectomy [18]. Overall, performance of any thyroid surgery (subtotal or total) was

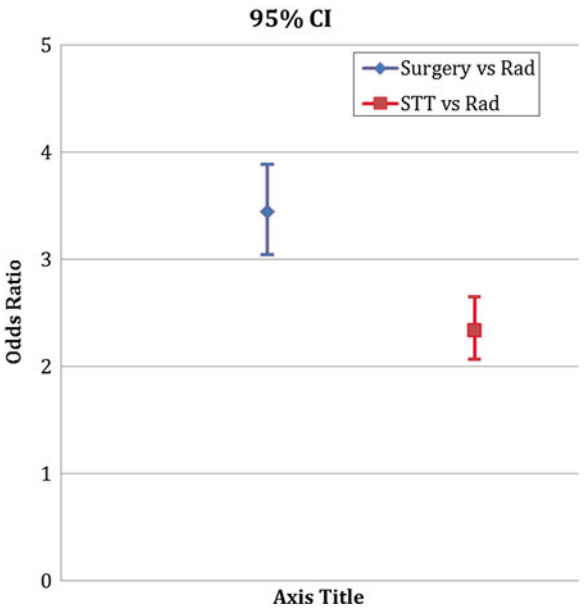

Fig. 8.2 Odds ratio and 95 % CI for surgery versus radioactive iodine and subtotal thyroidectomy (STT) versus radioactive iodine. (Reprinted with kind permission from Springer Science and Business Media; Genovese BM, et al. What is the best definitive treatment for Graves' disease? A systematic review of the existing literature. Ann Surg Oncol 2012;20(2):660–667)

favored over RAI (at any dose) for definitive treatment of Graves' disease, and total thyroidectomy was favored over subtotal thyroidectomy (OR = 40.37, 95 % CI 15.03–108.44, $p < 0.001$), as shown in Figs. 8.2, 8.3, and 8.4. Persistent or recurrent hyperthyroidism was identified in 2,080 (21 %) patients who received a single dose of RAI, 330 (10 %) patients who had a subtotal thyroidectomy, and only 4 (0.3 %) patients who had total thyroidectomy. There was no difference in rates of transient or permanent complications (hypocalcemia or recurrent laryngeal nerve injury) between the two surgical groups [18].

Thyroidectomy (total) also has been shown to be a cost-effective strategy. In et al. performed a meta-analysis of the cost-effectiveness of different treatment options in patients who had received 18 months of antithyroid medication but failed to achieve a euthyroid state [22]. The decision model was created with the assumption that 50 % of patients would fail therapy after this initial treatment period; these patients were then assigned to one of three treatment arms: antithyroid medications, RAI, or total thyroidectomy. Each treatment arm included all associated events, potential complications, probabilities of occurrence, and costs (limited to those of the third-party payor; societal costs were not included). In the base-case (30-year-old patient with uncomplicated Graves' disease who failed initial 18-month treatment), total thyroidectomy was the most cost-effective option. While RAI was less costly, it also had the lowest quality of life, as determined by quality-adjusted life-years [QALYs]; in contrast, total thyroidectomy had a higher QALY, with an incremental cost-effectiveness ratio (ICER) of $7,250/QALY over RAI. This finding was consistent as long as the cost of total thyroidectomy remained <$19,300, after which antithyroid medications became a more cost-effective treatment option [22].

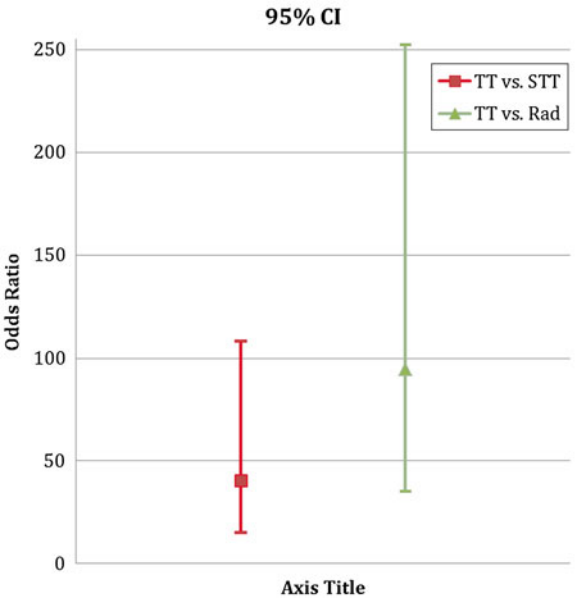

Fig. 8.3 Odds ratio and 95 % CI for total thyroidectomy (TT) versus subtotal thyroidectomy (STT) versus radioactive iodine. (Reprinted with kind permission from Springer Science and Business Media; Genovese BM, et al. What is the best definitive treatment for Graves' disease? A systematic review of the existing literature. Ann Surg Oncol 2012;20(2):660–667)

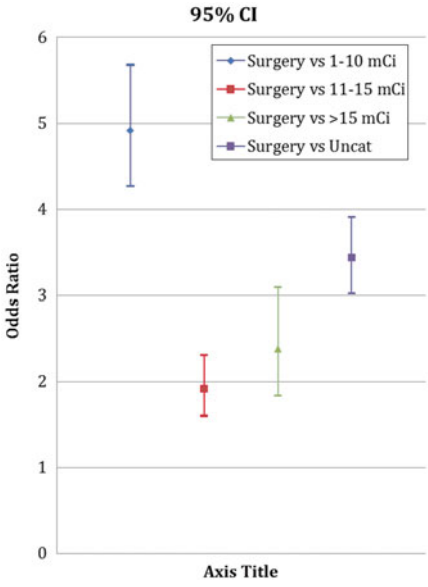

Fig. 8.4 Odds ratio and 95 % CI for surgery versus radioactive iodine doses. (Reprinted with kind permission from Springer Science and Business Media; Genovese BM, et al. What is the best definitive treatment for Graves' disease? A systematic review of the existing literature. Ann Surg Oncol 2012;20(2):660–667)

Extent of Surgery for Patients with Graves' Disease

The thyroid gland lies immediately caudal to the larynx and encircles the anterolateral portion of the trachea; as such, a portion of the thyroid, known as the tubercle of Zuckerkandl, can extent posteriorly behind the recurrent laryngeal nerve, which

ascends within the trachea-esophageal groove and crosses deep to the inferior thyroid artery. The inferior thyroid artery is the primary blood supply to the inferior and superior parathyroid glands in the majority of patients; the superior parathyroid gland most commonly lies within a centimeter of the junction of the inferior thyroid artery and recurrent laryngeal nerve. Subtotal thyroidectomy involves preservation of a remnant of thyroid gland, often the tubercle of Zuckerkandl, to preserve integrity of the nerve and blood supply to the parathyroid gland. However, total thyroidectomy has been shown to have acceptably low rates of morbidity in the hands of high-volume, experienced thyroid surgeons, and has become the standard of care in patients undergoing surgery for Graves' disease, as opposed to subtotal thyroidectomy [7].

The previously mentioned studies by Liu et al., Phitayakorn et al., and Genovese et al. have provided evidence to support total thyroidectomy as the surgical procedure of choice for patients with Graves' disease [16, 18, 24]. Stalberg et al. performed a systematic review on the extent of surgical resection; multiple retrospective studies reported comparable results (rates of disease recurrence, permanent recurrent laryngeal nerve injury, and hypoparathyroidism), but these results are difficult to interpret in light of limitations of retrospective case series, such as selection bias [23]. A meta-analysis by Palit et al. utilizing 35 studies and 7,241 patients also found comparable rates of permanent laryngeal nerve injury and transient and permanent hypoparathyroidism among patients undergoing subtotal or total thyroidectomy. However, in these studies, there was a 0 % rate of recurrence in the total thyroidectomy group, compared to 7.9 % in the subtotal thyroidectomy group [26].

Feroci et al. included studies from 1970 to 2012 in a meta-analysis of total thyroidectomy versus subtotal thyroidectomy, including only randomized controlled trials and select, nonrandomized comparative studies [27]. Twenty-three studies (four randomized controlled trials and 19 nonrandomized comparative studies) comprising 3,242 patients were included. Total thyroidectomy was associated with lower rates of recurrent hyperthyroidism, occurring in 7 of 1,665 patients undergoing total thyroidectomy and 128 of 1,577 patients undergoing subtotal thyroidectomy (OR = 0.10, 95 % CI, 0.06–0.18). There were no differences in rates of permanent recurrent laryngeal nerve injury between the two groups (OR = 0.91, 95 % CI, 0.41–2.02), although the total thyroidectomy group had higher rates of both temporary (OR = 2.70, 95 % CI, 2.04–3.56, $p < 0.00001$) and permanent (OR = 2.01, 95 % CI, 1.59–5.32, $p = 0.005$) hypoparathyroidism; the difference in rates of permanent hypoparathyroidism disappeared when comparing only the patients in the 4 randomized controlled studies (OR = 2.32, 95 % CI 0.73–7.38, $p = 0.15$) [27]. The authors concluded that total thyroidectomy is the gold standard for the surgical management of patients with Graves' disease, provided that reliable access to thyroid hormone replacement is available.

A recent cost-analysis of subtotal thyroidectomy, however, suggests that in certain circumstances, subtotal thyroidectomy may be a cost-effective strategy. Zanocco et al. created a decision model of four scenarios (antithyroid drugs, RAI, subtotal thyroidectomy, or total thyroidectomy) for a referent case of a 30-year-old woman with uncomplicated Graves' disease [28]. In the reference case, use of antithyroid medications was the least effective strategy, although it also was the least costly;

RAI had an ICER of $24,934/QALY over use of antithyroid medications. In contrast, subtotal thyroidectomy was more costly than RAI, but more effective, with an ICER of $26,602/QALY. Total thyroidectomy was more effective than both RAI and subtotal thyroidectomy, but associated with higher costs, in large part because of the need for lifelong thyroid hormone replacement. Importantly, subtotal thyroidectomy failed to be cost-effective if the initial rate of euthyroidism after surgery fell below 49.5 %; as the authors acknowledge, this requirement can be prohibitive, given the difficulty of leaving enough thyroid remnant to achieve euthyroidism and minimizing risks of recurrent hyperthyroidism [28].

Who Should Perform Thyroidectomy?

The high rates of hypoparathyroidism and recurrent laryngeal nerve injury experienced by the earliest thyroid surgeons and Mikulicz' initial description of partial thyroidectomy as a procedure intended to "prevent the evil consequences of total extirpation" likely set the stage for there being persistent safety concerns about offering thyroidectomy to patients with Graves' disease [1]. Yet recent literature examining outcomes following thyroidectomy in both the adult and pediatric populations has shown that in the hands of high-volume, experienced thyroid surgeons, complication rates are acceptably low and no higher in patients undergoing total thyroidectomy as compared to subtotal thyroidectomy [13–15, 19–21, 29–32]. Sosa et al. first demonstrated the importance of surgeon experience in thyroid surgery utilizing a statewide database of all patients undergoing thyroidectomy over a 5-year period [29]. In this study, high-volume surgeons were defined as those performing >100 thyroidectomies per year; these surgeons had the shortest length-of-stay and the lowest complication rates (5.1 %), compared to 6.1 % for moderate-volume surgeons (30–99 cases per year) and 8.6 % for low-volume surgeons (<10 cases per year) [29].

Kandil et al. recently examined the impact of surgeon volume on the outcomes of patients undergoing thyroidectomy using the Health Care Utilization Project–National Inpatient Sample (HCUP–NIS) [21]. Of 46,261 total thyroidectomies performed over a 10-year period, there were 3,127 (14.4 %) immediate postoperative complications; procedure-specific complications included (1) vocal fold paralysis or hoarseness; (2) hypoparathyroidism, hypocalcemia, or tetany; (3) tracheomalacia; (4) neck seroma or hematoma; or (5) wound complications. In this cohort, patients with Graves' disease (2,863 patients, 6.3 %) had the highest rates of postoperative complications (17.5 %), compared to patients undergoing total thyroidectomy for benign disease (13.9 %) or malignancy (13.2 %; $p < 0.001$). When stratified by surgeon volume, the presence of Graves' disease was found to be a predictor of postoperative complications when performed by low-volume (<10 cases per year) and intermediate-volume (10–99 cases per year) surgeons (low-volume: OR = 1.39, 95 % CI 1.08–17.79; $p = 0.01$; high-volume: OR = 1.34, 95 % CI 1.06–1.69; $p = 0.02$). This association did not exist for thyroidectomy performed by high-volume (>100 cases per year) surgeons (OR = 1.07, 95 % CI 0.62–1.83; $p = 0.81$) [21].

The safety of total thyroidectomy when performed by high-volume surgeons also has been documented in both the pediatric population and in pregnant women. In a HCUP–NIS study of 1,199 patients ≤17 years undergoing thyroidectomy/parathyroidectomy, children were found to have higher endocrine-specific complication rates following thyroidectomy than adult patients (9.1 % vs. 6.3 %: $p<0.01$) [14]. This observed difference in safety between children and adults was most notable for rates of hypocalcemia (9.3 % vs. 5.7 %, $p<0{,}01$) and most pronounced in children aged 0–6 years (22 %), compared to those aged 7–12 year or 13–17 years (15 and 11 %, respectively; $p<0.01$) [14]. Complication rates among pediatric patients also have been shown to be lower when performed by high-volume surgeons, irrespective of specialty [15].

Smaller institutional studies also have demonstrated that experienced surgeons can perform total thyroidectomy in pediatric patients with Graves' disease with low rates of morbidity. In a retrospective matched case-control study of 21 children (<18 years) and 21 adults undergoing total thyroidectomy for Graves' disease, Chioppini et al. found no significant difference between the two groups in rates of permanent hypocalcemia or recurrent laryngeal nerve injury; transient hypocalcemia was higher in children (28.6 % vs. 4.8 %), but this did not reach statistical significance ($p=0.093$) [19]. Breuer et al. performed a case-control study of 100 consecutive patients (32 children, 68 adults) undergoing total thyroidectomy for Graves' disease at a high-volume endocrine surgery center [13]. Although pediatric patients were more likely to receive postoperative intravenous calcium infusions for hypocalcemia (18.0 % vs. 1.4 % for adults; $p=0.004$), there was no difference in rates of permanent hypoparathyroidism. Similarly, there were two cases of transient recurrent laryngeal nerve paresis in children, compared to none in the adults and no permanent nerve injuries in either group. This demonstrates that while the surgical management of Graves' [7] disease may be more challenging in children, it can be performed safely by high-volume surgeons [13].

Preoperative and Postoperative Management

In patients undergoing thyroidectomy for Graves' disease, cervical ultrasonography can be useful, both to delineate the size of the thyroid and to identify any nodules that are indeterminate or suspicious on sonographic appearance and that may require fine needle aspiration (FNA) biopsy prior to thyroidectomy. Both adult and pediatric patients should be euthyroid prior to undergoing thyroidectomy, as thyrotoxic crisis during or after the procedure can result in extreme hypermetabolism, hyperthermia, tachycardia, hypertension, coma, or death. Beta-adrenergic blockade can be added to the treatment regimen if the patient remains tachycardic on antithyroid medications [7].

Patients should be given antithyroid medications until the day of surgery, and preoperative iodine solution should be given, except in patients with overt hyperthyroidism who are undergoing more urgent thyroidectomy secondary to inability to

tolerate, or an allergy to, antithyroid medications. The recommended dose of potassium iodide (SSKI; 50 mg iodide/drop) is 3–7 drops, three times daily for 10 days prior to surgery [7, 33]. Use of potassium iodide originated from the observation by Plummer that administration decreased the risk of thyroid storm during thyroidectomy; subsequently, potassium iodide has been noted to decrease the vascularity of the thyroid gland, allowing for a technically easier operation. However, clinical studies in humans have not all corroborated this theory, with several studies demonstrating no appreciable difference in blood loss between patients who received potassium iodide and those who did not [33–35].

Following thyroidectomy, antithyroid medications should be discontinued immediately, and beta-blockade should be slowly tapered. Thyroid hormone replacement should be initiated at a dose appropriate for the patient's weight (0.8 mcg/lb or 1.7 mcg/kg), with lower doses for the elderly. TSH and free T4 levels should be measured every 1–2 months until stable, and then annually [7].

Identification of Postoperative Hypocalcemia

The optimal protocol for detection and treatment of symptomatic hypoparathyroidism in the postoperative period is unknown and much debated. Current algorithms include routine supplementation with calcium and/or calcitriol versus selective supplementation, based on either serum calcium and/or parathyroid hormone (PTH) levels [36–43]. A cost-effectiveness study of the different protocols, including routine or selective supplementation, suggested that routine supplementation may be less costly and associated with higher utility compared to selective supplementation, although surgeons with low rates of hypocalcemia may benefit less from routine supplementation [38]. A recent prospective, randomized study found that a single POD1 PTH level <10 pg/mL accurately identified patients at risk for clinically significant hypocalcemia. Patients with PTH >10 were safely discharged home without calcium or calcitriol supplementation, and calcium carbonate was initiated in patients with a PTH <10; select patients received calcitriol supplementation for symptomatic hypocalcemia and/or a PTH <5 [42]. Irrespective of the protocol utilized, patients should be extensively counseled on the symptoms of hypocalcemia, including perioral and/or upper extremity paresthesias, which may progress to cramping and/or tetany if left untreated. At the onset of symptoms, patients should be advised to begin supplementation with oral calcium carbonate until symptoms resolve.

Conclusion

In patients with Graves' disease, thyroidectomy provides a relatively rapid and effective cure. If chosen, the procedure of choice should be total thyroidectomy, which has been shown to have lower rates of recurrent hyperthyroidism when

compared to subtotal thyroidectomy. Thyroidectomy can be performed safely, with low rates of morbidity, in the hands of experienced thyroid surgeons; referrals should be made to high-volume thyroid surgeons, particularly in the pediatric population. Postoperative care requires initiation of thyroid hormone replacement and follow-up to ensure continued euthyroidism.

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Chapter 9
Diagnosis and Management of Thyroid Storm

Alicia L. Warnock and Henry B. Burch

Introduction

The clinical presentation of thyrotoxicosis occupies a spectrum, ranging from asymptomatic (subclinical) disease to a life-threatening metabolic crisis characterized by multisystem dysfunction and a high mortality rate. A number of factors determine where in this continuum an individual thyrotoxic patient presents, including age, the presence of comorbidities, the rapidity of the increase in thyroid hormone levels, as well as the presence or absence of a precipitating event [1]. Thyroid storm occurs when the net effect of these factors surpasses an individual patient's ability to maintain adequate metabolic, thermoregulatory, and cardiovascular compensatory mechanisms [1]. At least one in ten thyroid storm patients dies from their

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disease. The high morbidity and mortality associated with thyroid storm require both early recognition and a decisive commitment to an aggressive multifaceted therapeutic intervention.

Clinical Presentation

Thyroid storm is in essence an exaggerated form of thyrotoxicosis. The heat intolerance and diaphoresis of simple thyrotoxicosis manifest in storm as moderate-to-severe hyperpyrexia with large insensible fluid losses and temperatures frequently in excess of 104–106 °F (40–41 °C) [2–5]. Sinus tachycardia in uncomplicated thyrotoxicosis becomes accelerated tachycardia in thyroid crisis, with a high propensity for atrial dysrhythmia [4, 6] and varying degrees of ventricular dysfunction and congestive heart failure [7]. The anxiety and restlessness typical of uncomplicated thyrotoxicosis may progress to severe agitation, delirium, psychosis, stupor, or coma in thyroid storm [3, 8–10]. Gastrointestinal and hepatic involvement, limited to enhanced intestinal transport and mild transaminase elevation in simple thyrotoxicosis, may dominate the presentation of thyroid storm, with nausea, vomiting, diarrhea, and hepatocellular dysfunction with jaundice [11, 12].

A key feature in thyroid storm is the presence of a precipitating event or intercurrent illness, yet such triggers are frequently not present or go unrecognized. Thyroid surgery, the most common precipitant of thyroid storm in early series, has become a relatively rare cause of this disorder [5, 6]. This relates to the current practice of rendering the thyrotoxic patient euthyroid before surgery as well as a decrease in the number of patients undergoing surgery for Graves' disease [13], due to the continued popularity of radioiodine ablation therapy for hyperthyroidism in the United States [13–15]. Still, nonthyroidal surgery in patients with unrecognized thyrotoxicosis continues to act as a precipitant of thyroid storm [16–18]. A recent survey-based report of thyroid storm cases in Japan found the abrupt withdrawal of antithyroid drugs to be the most common precipitant [5]. In this regard, the shift toward a greater reliance on antithyroid drug therapy as the primary treatment for Graves' disease in both the United States and Europe [13] might be expected to lead to an increased incidence of thyroid storm through this mechanism. Poor access to medical care has also been implicated as a cause of thyroid storm [19]. A list of common precipitants of thyroid storm is shown in Table 9.1. These can be broadly divided into conditions characterized by a rapid rise in circulating thyroid hormone levels and those associated with an acute nonthyroidal illness.

Diagnosis

Early series of thyroid storm patients were characterized by rapid deterioration, ending in death within hours to days of presentation [20–22]. The critical determinants of survival in life-threatening thyrotoxicosis are early diagnosis and

Table 9.1 Triggers or precipitants of thyroid storm

Conditions associated with a rapid rise in thyroid hormone levels
Abrupt discontinuation of antithyroid drugs
External beam radiation therapy
Iodinated contrast exposure
Radioiodine therapy
Thyroid hormone overdose
Thyroid surgery
Thyroid trauma (blunt trauma)
Conditions associated with an acute or ongoing nonthyroidal illness
Cerebrovascular accident
Diabetic ketoacidosis
Emotional stress
Infection
Nonthyroidal surgery
Parturition
Pulmonary thromboembolism

institution of appropriate therapy. Yet, diagnosis has not always been straightforward. Laboratory values fail to distinguish uncomplicated thyrotoxicosis from thyroid storm [5, 23, 24]. In addition, early diagnostic criteria for thyroid storm were far from uniform [4, 20, 22, 25–27]. To address these challenges, a diagnostic point scale for thyroid storm and impending thyroid storm was proposed in 1993. The Burch-Wartofsky Point Scale (BWPS) is an empirically derived scoring system which takes into account the continuum of end-organ dysfunction, the high variability of individual patient presentation, and the high mortality associated with a late diagnosis.

Akamizu and colleagues recently reported on 356 patients with definite or possible thyroid storm over a 5-year period in Japan [5], collected by a survey of providers in large (>500 bed) hospitals, university-affiliated hospitals, and a random subset of smaller Japanese hospitals. This report represents the largest series of thyroid storm patients published to date. The authors also empirically derived diagnostic criteria for thyroid storm based on literature review. The application of these criteria to reported cases of thyroid storm in Japan led to minor changes in the empirically derived criteria. The final criteria were referred to as the Japanese Thyroid Association (JTA) criteria for thyroid storm [5].

Although there is an overall agreement between these two diagnostic systems, the BWPS appears to select a higher percentage of patients for aggressive therapy than the JTA system [28]. It is noteworthy that inappropriate application of either system can lead to misdiagnosis, illustrating the importance of clinical judgment in assessing each individual patient.

Unusual Presentations

Thyroid storm has occasionally been described in patients with "apathetic" hyperthyroidism [29–32]. Although most classically described in the elderly, apathetic thyroid storm has been described in all age groups. Varied presentations for thyroid storm have included psychosis [33], coma [3, 8, 34], status epilepticus [9], nonembolic cerebral infarction [35], unexplained abdominal pain and fever in young women [36, 37], small bowel obstruction [38], hypercalcemia [39], and acute renal failure resulting from rhabdomyolysis [40].

Pathophysiology

The pathophysiology leading to thyroid storm remains poorly understood. However, important clues may lie in its known triggers or precipitants. Specifically, precipitants associated with a rapid increase in thyroid hormone levels suggest a sudden and overwhelming intracellular availability of free thyroid hormone, while those related to intercurrent illness suggest that a diminished physiological reserve plays a central role. Both mechanisms cause a failure of normal homeostatic mechanisms and ultimately lead to life-threatening systemic decompensation.

In patients with a rapid increase in circulating thyroid hormone, a transient saturation of plasma binding capacity sufficient to increase the concentrations of unbound hormone could lead to increased transporter-mediated intracellular entry of free thyroid hormone. Support for this mechanism comes from observations of a prompt clinical response in patients with refractory thyroid storm after a rapid decrease in circulating hormone levels through plasma exchange or charcoal plasma perfusion [41–43]. In addition, the development of thyroid crisis following the acute ingestion of thyroid hormone has been well documented in case reports [44–46]. Thyroid hormone induces a decoupling of oxidative phosphorylation, leading to the preferential production of thermal energy over adenosine triphosphate [47], which likely contributes to the hyperthermia seen in thyroid storm [48]. While an enhanced availability of free thyroid hormone for cellular entry would intuitively seem central in the development of thyroid storm, no clear distinction from uncomplicated thyrotoxicosis can be made based on absolute levels of circulating thyroid hormones [5, 23, 24].

Additional mechanisms are likely operative in patients who develop thyroid storm during an underlying acute or subacute nonthyroidal illness. A decreased hepatic and renal clearance of thyroid hormone during systemic illness [49] could accentuate the effects of increased thyroid hormone production [1]. Finally, an augmented tissue response to circulating thyroid hormone during nonthyroidal illness has been proposed. Theoretical mechanisms for such activity could include

enhanced intracellular transport or nuclear entry of thyroid hormone, an alteration in binding to the nuclear receptor, altered binding of the thyroid hormone-receptor complex to thyroid hormone response elements in target genes [1], or non-genomic thyroid hormone action. Other probable contributors include the cumulative effects of poor nutrition, changes in thyroid hormone binding, cellular uptake, metabolic clearance during an acute illness, and the individual patient's overall physiological reserve.

Adrenergic system activation plays an important contributory role in the pathogenesis of both uncomplicated thyrotoxicosis and thyroid storm. The interplay between thyroid hormone and the adrenergic system is bidirectional [50]. Hence, thyroid hormone enhances the effects of the β-adrenergic system, while the sympathetic nervous system in turn promotes thyroid hormone activation [50]. The hyperadrenergic state seen both in thyrotoxicosis and in thyroid storm may result from a thyroid hormone-mediated increase in β-adrenergic receptor density on target cells or post-receptor mechanisms [50, 51], and additional mechanisms for adrenergic enhancement have been suggested [50]. Many of the clinical features of severe thyrotoxicosis, including agitation, tachycardia, dysrhythmia, and hyperthermia, are related to either direct catecholamine action or an interaction between the adrenergic system and excessive circulating thyroid hormone [52]. The clinical evidence for the role of the adrenergic system in thyroid storm is the dramatic clinical improvement following the addition of β-adrenergic blockade to the therapeutic regimen [53–56]. Yet, circulating levels of catecholamines are normal or low in thyroid storm [57]. Furthermore, propranolol, even at high doses, does not prevent thyroid storm [58, 59] and has no effect on thyroid hormone synthesis or release [60].

Treatment

General Strategy

The treatment of established or impending thyroid storm is directed at each therapeutically accessible point in the thyroid hormone synthetic, secretory, and peripheral action pathways. Concurrently, aggressive intervention is directed at the reversal of the ongoing decompensation of normal homeostatic mechanisms. The requirement for continuous monitoring and rapid titration of therapy mandate an intensive care setting for the early management of thyroid storm. The therapeutic approach to thyroid storm may be grouped as: (1) therapy directed against the thyroid; (2) antagonism of the peripheral actions of thyroid hormone; (3) reversal or prevention of systemic decompensation; (4) therapy directed at the precipitating event or intercurrent illness; and (5) definitive therapy. These will each be considered separately below.

Therapy Directed Against the Thyroid Gland

A blockade of new hormone synthesis must be established early in the treatment course through the use of the antithyroid drugs propylthiouracil (PTU) or methimazole (MMI). PTU and MMI inhibit iodine organification as well as the coupling of iodotyrosine residues to form T4 and T3 [34]. A blockade of iodine organification is established within an hour of administration of either PTU or MMI. PTU has the advantage over MMI in decreasing the conversion of T4 to T3 and therefore has more pronounced effects on T3 during the critically important first 24 h of therapy [61]. Due to this unique property, thyroid storm continues to be one of a few conditions in which PTU is used preferentially over the more potent MMI [62].

PTU and MMI are generally given orally or per nasogastric tube in the stuporous, comatose, or uncooperative patient. Intravenous, rectal, and transdermal routes of administration have been utilized (see Sect. "Non-oral Administration of Antithyroid Drugs"). PTU should be loaded with a dose of 600–1,000 mg and then given at doses of 1,200–1,500 mg daily, divided as 200–250 mg every 4 h. MMI is given at a total daily dose of 120 mg in divided doses of 20 mg every 4 h. A history of antithyroid drug-related agranulocytosis or moderate drug-induced hepatocellular dysfunction should prompt the use of alternate modes of therapy; minor adverse reactions are not a sufficient cause to eliminate antithyroid drugs from the treatment regimen. Antithyroid drugs have no effect on the release of previously formed thyroid hormone.

Inorganic iodine inhibits colloid proteolysis and the release of T4 and T3 from the thyroid gland and also has inhibitory effects on thyroid hormone synthesis, through the Wolff-Chaikoff effect. Recommended oral doses are either saturated solution of potassium iodide (SSKI) (~35–50 mg/drop), five drops every 6 h, or Lugol's solution (8 mg/drop [0.05 ml]), eight drops every 6 h [1]. Parenteral administration by slow intravenous infusion of sodium iodide (NaI), 0.5–1 g every 12 h, has been employed, but sterile NaI for intravenous usage is not commercially available in the USA. Rectal administration of inorganic iodide has been described [63]. Sublingual iodine has been used effectively as well, with 0.4 mL of a SSKI sublingually three times daily in a patient with bowel obstruction. By measuring urinary iodine, the authors calculated that 70 % of the administered sublingual dose was absorbed [38].

It is essential that iodine therapy not be given until a blockade of new thyroid hormone synthesis has been established with thionamide antithyroid drugs (approximately 1 h), as iodine alone will eventually lead to further increases of thyroid hormone stores, thereby increasing the risk of exacerbating thyrotoxicosis. It should be noted that oral iodine therapy has been associated with acute gastrointestinal injury [64]. Lithium also reduces the release of hormone from the thyroid and could be considered in patients unable to be treated with iodide, provided adequate patient monitoring for lithium toxicity is performed [65].

Oral cholecystographic contrast agents such as ipodate and iopanoate (no longer available in the USA) have been used to treat severe thyrotoxicosis [66].

By virtue of a large content of stable iodine (308 mg/500 mg capsule for ipodate), these agents have beneficial effects on thyroid hormone release similar to inorganic iodide. In addition, these drugs are potent inhibitors of peripheral conversion of T4 to T3 and may antagonize thyroid hormone binding to nuclear receptors. Ipodate is given at a daily dose of 1–3 g and, as with iodide, should not be used without prior blockade of new thyroid hormone synthesis with PTU or MMI. Although the utility of ipodate in thyroid storm has not been extensively examined, dramatic reductions in circulating T4 and T3 levels (by as much as 30–54 % within 48 h of initiating therapy) have been reported in uncomplicated thyrotoxicosis [67].

Non-oral Administration of Antithyroid Drugs

Oral administration of antithyroid drugs can be problematic in a patient with a poorly functioning gastrointestinal tract or who is combative or comatose. Case reports have documented the effective use of intravenous methimazole [68, 69]. Hodak and colleagues prepared intravenous methimazole by reconstituting 500 mg of methimazole powder in 0.9 % sodium chloride solution to a final volume of 50 mL. The resulting solution of 10 mg/mL was then filtered through a 0.22-mm filter and administered as a slow intravenous push over 2 min, followed by a saline flush [68]. Standard sterile pharmacological techniques are required in the preparation process for these alternate medical vehicles.

Rectal administration of antithyroid drugs has also been reported, given either as enemas or as suppositories [70–73]. A retention enema was prepared by dissolving 600 mg of propylthiouracil tablets in 90 mL of sterile water, delivered to the rectum by Foley catheter with the balloon inflated to prevent leakage [74]. Other reports have described an enema preparation consisted of 400 mg of propylthiouracil dissolved in 90 mL of sterile water [71]. Another group has described the use of a propylthiouracil-based suppository [73]. A total of 14.4 g of propylthiouracil tablets were solubilized in 40 mL of light mineral oil and mixed in 36 g of cocoa butter solid suppository base, melted in a hot water bath, and maintained at less than 60 °C. The mixture was then distributed into thirty-six 1-g suppository molds and frozen until solid. Each suppository contained 400 mg of PTU, which was administered every 6 h, with demonstration of therapeutic drug levels by the authors [73]. Suppository formulations have the benefit of ease of administration compared to retention enema preparations and appear to have similar clinical effectiveness [72].

Emergent Thyroidectomy to Treat Thyroid Storm

Numerous case reports and small series have described the use of thyroidectomy in thyroid storm patients who continued to deteriorate despite the use of standard medical therapy [75]. Scholz and colleagues reviewed 39 cases from the literature and

10 additional cases from their own center, in which thyroidectomy was ultimately used to treat thyroid storm. Early or late postoperative mortality was reported in 5 of 49 (10.2 %) patients [75]. The authors advocated early thyroidectomy to treat thyroid storm, particularly in chronically ill elderly patients with concurrent cardiopulmonary and renal failure, who fail to respond to the standard intensive multifaceted therapy for thyroid storm.

Treatment Directed Against the Peripheral Effects of Thyroid Hormone

This category includes the treatment given to reduce the adrenergic manifestations of hyperthyroidism, inhibition of the peripheral conversion of T4 to T3, and procedures designed to physically remove thyroid hormone from the circulation. The striking clinical response to β-blockers makes them one of the most valuable forms of therapy available for both uncomplicated thyrotoxicosis and thyroid storm. In addition to antiadrenergic effects, these agents have the added benefit of a modest inhibition of the peripheral conversion of T4 to T3 [76]. The oral dose of propranolol in thyroid storm is 60–80 mg every 4 h, an amount higher than that typically used in uncomplicated thyrotoxicosis. Plasma propranolol levels in excess of 50 ng/mL may be necessary to maintain adequate blockade in thyrotoxicosis [77, 78], and it should be noted that the dose required to maintain this level may vary considerably in different thyrotoxic individuals due to the increased rate of plasma clearance [79, 80]. For a more rapid effect, intravenous propranolol may be given, using an initial dose of 0.5–1.0 mg with a continuous monitoring of the patient's cardiac rhythm and blood pressure. Subsequent intravenous doses as high as 2–3 mg have been given over 15 min, to be repeated while awaiting the effects of the oral formulation [54]. Esmolol, an ultrashort-acting intravenous β-blocking agent, has been used successfully in the management of severe thyrotoxicosis as well as in thyroid storm [81–84]. Because it is β1 selective, esmolol can be used in patients at risk for bronchospasm. Additionally, the half-life of esmolol's β1-selective blockade property is 9 min (versus 2.5 h with propranolol), allowing minute-to-minute titration of the medication [84]. Esmolol should be loaded with a dose of 250–500 μg/kg followed by continuous infusion rates of 50–100 μg/kg per minute, facilitating a rapid titration of drug level to the desired clinical effect [81–83].

Inhibition of the peripheral conversion of T4 to T3, an important element in the pharmacological management of thyroid storm, is accomplished as an ancillary effect of PTU (but not MMI), propranolol, ipodate (not available in the USA), and glucocorticoids. In regard to PTU, this is achieved through inhibition of the type I deiodinase (DIO1) located primarily in the liver and thyroid gland. PTU is theoretically most effective in hyperthyroid states such as Graves' disease or toxic nodules where the DIO1 is enhanced [85, 86].

Physical Removal of Thyroid Hormone from the Circulation or Gastrointestinal Tract

Both plasma exchange and charcoal plasma perfusion techniques have been used for the physical removal of circulating hormone in thyroid storm with generally beneficial results [41, 42, 46, 87–95]. Plasma exchange is considered in those patients who fail to respond rapidly to conventional therapy, those with a history of antithyroid drug-associated agranulocytosis or moderate hepatocellular dysfunction, and those who are being prepared for emergent thyroidectomy [42, 91]. It should be recognized, however, that the beneficial effect of plasmapheresis is transient, generally lasting only 24–48 h [42]. Binding resin therapy, such as cholestyramine, 4 g four times daily [96], is another adjunctive measure used to physically remove thyroid hormone, in this case from the enterohepatic circulation.

Measures Directed Against Systemic Decompensation

The treatment for systemic decompensation occurring in thyroid storm requires reversal of hyperthermia, dehydration, congestive heart failure, and dysrhythmia, as well as prevention of concomitant adrenal crisis. Hyperthermia should be aggressively treated with measures aimed at thermoregulatory set point modification and peripheral cooling. Hence, acetaminophen is given as antipyretic therapy, and cooling techniques such as alcohol washes, ice packs, and cooling blankets are used to enhance the dissipation of thermal energy. Salicylates should be avoided, owing to their ability to displace thyroid hormone from serum-binding proteins, which could aggravate the state of thyrotoxicosis. Gastrointestinal and insensible fluid losses are potentially immense during thyroid crisis and should be aggressively replaced to prevent cardiovascular collapse and shock. Fluid requirements of 3–5 L/day are not uncommon in thyroid storm. Elderly patients and individuals with evidence of congestive heart failure should be carefully monitored. Depletion of hepatic glycogen stores occurs readily during thyroid storm and has been cited as a characteristic histological finding at autopsy in patients dying from this disorder [11, 16]. As such, intravenous fluids containing 5–10 % dextrose in addition to required electrolytes should be used in patients with thyroid storm. Vitamin supplementation, particularly thiamine, can be given intravenously to replace any possible coexisting deficiency.

Cardiovascular manifestations of thyroid storm, including congestive heart failure and atrial dysrhythmia, are treated with conventional means including antiarrhythmic agents, vasodilators, and diuretics. Congestive heart failure occurs largely as a result of impaired myocardial contractility and is aggravated by atrial dysrhythmia, particularly fibrillation. Consideration should be given to Swan-Ganz monitoring of central hemodynamics in these patients, since despite modern critical care advances, the management of heart failure in thyroid storm remains difficult. Beta-blockers are a mainstay of therapy, but there are several special considerations. Propranolol is contraindicated in patients with a history of asthma

or chronic obstructive pulmonary disease, who thus should be considered for other agents such as β1-selective beta-blockers, calcium channel blockers, or reserpine. Propranolol has also been associated with cases of cardiorespiratory arrest in thyroid storm patients [97], further justifying the use of intensive monitoring during its usage. Intravenous esmolol therapy was discussed previously (see Sect. "Treatment Directed Against the Peripheral Effects of Thyroid Hormone").

As is the case with salicylates, furosemide at high doses inhibits T4 and T3 binding to thyroxine-binding globulin, leading to increases in free thyroid hormones. If utilizing digoxin, somewhat larger loading and maintenance doses may be required in thyrotoxic patients, owing, presumably, to an increased distribution space and/or rapid metabolism of this drug [98]. Serum digoxin levels should be closely monitored, particularly as thyrotoxicosis improves, to prevent digitalis toxicity.

The use of glucocorticoids in the treatment of thyroid storm was begun in the 1950s in an attempt to address the accelerated release and metabolism of corticosteroids in thyroid storm [99, 100]. Inappropriately, normal (rather than elevated) levels of serum cortisol have been observed in thyroid storm compared to the other periods of significant stress [24]. In addition to the prevention of adrenal crisis and promotion of vasomotor stability, glucocorticoids such as dexamethasone and hydrocortisone have inhibitory effects on the peripheral conversion of T4 to T3. Hydrocortisone is given intravenously at an initial dose of 300 mg, followed by 100 mg every 8 h during the initial stages of thyroid storm. The dose may be subsequently reduced and discontinued as allowed by the clinical response of the individual patient. The use of these agents appears to have led to improved survival in thyroid storm [10, 24].

Measures Directed Against Precipitating Events in Thyroid Storm

Although the event precipitating thyroid storm may be obvious, such as surgery, labor, diabetic ketoacidosis, withdrawal of thionamides [5, 22], or the recent use of radioiodine [101], this is sometimes not the case. The fever and leukocytosis found in thyroid storm even in the absence of an infection may be difficult to distinguish from an occult infectious process [102]. A careful culturing of blood, sputum, and urine is therefore indicated in the febrile thyrotoxic patient. While empiric antibiotic therapy is not generally recommended, infectious disease accounted for 29 % of cases of thyroid storm in a recent survey [5], so a case-to-case decision must be made based on clinical judgment. In cases of thyroid storm precipitated by hypoglycemia, diabetic ketoacidosis, stroke, or pulmonary embolism, standard therapeutic approaches apply and should be instituted simultaneously with the treatment of thyroid storm. A high index of suspicion for these varied etiologies must be maintained in a comatose patient or otherwise uncommunicative patient, unable to provide a history suggestive of a particular precipitating event. In some individuals, no precipitant will be identified, even in retrospect. In older series, 25–43 % of cases of thyroid storm occurred without an identified precipitating event [16, 24, 26], a rate which fell to 10 % in the most recent series from Japan [5].

After the Storm: Definitive Treatment

For the patient successfully treated during the acute stages of thyroid storm, a key objective should be the prevention of a recurrent crisis, preferably by planning for definitive therapy with either radioactive iodine ablation or surgery. As the severely thyrotoxic patient improves clinically, a gradual withdrawal of treatment modalities is often possible. Corticosteroids should be gradually tapered and discontinued, while β-blockade, unless contraindicated, should generally be continued during this period.

The inorganic iodine used in the acute stages of thyroid storm must be cleared, as indicated by a return to normal levels of urinary iodine excretion and an appropriate radioactive iodine uptake value before radioactive iodine can be used therapeutically. In the interim, the patient should be continued on antithyroid drug therapy. A surgical ablation with subtotal thyroidectomy is another therapeutic option in a patient who has adequate control of thyrotoxicosis in order to reduce the risk of another episode of storm during anesthesia induction or the surgery itself.

Prevention of Thyroid Storm

The majority of cases of thyroid crisis today are considered "medical" rather than perioperative storm, and thus greater awareness of predisposing factors is warranted. Any illness occurring in a patient undergoing medical management of Graves' disease warrants scrutiny for signs of metabolic decompensation. Likewise, elective surgical procedures should be deferred until euthyroidism has been fully established. Patients unable to use or responding poorly to antithyroid drugs require preparation for surgery using all available pharmacological means to correct thyrotoxicosis preoperatively. (See Sect. "Rapid Preparation for Surgery" below.)

Selective Pretreatment with Antithyroid Drugs Before Radioiodine Therapy

Radioiodine therapy for hyperthyroidism exposes patients to two common precipitants of thyroid storm, namely, thionamide withdrawal (in pretreated patients) and the ablation therapy itself. The administration of radioiodine to severely thyrotoxic patients can occasionally lead to rapid increases in thyroid hormone levels and thyroid storm in the weeks immediately following radioiodine therapy [101]. Thyroid storm has even been described, following the use of radioiodine in patients with metastatic differentiated thyroid cancer [103, 104]. Hence, patients at increased risk for developing thyroid storm such as the elderly, patients with severe thyrotoxicosis, and those with extensive comorbidity should receive pretreatment with antithyroid

drugs before radioiodine ablation therapy [62, 105]. In these patients, an attempt should be made to minimize the duration of antithyroid drugs to 3–5 days before radioiodine is given, as antithyroid drug discontinuation in this setting leads to rapid increases in thyroid hormone levels [105, 106]. The use of β-adrenergic blockade in the period preceding and immediately following radioiodine provides additional protection. Consideration should also be given to restart antithyroid drugs 3–7 days after radioiodine and then slowly taper this therapy over the ensuing 4–6 weeks [62] in particularly vulnerable patients.

Rapid Preparation for Surgery

Rapid preoperative preparation is occasionally needed for patients requiring urgent thyroid or nonthyroidal surgery [96]. These patients either have insufficient time to be rendered euthyroid by thionamides before surgery or have contraindications to their use. Safe and effective oral therapy with a combination of β-blockers (propranolol 40 mg every 8 h), high-dose glucocorticoids (betamethasone 0.5 mg every 6 h), and sodium iopanoate (500 mg every 6 h) has been reported in a small number of patients requiring urgent surgery [107]. This regimen was given for 5 days with surgery performed on the sixth day. As noted previously, dexamethasone and hydrocortisone decrease T4-to-T3 conversion and have an important role in this setting. Emergent preparation for surgery in thyrotoxic patients unable to use or responding poorly to antithyroid drugs at the authors' center [96] has successfully involved the following inpatient regimen with rapid correction of thyrotoxicosis when given for 5–10 days before thyroidectomy: (1) propranolol 60 mg orally, twice daily; (2) dexamethasone 2 mg intravenously, four times daily; (3) cholestyramine 4 g orally, four times daily; and SSKI, two drops orally, three times daily.

Summary

Thyroid storm continues to be a rare complication of a common disorder and one which most endocrinologists will be asked to manage during the course of their careers. Despite the improvement in both the early diagnosis and treatment of thyroid storm, survival is by no means assured. Most modern series report fatality rates between 20 and 50 %, and a very recent survey conducted in Japan revealed a mortality of 11 % [5, 24, 108]. Many cases of thyroid storm occur after a precipitating event or intercurrent illness. Effective management requires early recognition of impending thyroid storm, followed by an unwavering commitment to an aggressive therapeutic intervention.

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Chapter 10
Impact of Hyperthyroidism on the Cardiovascular and Musculoskeletal Systems and Management of Patients with Subclinical Graves' Disease

Bernadette Biondi

Graves' disease (GD) is an autoimmune condition characterized by goiter and hyperthyroidism [1, 2]. Ophthalmopathy may develop in 25 % of patients with GD [3]; other endocrine and nonendocrine autoimmune disorders may be associated with this disease [4].

Autoimmune hyperthyroidism is the most common cause of thyroid hormone excess in areas of iodine sufficiency [5]. Genetic factors are responsible for about 80 % of the risk of developing GD [6, 7], although environmental risk factors (cigarette smoking, stress, infections, and excessive iodine intake) may also play an important role [8, 9].

About 80–100 % of untreated patients with GD have detectable antibodies against the TSH receptor (TRAb) in their serum, which induces thyroid hypertrophy and hyperfunction by interacting with the TSH receptor on thyroid follicular cells [7]. The majority of patients with Graves' disease gradually enter remission of TSH-receptor autoimmunity during medical treatment or after surgery [10]. The persistence of TRAb at high concentrations often predicts a recurrence of hyperthyroidism after antithyroid drug (ATD) treatment [10].

Although individuals of any age can be affected, GD usually occurs in young patients [11]. Among patients aged over 55, hyperthyroidism due to Graves' disease was reported to be overt in 21.4 % and subclinical in 6 % [12]. Overt hyperthyroidism may by easily diagnosed in these patients for the onset of severe clinical symptoms of thyroid hormone excess. Subclinical hyperthyroidism (SHyper) is not a long-term dysfunction in GD [12]; it frequently precedes the onset of overt hyperthyroidism in patients with undetectable serum TSH, although some patients with mild SHyper may have a remission even without ATD therapy [13].

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In the last years, an increased cardiovascular (CV) mortality has been associated with overt and subclinical hyperthyroidism [14–19]. Recent data in hyperthyroid patients with GD suggest that these findings might be the effect of both the thyroid hormone excess and specific autoimmunity per se.

Effects of Hyperthyroidism on the Cardiovascular System

Thyroid hormones affect the respiratory system, skeletal muscle, and cardiac function [20, 21]. Short-term hyperthyroidism induces positive cardiovascular changes. Cardiac preload is increased in the presence of thyroid hormone excess as a consequence of the increase in blood volume and the improvement in diastolic function [21]. Cardiac afterload is reduced for the positive effect of T3 on vascular smooth muscle cells and endothelial nitric oxide production [21]. The increase in stroke volume and heart rate results in a high cardiac output state and hyperdynamic circulation [20, 21]. However, hyperthyroid patients have an impaired cardiopulmonary function, which in part reflects their reduced cardiovascular and respiratory reserve [22, 23]. Exercise intolerance and dyspnea during effort represent the first symptoms of the inadequate increase in cardiac output during exercise in hyperthyroid patients [20]. The analysis of respiratory gas exchange suggests a low efficiency of cardiopulmonary function and respiratory muscle weakness in overt hyperthyroidism [23]; maximal work rate is significantly reduced with a decreased forced vital capacity and oxygen pulse at the anaerobic threshold and at maximal exercise [23]. In young patients, these alterations are reversible after normalizing thyroid function. Older patients may have a marked alteration of cardiovascular and respiratory exercise capacity compared to younger patients with hyperthyroidism [11].

Effects of Hyperthyroidism on Skeletal Muscle

Muscle weakness, myalgias, fatigue, and poor exercise tolerance may occur in a high percentage of patients with GD [24]. Thyroid hormone excess has catabolic effects on the muscle, resulting in a negative nitrogen balance and a net loss of muscle protein. Work efficiency is usually decreased because thyrotoxic muscle requires more energy than normal; glucose uptake and utilization by muscle and mitochondrial oxidation are enhanced [25–27]. One half to two thirds of hyperthyroid patients have proximal thyrotoxic myopathy; they rarely have distal and bulbar weakness [28]. Serum creatine kinase (CK) and myoglobin concentration are usually normal. The electromyography occasionally shows alterations similar to muscular dystrophy [29].

β-adrenergic antagonist drugs may improve muscle weakness in thyrotoxic patients, although myopathy completely resolves within 3–6 months of euthyroidism without specific treatment [30]. However, rhabdomyolysis, myoglobinuria, and

renal failure may occur in severe thyrotoxicosis [31]. High concentration of CK and myoglobin should raise the suspicion of rhabdomyolysis or inflammatory myopathy. Fiber atrophy, muscle cell necrosis, and lymphocyte infiltration can be detected histologically [24].

Hyperthyroidism occurs in 3 % of patients with myasthenia gravis [32, 33]. Autoimmunity against the TSH and acetylcholine has been linked to this condition [32, 33].

Periodic paralysis is worsened by thyrotoxicosis [34, 35]. The incidence of thyrotoxic periodic paralysis ranges from 2 to 24 % in Asian people compared to 0.1–0.2 % in non-Asian North Americans [35]. The estimated male:female ratio is 20:1. The pathogenesis of thyrotoxic periodic paralysis is related to increased Na+–K+ ATPase activity stimulated by thyroid hormone, hyperadrenergic activity, and hyperinsulinemia. Recent findings have suggested that the loss of function mutations of the skeletal muscle-specific inward rectifying K+ (Kir) channel, Kir2.6, might explain this correlation [36].

Cardiovascular Risk in Overt Hyperthyroidism

About 7–8 % of middle-aged patients with overt hyperthyroidism may develop atrial fibrillation or flutter compared to 0.5–9 % of the euthyroid population [37]. The risk of AF increases 10–20 % in elderly hyperthyroid patients and may raise 20–35 % in those with ischemic heart disease or heart valve disease [37]. An hypercoagulable and/or hypofibrinolytic state has been associated with hyperthyroidism [38]. Ischemic stroke is 1.44-times greater (95 % CI, 1.02–2.12; $P = 0.038$) [39] and pulmonary embolism is 2.3 times enhanced (95 % CI 1.20–4.45, $P = 0.012$) [40] in young adults with hyperthyroidism compared to euthyroid subjects. Atrial fibrillation may increase the risk of cardioembolic events [41].

An increased risk of heart failure has been recognized in hyperthyroidism [42–44]. Recurrent tachycardia can cause a rapid decline in left ventricular function in the presence of severe hyperthyroidism, leading to the so-called “rate-related cardiomyopathy” [42–44]. Young patients with untreated hyperthyroidism may develop this condition which is characterized by a normal systolic function and low systemic vascular resistance inducing a high-output state with congestive circulation for the increased cardiac preload. Peripheral edema, pleural effusion, hepatic congestion, and increased pulmonary arterial hypertension are the clinical signs of this “high-output HF.” Therefore, this term is inappropriately used to indicate the congestive circulation correlated with severe hyperthyroidism; this condition may be improved rapidly with the achievement of euthyroidism, especially in young people [42–45].

Atrial fibrillation at presentation may be an independent predictor of congestive HF in middle-aged and elderly hyperthyroid patients [46]. The loss of sinus rhythm, the depression of myocardial contractility, and the onset of negative changes in the loading conditions may impair the efficiency of the cardiovascular system in hyperthyroid patients. Thereby, a true state of HF may develop; it is characterized

by a low ejection fraction, increased systemic vascular resistance and impaired left ventricular filling. This frequently occurs in elderly patients with hyperthyroidism and in those who have underlying cardiac conditions (such as ischemic, hypertensive, and valvular disease) [46, 47]. Heart failure is recognized in these patients for the development of orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and neck vein distension [42].

Diastolic HF with preserved left ventricular ejection fraction has also been reported in some elderly hyperthyroid patients [48]. This condition may be partially reversible after achieving euthyroidism.

Autoimmune Cardiovascular Involvement in Patients with GD

A specific autoimmune cardiovascular involvement (cardiac valve disease, pulmonary arterial hypertension, dilated cardiomyopathy, peripartum cardiomyopathy) has been demonstrated in patients with autoimmune hyperthyroidism, suggesting that specific cardiovascular risk factors might play a role in determining the negative cardiovascular outcome in GD [11] (Table 10.1).

Cardiac valve involvement may develop in patients with GD due to the hydrophilic mucopolysaccharides accumulation. The mitral valve can be affected by a myxoid degeneration with a potential risk of mitral regurgitation, endocarditis, thromboembolism, arrhythmic sudden death, and cerebral embolic events [49–53].

Pulmonary arterial hypertension is characterized by an increase in systolic pulmonary artery pressure above 30 mmHg at rest and a progressive increase in pulmonary vascular resistance, leading to right ventricular insufficiency. In some prospective studies, about 40–94 % of patients with autoimmune thyroid disease have had pulmonary arterial hypertension as a consequence of the immune-mediated endothelial damage [11]. Asymptomatic pulmonary hyperthyroidism has been detected in 45 % hyperthyroid patients at echocardiographic examination [54–62]. A significant reduction in pulmonary arterial pressure has been usually observed after correcting hyperthyroidism; severe pulmonary hypertension may also be completely reversible after successfully treating hyperthyroidism [59]. A specific vasoactive effect of methimazole has been postulated to explain the significant

Table 10.1 Autoimmune cardiovascular conditions associated with Graves's disease

Cardiac valve involvement
Pulmonary arterial hypertension
Right heart failure
Reversible and irreversible dilated cardiomyopathy
Takotsubo cardiomyopathy
Peripartum cardiomyopathy
Antiphospholipid antibody syndrome
Anticardiolipin antibodies

improvement in the pulmonary vasculature after medical treatment of hyperthyroidism [56]. Few cases of hyperthyroid GD with severe right ventricle volume overload, tricuspid regurgitation, and isolated right heart failure have been described in the literature [63–66]. Some of these cases have been reversible with the achievement of euthyroidism.

Autoimmune myocarditis is another cardiac complication of GD; myocardial changes are characterized by lymphocytic infiltrations, mucopolysaccharide deposits, necrosis, and fibrosis [67, 68]. Approximately one-third of hyperthyroid patients will develop a specific cardiomyopathy [54]. A reversible dilated cardiomyopathy has been recognized in GD; the autoimmune origin of this disease is supported by endomyocardial biopsies [69]. Moreover, an irreversible dilated cardiomyopathy has also been reported in GD [69], even after 12–15 years of effective treatment [70–72].

Takotsubo cardiomyopathy has been linked to GD [73]. Twelve cases of this cardiomyopathy have been reported as a presenting manifestation of thyroid storm. An excess of or an increased sensitivity to catecholamine might be a potential cause of this cardiovascular manifestation associated with severe thyroid hormone excess [73].

Peripartum cardiomyopathy (PC) has been detected in Graves' disease, particularly in African American women [74–77]. It usually occurs during the last month of pregnancy or up to 5 months after delivery. PT can be suspected for the onset of cardiac symptoms in the absence of preexisting cardiac dysfunction [74–77]. The prognosis depends on the extent of the ventricular dysfunction.

Graves' disease represents a risk factor for both venous and arterial thrombosis. Patients with GD may have anticardiolipin antibodies and antiphospholipid syndrome [11]. Nabriski et al. found a 43 % prevalence of antiphospholipid antibodies (IgG) in GD; they did not find any related clinical events, suggesting the possibility of an epiphenomenon [78]. However, some case reports have pointed out the association of GD with antiphospholipid antibody syndrome in the context of cerebrovascular accident, Budd–Chiari syndrome, recurrent venous thrombosis, and extensive inferior vena cava thrombosis [79–83].

Cardiovascular Mortality in Patients with Overt Hyperthyroidism

Two meta-analyses have assessed the cardiovascular mortality in overt hyperthyroidism [84, 85]. The first meta-analysis performed by Völzke et al. on seven cohort studies detected a 1.7-fold elevated risk for CV mortality rate in overt hyperthyroidism [84]. A meta-analysis by Brandt et al. based on seven different studies confirmed that a significantly increased all-cause mortality (relative risk (RR) 1.21, 95 % confidence interval (CI): 1.05–1.38) and cardiovascular mortality (RR 1.27, 95 % CI: 1.05–1.53) were associated with hyperthyroidism [85]. Similar results have been recently proved by the analysis of a register-based data on the Danish population where hyperthyroidism was linked to about 30 % increased risk of mortality [86–88].

Regarding treatment with radioiodine (RAI), an increased, but statistically nonsignificant, mortality risk was observed when pooling all of the available studies in the meta-analysis performed by the same Danish group [85]. Interestingly, a recent study by Boelaert et al. not included in the above meta-analysis has reported that only an effective treatment with RAI, able to induce hypothyroidism, may reduce mortality when compared to an ineffective RAI treatment or medical therapy with thionamides [89].

The population-based cohort study by Ryodi et al. (4,334 relatively young hyperthyroid patients treated with thyroidectomy in Finland) assessed the cardiovascular morbidity and mortality in surgically treated hyperthyroid patients [90]. This study reported that the risk of hospitalization for cardiovascular disease was 50 % higher in hyperthyroid patients compared to controls (HR 1.15; $P<0.001$). This risk had started to increase 5 years before thyroidectomy and persisted for two decades after effective surgical treatment. The increased rate of hospitalization was due to heart failure, valvular disease, or cardiomyopathies (HR 1.55) [90].

Morbidity and Mortality in GD Versus Toxic Nodular Goiter

GD and toxic nodular goiter (TNG) may differ in their CV risk factors and mortality [11]. Thyroid autonomy due to TNG accounts for approximately 60 % of cases of overt and subclinical hyperthyroidism in iodine-deficient areas, with an increasing prevalence in the elderly and in patients with comorbidities [11]. Unfortunately, only a few studies have assessed the risk of morbidity and mortality linked to these two different phenotypes of hyperthyroidism.

The study by Metso et al. found that only patients with TNG but not GD had an increased mortality (median age 62 years) after radioiodine [91]. In contrast, Nyirenda et al. did not report an increased mortality in either GD or TNG after similar treatment [92]. Interestingly, in the study by Ryodi et al., the risk of hospitalization due to CV disease was higher in patients with TNG than in those with GD (OR 1:56 vs. 1:32) before thyroidectomy; however, in a multivariate analysis, the increased morbidity was not related to the etiology of hyperthyroidism after surgery [90].

By using information from the Danish National Patient Registry and death certificates from the Danish Registry of Causes of Death, a recent Danish study by Brandt et al. has been able to stratify the risk of mortality, according to the cause of hyperthyroidism [86]. A significantly increased all-cause mortality was associated with both GD and TNG, which did not change after adjustment for preexisting comorbidity. However, the cause-specific mortality varied between GD and TNG. In fact, only GD was associated with a statistically significant increased cardiovascular mortality (HR 1.36, 95 % CI: 1.10–1.76), even after adjusting for the age difference. Furthermore, GD was correlated to increased mortality from lung diseases (LD), whereas TNG was only associated with significantly increased cancer mortality. After a further stratification for the period before and after the diagnosis of hyperthyroidism, the authors showed that hyperthyroid individuals had an increased risk

of being diagnosed with CVD, LD, diabetes mellitus (DM), and rheumatic disease (RD) prior to the diagnosis of hyperthyroidism. Moreover, after the diagnosis, there was an increased risk of CVD, LD, and DM [86, 88].

The same authors have recently investigated the risk of death related to hyperthyroidism in the twin population to assess the potential impact of genetic confounding [87]. Hyperthyroidism was linked to increased all-cause mortality in dizygotic (DZ) twins (HR 1.80, 95 % CI: 1.27–2.55), while the effect was completely attenuated in monozygotic (MZ) twins (HR 0.95, 95 % CI: 0.60–1.50). These findings could suggest that genetic factors might explain the association between hyperthyroidism and mortality [87].

Some limits of all of the available studies prevent us from making a solid conclusion on the influence of the type of hyperthyroidism as well as environmental and/or genetic confounders in hyperthyroid patients. Unfortunately, in all of these studies, the severity of hyperthyroidism has not been considered. Moreover, the heterogeneity of the studies (in terms of study design, definition of hyperthyroidism, and length of follow-up) and the lack of smoking data and/or information on the efficacy of treatment of hyperthyroidism did not allow the possibility to explain a pathophysiological mechanism, which may lead to a different cardiovascular outcome in GD and TNG.

Cardiovascular Risk in Subclinical Hyperthyroidism

Long-term hyperthyroidism may impair cardiac performance by increasing left ventricular mass and arterial stiffness and by inducing diastolic dysfunction [93]. Systolic performance on effort is impaired with a reduced exercise tolerance [94–96]. Higher heart rate and increased prevalence of supraventricular arrhythmias have been reported in most clinical studies in patients with SHyper [97, 98]. The progressive increase in left atrial size may explain the increased risk of atrial fibrillation which has been found 2- to 3-fold higher in elderly patients with SHyper compared to euthyroid subjects in some longitudinal studies [97, 98].

The Thyroid Studies Collaboration, a recent network of experts, has recently performed a systematic pooled analysis of all individual participant data (IPD) from the published cohorts, which prospectively assessed the association between endogenous subclinical hyperthyroidism and cardiovascular outcomes [19, 99]. The IPD analysis showed that subclinical hyperthyroidism was linked to an increased risk of atrial fibrillation (HR 1.68, 95 % CI 1.16–2.43) compared to euthyroidism. The risk was higher for TSH levels <0.1 mIU/L compared to 0.1–0.44 mIU/L (HRs 2.54 CI 1.08–5.99 vs. 1.63 95 % CI 1.10–2.41) (*p* for trend 0.02) [19]. Importantly, cardiovascular morbidity and mortality were also significantly increased in patients with endogenous SHyper. In fact, the risk of coronary heart disease (CHD) mortality from 10 cohorts was higher in patients with endogenous subclinical hyperthyroidism compared to euthyroidism (HR 1.29, 95 % CI 1.02–1.62), with a significant increased risk for lower TSH levels (<0.10) compared to levels between 0.1 and 0.44 mIU/L (HR 1.84 vs. 1.24) (*p* for trend 0.02) [19]. Moreover, the pooled analysis of individual

data from six prospective cohort studies showed that patients with TSH levels <0.10 mIU/L had a higher risk of heart failure (HR 1.94, 95 % CI 1.01–3.72), which persisted after excluding preexisting HF or AF [99]. The risk of HF was not significantly increased in patients with TSH levels of 0.1–0.44 mIU/L. The HR for total mortality from subclinical hyperthyroidism (10 prospective cohorts) was 1.24, 95 % CI 1.06–1.46 after age and gender adjusted risk. This risk did not increase with lower TSH levels; however, a low number of events occurred in this category [19].

Unfortunately, there are no prospective studies which have assessed the different cardiovascular outcome between patients with subclinical hyperthyroidism due to GD or MNG.

Management of the Cardiovascular Risk in Patients with Overt and Subclinical GD

Prompt and effective recognition of the cardiac manifestations in GD patients with hyperthyroidism is crucial because cardiovascular complications account for most of the deaths in hyperthyroid patients. Graves' disease should be considered in patients with pulmonary hypertension, dilated cardiomyopathy, and peripartum cardiomyopathy of an unknown etiology. Physicians should also consider the possibility of antiphospholipid syndrome and/or myxomatous cardiac valve involvement in patients with GD who have a history of stroke or arterial and venous thrombosis. Doppler echocardiography is a useful technique to assess the cardiovascular complications of hyperthyroid patients with cardiac symptoms. The use of this technique is justified in symptomatic GD patients to assess the possibility of the autoimmune cardiovascular involvement.

The correction of overt and subclinical hyperthyroidism should be the first procedure in the presence of cardiovascular symptoms because a prompt treatment may improve the prognosis of patients with GD [100–102]. Treatment of SHyper should be considered in elderly patients with serum TSH concentrations less than 0.1 mIU/L and in younger patients with underlying heart disease or autoimmune cardiovascular involvement [95, 96, 100] (Fig. 10.1). A periodic follow-up should be considered in younger patients with only minimally suppressed serum TSH concentrations (0.1–0.4 mIU/L), in absence of cardiovascular risk factors and symptoms of hyperthyroidism (Fig. 10.1). In fact, no benefits were reported following treatment of these patients and prospective studies have demonstrated that their thyroid function may normalize with time [95, 96, 100].

Antithyroid drugs, radioactive iodine (RAI), or surgery are all effective in treating hyperthyroidism, although a high relapse rate of ATD therapy has been observed in comparison to RAI or surgery [103]. Radioiodine is the preferred option in elderly patients when the aim of treatment is to obtain a rapid control of hyperthyroidism. Severe hyperthyroidism should be controlled before RAI because an increased mortality has been reported after this treatment [11, 101, 102]. Therefore, short-term antithyroid drug therapy should be considered in these patients with AF or underlying heart disease to avoid the worsening of thyroid dysfunction after therapy [11].

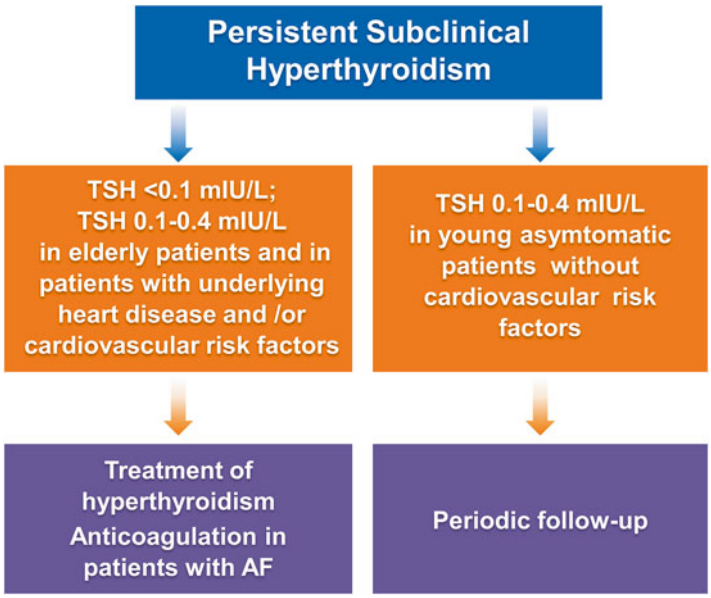

Fig. 10.1 Algorithm for treatment of patients with persistent subclinical hyperthyroidism

Methimazole should be the preferred option and should be discontinued 2–3 days before RAI administration. Higher doses of RAI should be used in hyperthyroid patients with cardiac disease to avoid the risk of treatment failure after pretreatment with antithyroid drugs [100] and to improve the prognosis of these patients [88]. An increased risk of Graves' ophthalmopathy progression following RAI has been reported suggesting the importance to identify patients at highest risk that might benefit from prophylaxis with glucocorticoids [104]. Surgery represents the definitive treatment for hyperthyroidism in the presence of large goiter with airway compression or suspicious malignant disease.

Randomized controlled trials are necessary to demonstrate the best treatment (medical therapy vs. RAI or surgery) to improve the cardiovascular complications and the increased cardiovascular mortality reported in patients with GD.

Tachycardia and atrial arrhythmias usually develop in hyperthyroidism. β-blocking drugs may control cardiovascular symptoms before attaining euthyroidism in patients treated with antithyroid drugs. Rate control is very important in patients with AF to reduce the mortality rate [105, 106]. Anticoagulation should be performed to prevent embolism in subjects with paroxysmal or persistent AF, especially when associated with left atrial enlargement, risk factors for stroke, and heart disease [107]. Atrial fibrillation spontaneously converts to sinus rhythm after treatment of hyperthyroidism in about two-thirds of hyperthyroid patients under 50 years of age, particularly in a new onset of AF without underlying heart disease [11]. Disopyramide has been able to restore sinus rhythm in about 15 % of hyperthyroid patients with AF [105]. Persistent AF after 4 months of euthyroidism should be treated with pharmacological or electrical cardioversion during anticoagulation [11, 105–107].

Pharmacological or electrical cardioversion should be considered in patients who do not regain normal rhythm spontaneously within 4 months of TSH normalization, after the evaluation of the age of the patient and the underlying cardiac conditions. Antiarrhythmic drugs should be used to avoid the recurrence of atrial fibrillation after successful cardioversion. Anticoagulant therapy with warfarin should be administered for at least 3 weeks before cardioversion and should be continued for at least 4 weeks after successful cardioversion to avoid the risk of embolic events [11, 105–107].

A variety of mechanisms may contribute to the onset of HF in hyperthyroid patients. Beta-blockers and diuretics may rapidly improve the congestive circulation in the "high-output HF," a congestive circulation associated with severe hyperthyroidism [42]. On the contrary, hospitalization is required in patients with low cardiac HF when cardiac hemodynamic and ventricular rate do not improve after successful treatment of hyperthyroidism [42].

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Chapter 11
Graves' Disease in Childhood

Scott A. Rivkees

Graves' Disease

Graves' disease (GD) is the most common cause of hyperthyroidism in children and is a considerably more pernicious condition than hypothyroidism [1]. The prevalence of GD is 1 in 1,000 adults [2, 3] and is 1 in 10,000 in the pediatric population [4]. GD is due to thyroid gland stimulation by thyroid receptor antibodies [TRAbs, or thyroid-stimulating immunoglobulins (TSI)] [5]. Toxic nodules, toxic multinodular goiters, acute and subacute thyroiditis, and thyroid hormone ingestion can also cause childhood thyrotoxicosis, but much less commonly than GD [6–9].

Symptoms of hyperthyroidism include excessive physical activity, tremor, tachycardia, flushing, palpitations, weight loss, accelerated linear growth, reduced bone mineralization, and poor school performance [6–9]. In childhood GD, ophthalmopathy occurs in less than 50 % of patients and is usually mild when present [6–9].

Because GD spontaneously resolves uncommonly, hyperthyroidism treatment is mandatory. Therapeutic approaches for GD include the antithyroid drugs (ATDs) propylthiouracil (PTU) or methimazole (MMI), radioactive iodine (^{131}I), or surgery [6, 10–14]. Each of these modalities has uniquely associated benefits and risks that must be considered when children are treated.

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Antithyroid Drugs

ATDs were introduced in the 1940s with thiouracil being the first compound used clinically [15]. Because of the high incidence of toxic reactions associated with thiouracil, this medication was replaced for clinical use by PTU in 1947 [15]. MMI became a treatment option for GD in 1950 [15].

ATDs act by inhibiting oxidation and organic binding of thyroid iodide to impair thyroid hormone production [16, 17]. MMI is 10- to 20-fold more potent than PTU and has a longer half-life [16, 17]. Importantly, these medications do not cure the hyperthyroid state, rather they palliate the condition. Each of these medications is associated with adverse events that must be considered when prescribed. As such, prior to the initiation of ATD therapy, a backup plan that takes into account the patient's age and treatment risks, in the event that a toxic reaction occurs, should be considered.

Propylthiouracil Hepatotoxicity

In 2008, a number of serious complications associated with PTU therapy in children were brought to public attention by Rivkees [18–20]. PTU-induced liver injury at that time accounted for 15 % of liver transplants in the USA [21]. From 1990 to 2007, 23 PTU-related liver transplants took place, and 30 % of the PTU-related transplant recipients were children. Based on prescribing data, the risk of PTU-induced liver failure leading to transplantation was estimated to be 1 in 2,000 children [4].

Despite a common perception, because PTU-induced liver injury occurs rapidly and is often irreversible, serial monitoring of transaminase levels in a child on PTU is not viewed to be useful in helping to reduce drug hepatotoxicity risk [4]. As such, the only way to reduce the risks of PTU-related hepatotoxicity is to avoid the use of the medication.

In 2009, Rivkees and Madison recommended that PTU not be used in children and that PTU be stopped in all children taking the medication in favor of alternative treatments (Table 11.1) [19]. In April, 2010, the US Food and Drug Administration issued a black box regarding the use of PTU stating that PTU should not be used in children [18], except in special settings, solidifying the notion that the drug should not be used.

Table 11.1 Recommendations for the use of propylthiouracil (PTU)

PTU should NEVER be used as a first-line treatment in children
The use of PTU should only be considered in rare circumstances, such as in preparing a patient allergic to MMI for surgery or in pregnancy
Current PTU use in children who are taking this medication should be discontinued in favor of alternative treatments

Appropriate Limited Use of Propylthiouracil

Although PTU should be avoided clinically, there is a role for its limited use in special circumstances. PTU can be used when neither prompt ^{131}I nor surgical treatment is an option in a patient who has had a toxic reaction to MMI, and ATD medication is necessary. In this situation, PTU should only be used short term while plans for ^{131}I or surgery are developed.

When PTU is used, patients and guardians need to be informed of the risk of liver failure and to be alert for signs and symptoms of liver abnormalities. These features include pruritus, jaundice, anorexia, light-colored stools, dark urine, and abdominal pain. If these problems occur, the patient should immediately stop the medication, a practitioner contacted, and laboratory tests obtained (white blood cell count, bilirubin, alkaline phosphatase, ALT/AST).

Methimazole

MMI is now the drug of choice for GD. Carbimazole, which is a prodrug that is converted to MMI, can be used in place of MMI in countries where it is available. Although MMI is often prescribed in divided doses over the day, once a day dosing is sufficient [22] and is associated with better compliance than multiple daily doses [23]. The typical MMI dose is 0.2–0.5 mg/kg per day, and doses can range from 0.1 to 1.0 mg/kg per day [5, 24–30].

MMI is available in 5, 10, and 20 mg tablets. When used in children, the following doses that are fractions of tablets can be used: infants, 1.25 mg/day; 1–5 years, 2.5–5.0 mg/day; 5–10 years, 5–10 mg/day; and 10–18 years, 10–20 mg/day. When there is severe hyperthyroidism, one can use double the above doses.

The response to ATDs influencing circulating thyroid hormone levels is not instantaneous, and several months are needed for thyroid hormone levels to normalize [13, 22]. Thyroid function tests should thus be obtained monthly after therapy onset. After T4 levels become normal, the MMI doses can be cut by half to maintain euthyroidism [31].

Rather than titrating the MMI dose lower when circulating thyroid hormone levels fall, some physicians prefer the block-and-replace approach and add levothyroxine while not changing the MMI dose; however, there is a greater risk of adverse events using block and replace vs. dose reduction [31, 32]. Recognizing that there is a potential dose-response relationship for some MMI-related complications [33, 34], it is preferable to use the lowest MMI dose that achieves control, rather than using the block-and-replace approach.

Although MMI is the drug of choice for GD, MMI therapy is not without risks. Minor side effects may affect up to 17 % of children [35]. The most common minor adverse side effects related to MMI are hives, arthralgia, and neutropenia [35]. Children may also develop major side effects, including Stevens-Johnson syndrome

and vasculitis [35]. MMI adverse events most commonly occur within 6 months of therapy onset [35]. Yet, 4 % of children will develop adverse events 18 months of MMI therapy, highlighting the need for constant vigilance while on treatment.

Agranulocytosis is another potential serious ATD adverse event and occurs in 0.3 % of adults taking PTU or MMI [13, 33, 36]. With MMI, agranulocytosis is dose dependent and is rare at low doses [13, 33, 36]. If an individual receiving MMI feels ill, becomes febrile, or develops pharyngitis, MMI should be stopped immediately, a practitioner contacted, and a complete blood cell count obtained.

Agranulocytosis typically develops in the first 3 months of therapy [13, 33, 36]. Thus, whereas it is tempting to treat with high doses of ATD therapy at onset, this approach should be avoided. Rather, relatively lower doses of MMI should be employed initially and symptoms managed with beta-blockers. Furthermore, the time to normalization of thyroid function tests is only modestly different in individuals treated with high vs. low ATD doses [22]. Although ATDs can be used long term, reports describe the development of antineutrophil cytoplasmic antibodies (ANCAs), which are associated with vasculitis and may limit prolonged medical therapy of GD [37–39]. In adults up to 15 % of individuals treated with PTU develop ANCAs after 2 years of therapy [37, 38]. MMI use is also associated with ANCA-positivity conversion, albeit with a lower incidence than with PTU [37, 38].

In the pediatric population, ANCA-mediated disease has been observed with either PTU or MMI [40, 41]. Because these antibodies can trigger serious vasculitis events, antithyroid medications should be stopped and definitive therapy considered when ANCA antibodies are detected [42]. To test for this potential problem, it is reasonable to perform annual assessment of ANCAs on children on prolonged ATD therapy, i.e., more than 2 years.

Duration of Therapy

Remission of GD is defined as being biochemically euthyroid or hypothyroid for 1 year or more after the discontinuation of ATDs. The collective literature indicates that remission rates in children are less than 25 % following many years of ATD therapy [43–47] (Table 11.2).

Table 11.2 Studies of rates of remission related to antithyroid drug use

Author	Date	Sample	Outcome[a]	Reference
Hamburger	1985	262	14 %	[54]
Glaser	1997	184	24 %	[44]
Glaser	2008	58	29 %	[45]
Kaguelidou	2008	154	28 %	[46]
Leger	2012	154	48 %	[47]

[a]Remission rate

Although prolonged ATD treatment will control biochemical hyperthyroidism, it is not clear that prolonged ATD use increases the likelihood of lasting spontaneous remission [48]. In a French study of 94 patients, following treatment for 6 or 18 months, remission rates were 42% and 62 %, respectively, after 2 years of treatment [49]. In 52 Spanish patients, following treatment for 12 or 24 months, remission rates were 46 % and 54 %, respectively, 2 years after cessation of therapy [50]; at 5 years, the relapse rate was 85 %. Another study of 134 French patients found no benefit of 18 vs. 43 months of treatment [51]. Thus treating beyond 18 months does not increase remission likelihood in adults.

In the pediatric age group, remission rates range from 20 to 30 % following ATD use for 2 years or more [26, 45, 46, 52, 53]. More than 25 years ago, Lippe and coworkers estimated that 25 % of children go into remission for every 2 years of treatment [54]. Of the 63 patients followed on ATDs, 36 (57 %) remitted after an average of 4 years of therapy [54]. Yet, there were little data to show if the patients who came off ATDs remained in remission [54].

Other large cohort studies of ATD use for many years [43, 44] show low remission rates. Of more than 200 children with GD in Minnesota, 25 % were in remission after 1 year, 25 % after 2 years, 26 % after 4 years, and 15 % after 10 years. In addition, 30 % of the boys and girls who went into remission had disease recurrence [43].

When 184 pediatric children in California were followed for up to 4 years, the overall remission rate was 23 % [44]. After 1 year of ATDs, 10 % were in remission; after 2 years, 14 % were in remission; after 3 years, 20 % were in remission; and after 4 years, 23 % were in remission.

In a study of children in Argentina, 113 patients received ATDs for prolonged periods [14]. After 10 years of treatment, 33 % of patients treated with ATDs went into remission [14].

Most recently, a study performed in France reported that prolonged drug therapy was associated with 50 % remission rates in children [47]. One-hundred fifty-four children with GD diagnosed between 1997 and 2002 were examined following treatment with carbimazole. The estimated rates of remission were 20 %, 37 %, 45 %, and 49 % after 4, 6, 8, and 10 years of therapy, respectively [47].

Age-related factors also influence remission likelihood. In a study of 32 prepubertal vs. 68 pubertal children with GD, remission occurred in 17 % of prepubertal children treated for 6 years vs. 30 % of pubertal children [52]. In another report with pre- and postpubertal cohorts, remission occurred in 28 % of children [55], but the time to remission was three times longer in the prepubertal children than pubertal children [55]. Of note, adverse reactions to ATDs occurred with greater frequency in prepubertal children (71 %) than in pubertal (28 %) and postpubertal (25 %) children [55].

In addition to puberty, TRAb levels and gland size influence remission rates. The efficacy of ATDs is inversely related to circulating levels of TRAbs [56–60]. Remission rates of GD in adults are about 15 % in patients with high TRAb levels at diagnosis and 50 % when the pretreatment levels are normal [56]. Large glands at presentation are also associated with much lower remission rates than when gland size is normal [61–63].

Symptomatic Management

In patients treated with ATDs for GD, it may take 1 or 2 months until biochemical hyperthyroidism resolves [22]. In the interim, treatment with beta-blockers, including propranolol, atenolol, or metoprolol, can be used to control GD symptoms. When the patient has asthma, metoprolol is preferred over nonselective beta-blockers, with the patient carefully monitored [64]. When thyroid hormone levels normalize, beta-blockers can be stopped.

Metabolic Complications of GD

Increasing evidence shows that GD can be associated with metabolic complications. GD can be associated with either hyper- or hypoglycemia at presentation [65, 66]. Myopathy has been observed both at initial presentation and when hypothyroidism occurs after therapy [67]. Excessive weight gain has been observed after initiation of therapy, leading to the recommendation that dietary counseling take place when treatment is initiated [68].

Radioactive Iodine

Radioactive iodine uptake by the thyroid is not distinguishable from ordinary iodine; thus radioactive iodine is trapped in thyroid cells [69]. After being taken up by thyroid cells, beta-emissions bring about the destruction of the iodine trapping cells and those in close proximity [69].

Around ten different isotopes of iodine have been used in medicine. ^{123}I is the isotope most frequently used for diagnostic studies of thyroid structure and function [69]. ^{121}I has a short half-life (13.3 h) and emits X-rays and gamma-photons, but no beta particles. By comparison, ^{131}I has a half-life of 6–8 days and emits beta particles and gamma rays.

Radioactive iodine use for thyroid ablation was introduced in the 1940s at the Massachusetts Institute of Technology and Massachusetts General Hospital [12, 70]. When the US Atomic Energy Commission was permitted to supply uranium fission products for medical usage, ^{131}I, with an 8-day half-life, became available for GD treatment. Because of the intrinsic advantages a longer half-life isotope, ^{131}I quickly became the favored iodine isotope for treating thyroid cancer and hyperthyroidism.

Treatment Approach

The goal for ^{131}I therapy for GD is to induce hypothyroidism. Radioactive iodine should not be given to cause euthyroidism in children, as this results in partially irradiated residual thyroid tissue that will be associated with a risk of thyroid

neoplasm [71, 72]. It has been suggested that dosages delivering 30,000–40,000 cGy (rad) to the thyroid are necessary to ablate the thyroid gland [73, 74]; however, doses delivering 10,000–20,000 cGy to the thyroid are more often used and result in partial or complete destruction of the thyroid [6, 75, 76].

Typically, administered thyroid doses of 150 μCi/g (5.5 MBq/g) generate radiation doses of 12,000 cGy to the thyroid [77]. After ^{131}I treatment, radiation exposure to the stomach, marrow, liver, and gonads is about 14, 6.8, 4.8, and 2.5 cGy per organ, respectively, with total body exposure at about 4.0 cGy [77]. Because of fetal risks, ^{131}I should not be given to women who are pregnant.

The rate of iodine uptake and the amount of thyroid tissue present influences thyroid destruction potential. Dosages of radioiodine administered are thus based on iodine uptake and gland size using the Quimby-Marinelli equation: dosage (radiation; in Gy) = 90 × oral iodine-131 dose (μCi) × oral 24-h uptake (%)/gland mass (gm) × 100 %). This calculation assumes an effective $T/_{1/2}$ of 6.0 days for ^{131}I. Thyroid size is estimated by palpation or ultrasound (ultrasound volume = 0.48 × length × depth × width) [78]. If a patient is taking antithyroid medication, treatment should be stopped 3–5 days before radioactive iodine is administered (Table 11.3). After ^{131}I administration, the circulating levels of thyroid hormones may increase within 4–10 days, as thyroid hormone is released from degenerating follicular cells [79]. Thus if antithyroid medication is discontinued too soon, there can be accumulation of excess thyroid hormone within the gland, leading to an increased risk of thyroid storm following treatment [80].

It usually takes 6–12 weeks after ^{131}I treatment for the patient to become biochemically euthyroid or hypothyroid. Until then, symptoms of hyperthyroidism can be controlled using beta-blockers [79, 81, 82]. The use of SSKI or Lugol's solution 1 week after ^{131}I will also quickly attenuate biochemical hyperthyroidism without adversely affecting the outcome of radioiodine therapy [82].

In as many as 5 % of patients, receiving properly calculated dosages, hyperthyroidism will linger after ^{131}I. It is recommended that these patients receive a second dose of radioiodine [75], which can be given 6 months after initial therapy.

Cure rates are higher in patients treated with larger than smaller amounts of ^{131}I. When treated with relatively low dosages (50–75 μCi/g), hyperthyroidism persists in 30–50 % of adults 1 year after therapy [83–86]. By comparison, after treatment with higher dosages (150–250 μCi/g), only 5–10 % of patients will remain hyperthyroid at 1 year [77, 87, 88].

Radioiodine therapy's success is influenced by the thyroid gland size and by circulating levels of TRAb. Patients with very large glands (>80 g) and high TRAb

Table 11.3 Recommendations for the use of ^{131}I

[a]Stop antithyroid drugs 3–5 days before therapy
[a]Begin beta-blocker when antithyroid drugs stop
[a]No need to restart antithyroid drugs after ^{131}I
[a]Check thyroid hormone levels every 30 days after therapy
[a]2–4 months before hypothyroidism ensues
[a]5 % need retreatment

[a]Not effective if gland > 80 g

levels have lower responses to ^{131}I therapy than patients with smaller glands [76, 89–92]. Because of poor response rates with very large glands, thyroidectomy should be considered for individuals with glands greater than 80 g.

Radioactive Iodine Use in Children

Several studies have reported the details of ^{131}I therapy for childhood GD [43, 93–99]. Children as young as 1 year old have been treated with ^{131}I with excellent results [99, 100]. But, treatment of such young children is not common, nor is recommended. ^{131}I dosages in children and teenagers have ranged from 100 to 400 μCi/g of thyroid tissue [6]. Similar to that found in adults, responses to ^{131}I therapy are related to gland size and dose. 25–40 % of children treated with 50–100 μCi of ^{131}I per gm of thyroid tissue are hyperthyroid several years after therapy [71]. In children treated with 150–200 μCi of ^{131}I per gm thyroid, hyperthyroidism remains in 5–20 %, and 60–90 % become hypothyroid [6, 75, 94, 100].

Our group analyzed outcomes of the children treated with radioactive iodine therapy to assess the effectiveness of therapy as related to gland size and dose [101]. Following treatment, when treated with 80–120 μCi of ^{131}I per gm of thyroid tissue, 28 % of children were hyperthyroid, 28 % of children were euthyroid, and 42 % of children were hypothyroid. Following treatment with 200–250 μCi/g of thyroid tissue, 37 % of children were hyperthyroid and 62 % were hypothyroid. Following treatment with 300–400 μCi/g of thyroid tissue, 0 % of children were hyperthyroid, euthyroid, and 93 % were hypothyroid. Comparing these pediatric data with those from adults [76, 78, 101], thyroid tissue of children appears to be more sensitive to ^{131}I-induced ablation than adults.

As in adults, we find that gland size influences therapy outcomes. In general, higher dosages per gm of thyroid tissue are needed with larger than smaller glands. Yet, with glands larger than 80 g, ^{131}I efficacy is low and is not recommended.

As in adults, when children are to be treated with ^{131}I, ATDs should be stopped 3–5 days prior to treatment [101]. Patients are then placed on beta-blockers until T4 and/or free T4 levels normalize post-therapy. Whereas some clinicians restart ATDs after treatment with ^{131}I, this is rarely required in children [6, 75, 101, 102]. Thyroid hormone levels begin to decrease about 7 days after radioiodine therapy in children, and continued ATD use can make it difficult to assess if posttreatment hypothyroidism is the result of ^{131}I or the ATD.

Some centers give a fixed administered dosage of 10 or 15 mCi ^{131}I to all children [102] rather than individually calculated administered activation. There are no studies comparing outcomes of fixed doses vs. calculated doses in children. In adults, the two different approaches lead to similar outcomes [103, 104]; however, in children, a potential advantage of calculated vs. fixed dosing is that it might be possible to use lower dosages of ^{131}I if the administered dose is calculated.

Side effects of ^{131}I therapy are unusual. Less than 10 % of children will complain of mild tenderness over the thyroid in the first week after ^{131}I therapy. This can be treated with either acetaminophen or nonsteroidal, anti-inflammatory agents for 24–48 h [75, 101].

There are rare reports of children with severe hyperthyroidism developing thyroid storm after ^{131}I [80]. In general, these children were severely hyperthyroid when ^{131}I was rendered. Thus, if T4 levels are >20 μg/dl (200 nmol/l) or free T4 levels are >5 ng/dl (60 pmol/l), children should be treated with MMI until T4 and/or free T4 levels normalize before proceeding with ^{131}I therapy [101]. It is important to recognize that most children with GD have been hyperthyroid for months prior to diagnosis; there is no need to rush to ^{131}I therapy.

Following ^{131}I, T3, T4, and/or free T4 levels should be obtained monthly, because TSH levels may be suppressed for several months after the hyperthyroid state is corrected. Thus, TSH determination may not be useful post-therapy. Typically, hypothyroidism develops by 2–3 months after treatment [101, 102]. When T4 levels fall below normal, levothyroxine is prescribed.

Ophthalmopathy

The development of progression of ophthalmopathy following ^{131}I in adults has been reported [105, 106]. However, unlike adults, children rarely develop severe ophthalmopathy and proptosis is mild [107, 108].

Studies show that disease worsens in only a small percentage of children with GD, irrespective of therapy type. Of 87 children treated with ^{131}I for GD at one center, proptosis improved in 90 % of children, did not change in 7.5 %, and worsened in 3 % post-therapy [88, 100]. In 45 children who had ophthalmopathy at the onset of treatment at another center, eye disease improved in 73 % and worsened in 2 % after 1 year or more of drug therapy [109]. After subtotal thyroidectomy in 80 children, eye disease was worsened in 9 % [110] and was stable in 75 % after total surgical thyroidectomy [110].

In adults, it has been shown that progression of ophthalmopathy can be prevented by treatment with prednisone for 3 months following ^{131}I therapy [111]. Adjunctive prednisone therapy is not routinely recommended for the majority of children, as most do not have significant eye disease. The prolonged administration of prednisone is also associated with growth failure, weight gain, and immune suppression. Nevertheless, prednisone may be useful for the child who has severe eye disease and will be treated with ^{131}I.

The Risks of Genetic Damage with Radioactive Iodine

There is no evidence showing adverse effects to offspring of children treated with ^{131}I. Birth defects were not higher in 500 offspring born to about 370 individuals treated with ^{131}I for hyperthyroidism during childhood or adolescence [6]. Additionally, the rates of birth defects are not higher in children treated with 80–700 mCi of ^{131}I for thyroid cancer, which are dosages that are much higher than those used for GD [112].

Thyroid Neoplasm Risk with Radioactive Iodine

The thyroid gland is unique in its developmental sensitivity to malignancy after low-level radiation exposure [113–116]. There is an increased risk of thyroid cancer in individuals less than 20 years of age at the time of low-level thyroid irradiation, and the younger one is, the greater the thyroid cancer risk [113–115]. In contrast, individuals who are older than 20 years of age do not exhibit an increased risk of thyroid cancer when exposed to low-level thyroid irradiation [113–116].

Importantly, the risk of thyroid neoplasms is greatest with exposure to low-level external radiation (0.1–25 Gy; ~0.09–30 μCi/g) [113–117] and not with the higher dosages used to treat GD. At present, we are not aware of any cases of thyroid cancer that developed in pediatric patients treated with >150 μCi of ^{131}I per gm of thyroid tissue for childhood GD that can be attributed to ^{131}I therapy. Thus, it is important that low dosages be avoided.

Non-thyroid Cancer Risks with Radioactive Iodine

Along with the risk of thyroid cancer, the potential influences of ^{131}I therapy on other cancers must be considered since ^{131}I therapy results in low-level, whole body radiation exposure. Several studies in adults have examined potential risks of ^{131}I therapy for GD on cancers (Table 11.4). These studies have not revealed increased mortality or increased rates of cancer following ^{131}I for GD [118–124].

In comparison with studies in adults, few studies have focused on outcomes of ^{131}I therapy for childhood GD. The most extensive study of pediatric patients involved 36-year outcomes of 116 patients who were less than 20 years old when treated with ^{131}I therapy for GD [125]. There was no evidence for increase in cancer risk in this population.

Table 11.4 Total cancer and cancer mortality related to ^{131}I therapy for hyperthyroidism in adults

Author	Date	Site	Sample	Outcome	Reference
Ron	1998	USA	23,020	No effect[a]	[124]
Holm	1991	SW	10,000	No effect[b]	[122]
Franklyn	1998	UK	7,209	No effect	[119]
Flynn	2006	UK	3,888	No effect	[118]
Metso	2007	FN	2,793	No effect[c]	[123]
Franklyn	2005	UK	2,668	No effect	[120]
Goldman	1982	USA	1,762	No effect	[121]

[a]Increase in thyroid CA with nodular disease
[b]20 % increase in stomach CA
[c]15 % increase in stomach CA in elderly men with nodular disease

The total body radiation dose after ^{131}I varies with age, and the same absolute dose of ^{131}I will result in more radiation exposure in a young child than in an adolescent or adult [126, 127]. Currently, we do not have dosimetry data on ^{131}I use in pediatric patients with GD to assess total body exposure in pediatric patients. Based on phantom modeling, it is estimated that at 0, 1, 5, 10, and 15 years and adulthood, respective total body radiation doses will be 11.1, 4.6, 2.4 1.45, 0.90, and 0.85 rem (0.01 Sv) per mCi of ^{131}I administered [126, 127]. Based on the Biological Effects of Ionizing Radiation Committee V (BEIR VII) analysis of low-level, acute exposure to radiation [128], theoretical lifetime attributable risk of cancer mortality and all cancer incidences can be projected. Based on these theoretical calculations, we feel that it is prudent to avoid radioactive iodine therapy in children under 5 years of age and to avoid >10 mCi in patients less than 10 years old. Yet, these recommendations are based on theoretical concerns and not on hard data.

We recognize that there may be circumstances when ^{131}I therapy is necessary for young children. The need for ^{131}I in a young child may occur when the child develops a toxic reaction to an ATD, proper surgical expertise is not accessible, or the child is not a suitable surgical candidate.

Surgery

The oldest form of definitive GD therapy is surgery, with the Nobel Prize in Physiology or Medicine awarded in 1909 to Koker for developments in this area [129]. When surgery is considered, near total or total thyroidectomy is indicated, as subtotal thyroidectomy is associated with a higher relapse rate [110]. Hypothyroidism is nearly universal in children and adults who undergo total thyroidectomy [110, 130–132]. In comparison, after subtotal thyroidectomy, hyperthyroidism recurs in 10–15 % of patients [110, 130, 131].

Surgery is preferred in children younger than 5 years when definitive therapy is needed and can be performed by a skilled thyroid surgeon. In individuals who have large thyroid glands (>80 g), the response to ^{131}I is poor [76, 133]. Thus, surgery is recommended for these patients.

In preparation for surgery, the patient should be rendered euthyroid. Typically, this is done by continuing MMI until T4 levels normalize. A week before surgery, iodine drops are started (5–10 drops, t.i.d.), which inhibits thyroid hormone production and causes the gland to become firm and less vascular, facilitating surgery.

Postoperatively, younger pediatric patients are at a higher risk for transient hypoparathyroidism than adolescents or adults [134]. To mitigate postoperative hypocalcemia, we treat children with 0.5 mcg of calcitriol twice a day for 3 days prior to surgery. Postoperatively, the calcitriol is weaned over 15 days (0.5 mcg bid × 5 days; 0.5 mcg qd × 5 days; 0.5 mcg qod × 5 days) [135]. Using this approach only 5 % of patients require postoperative calcium infusions vs. 40 % of patients without preoperative treatment [135].

Complications of Surgery

Acute complications that follow thyroidectomy include hemorrhage, hypocalcaemia, and recurrent laryngeal nerve paresis [134, 136–139]. In children, rates from 0 to 6 years were 22 %; from 7 to 12 years, 11 %; and from 13 to 17 years, 11 % [134]. These rates are higher than those in adults.

Complication rates are also related to the type of surgeon. When performed by pediatric surgeons, the complication rate for total thyroidectomy is approximately 15 %. In comparison, the complication rate in children for high-volume thyroid surgeons (>30 thyroidectomies/year) is approximately 4 %.

Considering these data, if local pediatric thyroid surgery expertise is unavailable, referral of a child with GD to a high-volume, thyroid surgery center with pediatric experience should be considered [140, 141]. Very low complication rates for children undergoing the thyroidectomies for GD have been reported with this type of multidisciplinary model [135, 140].

Conclusions

Based on what we know about both the risks of different treatments and the pathogenesis of GD, we can be discriminating in our approach to therapy. To reduce the risks of treatment and to expedite cure, treatment should be guided by the patient's age, by the nature of the intrinsic autoimmune disease, and by expertise.

For children less than 5 years old, MMI should be considered as a first-line therapy. While radioactive iodine has been successfully used in this age group without an apparent increase in cancer rates [100, 142], it may be wisest to defer radioactive iodine therapy until older.

Because young children are less likely to have remission on drug treatment vs. older children [52, 55], prolonged drug therapy may be necessary. Assuming there are no toxic effects, continuing MMI is sensible until the child is old enough for ^{131}I. If reactions to medication develop, or there is the desire to avoid prolonged drug use, thyroidectomy or ^{131}I can be considered. Fortunately, less than 5 % of children with GD present at 5 years or younger [1].

It is important to emphasize that when ATDs are used, only MMI should be prescribed. PTU use should be restricted to special circumstances when neither prompt surgery nor ^{131}I treatments are possibilities in a patient who has developed a toxic reaction to MMI, and ATD therapy is required. In this setting, the use of PTU should be short term.

Fifteen percent of children with GD will present between 6 years and 10 years of age [1]. It is reasonable to consider MMI therapy as a first-line measure for this age group. As 10 years of age is approached, either drug therapy or radioactive iodine can be considered as an initial therapy.

Children who are 10 years and older account for 80 % of the pediatric GD cases. Radioactive iodine and MMI can be considered as first-line treatment options for this age group. TRAb levels and thyroid size may be predictive of remission rates. The presence of low TRAb levels and a small thyroid is suggestive of the possibility of spontaneous remission after at least 1 year of medical therapy. Yet, if the thyroid is large and TRAb levels are high, the odds of spontaneous remission are low [56, 58, 60].

For those patients who have normal TRAb levels and a small thyroid, it is reasonable to treat for 1–2 years and stop the drug when clinical remission is achieved. If relapse occurs, medical treatment can be resumed or an alternative form of therapy chosen. For patients with elevated TRAb levels and a large thyroid size, it is less likely that remission will occur after medical therapy. Thus, definitive treatment soon after euthyroidism is achieved can be considered.

When radioactive iodine is used, it is important that the appropriate dosage be administered. The objective of radioactive iodine therapy in pediatric patients should be to ablate the thyroid gland and achieve hypothyroidism. The risk of thyroid cancer will be very small, if present at all, if no thyroid tissue remains. To achieve this objective, doses of ^{131}I >150 μCi/g of thyroid tissue are needed, with higher doses needed for larger glands.

Finally, regardless of the treatment option selected, careful follow-up is essential for all patients treated for GD. Long-term follow-up should include, once or twice a year, regular examination of the thyroid gland and measurement of circulating levels of thyroid hormones.

Selecting a treatment approach for childhood GD can be challenging and personal decision. It is essential that physicians discuss the advantages and risks of each therapeutic option to help the patient and family select the treatment plan they feel comfortable with.

Conflicts of Interest The authors have no potential conflicts of interest to declare.

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Chapter 12
Graves' Disease and Pregnancy

Alex Stagnaro-Green

Introduction

Graves' disease is the most common etiology of thyrotoxicosis during pregnancy. As an autoimmune disorder, the immune changes that allow pregnancy to progress without rejection of the fetal allograft result in alterations in the severity of the thyrotoxicosis during the three trimesters. The challenge in optimizing therapy during pregnancy is impacted by the teratogenic effects of methimazole and the potential for rare but serious hepatic side effects, with the administration of propylthiouracil. Therapeutic intervention must also take into account the health and development of the fetus which is impacted by the potential troika of excess thyroid hormone, TSH-stimulating antibody, and antithyroid medications. Finally, the postpartum, and the attendant immunologic rebound, frequently results in a worsening of preexisting Graves' disease or the occurrence of de novo Graves' disease in genetically susceptible women. The following chapter will review these aspects of Graves' disease during pregnancy and provide recommendations for optimal management.

History

Graves' disease complicating pregnancy was reported as early as 1825 at which time Parry described a pregnancy resulting in miscarriage due to thyrotoxicosis [1]. One of the earliest series was published in 1913 by Seitz who reported on 112 pregnant women with a goiter and exophthalmos [2]. Seitz concluded that in the

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majority of cases the Graves' disease worsened (67/112) during pregnancy while 40 % of the pregnancies were unaffected by the hyperthyroidism. On the other hand, Hyman and Kassel described symptomatic improvement of Graves' disease during pregnancy [3]. In 1929, Gardiner-Hill described 26 cases of Graves' disease and pregnancy. In 12 of the women, Graves' disease was first diagnosed during adolescence [4]. Twelve of the 14 women who developed Graves' disease as adults first presented during pregnancy or the postpartum resulting in the author to conclude that Graves' disease…"developing in adult married women at times other than these (pregnancy and postpartum) is relatively rare." The early literature documents both maternal and fetal mortality in untreated Graves' disease, thereby underscoring the significance of the 1951 article by Astwood which reported no fetal or maternal mortality in 19 women treated with antithyroid medicines during pregnancy [5].

Etiology

Graves' disease is an autoimmune disorder caused by an IgG immunoglobulin stimulating the TSH receptor (TSI – thyroid-stimulating immunoglobulin). During pregnancy, the immune system undergoes a selective immunosuppression which allows the mother to accept the fetal allograft. The immunosuppression results in a progressive decline in the titer of TSI with a concomitant improvement in the severity of the Graves' disease as pregnancy progresses throughout the three trimesters.

In the postpartum period, the immune system, no longer under the immunosuppressive effects of pregnancy, undergoes a rebound. In the first 6 months postpartum, TSI levels return to, and at time surpass, the titer present prior to conception. The immunologic rebound in the postpartum period may lead to a number of different clinical scenarios including: (a) recurrence of Graves' disease that was in remission prior to pregnancy, (b) relapse of Graves' disease that had gone into remission during pregnancy, and (c) and the occurrence of de novo Graves' disease.

Graves' disease results from a breakdown of immune tolerance involving both T and B cells and specific antigens [6]. A possible mechanism for the apparent increase in Graves' disease postpartum is microchimerism, the presence of foreign cells in an individual with a genetically distinct background. Microchimerism has multiple etiologies, including organ transplantation. However, the most common etiology is pregnancy. The placental trophoblast is an imperfect barrier and therefore allows the trafficking of cells between the mother and fetus [7]. Davies and colleagues reported in 2002 the persistence of male fetal cells (fetal microchimerism), in the thyroid glands of women with prior pregnancies who had thyroidectomy as a definitive treatment for Graves' disease [8]. It is hypothesized that the postpartum immunologic rebound activates the fetal cells in the maternal thyroid gland resulting in the development of Graves' disease in the postpartum [7].

Prevalence During Pregnancy

Graves' disease during pregnancy is much less frequent than hypothyroidism and pregnancy. A review performed by Stagnaro-Green in 2011, which included all studies conducted in the previous 20 years with a minimum of 500 women, revealed an overall prevalence rate of 0.5 % with a range of 0.2–1.0 % [9]. A particularly interesting group of studies were reported by researchers at Parkland Hospital in Texas. Davis et al. reported the prevalence in 116,800 women that delivered at Parkland Hospital from 1974 through 1985 [10]. Women who were diagnosed with Graves' disease prepregnancy and who remained euthyroid throughout gestation were excluded from the analysis. Sixty women were identified with Graves' disease during pregnancy (0.5 %), with the diagnosis first made during pregnancy in 32 of the 60 women (0.3 %). In a 2004 follow-up study, Sheffield and Cunningham extended the analysis of deliveries at Parkland Hospital through 2001, resulting in over 300,000 pregnancies evaluated [11]. The prevalence of Graves' disease and pregnancy was evaluated by time periods and were as follows: 1:2,000 between 1974 and 1985, 1:1,500 between 1991 and 1999, and 1:1,000 between 2000 and 2001. The overall prevalence across the entire 28 years was 1:1,500. The data indicate an increasing prevalence of Graves' disease during pregnancy over the three decades studied. Korelitz et al. reported on the prevalence rate of Graves' disease during pregnancy in 904,497 women using a retrospective claims analysis review [12]. Prevalence rates between 2005 and 2009 were 2.46 per 1,000 utilizing an ICD code of 242.0 and 5.88 per 1,000 utilizing the ICD classification of either 242.0 or 242.9. There was a marked increase in prevalence rates with increasing age.

Prevalence of New-Onset Graves' Disease in the Postpartum

A number of studies have evaluated the impact of the postpartum rebound of the immune system, which follows the selective immune suppression of pregnancy, on the de novo occurrence of Graves' disease. The observation that Graves' disease in remission may recur postpartum provided observational support for the theory that postpartum might be a time of new-onset Graves' disease. In 1982, Amino and colleagues reported the postpartum recurrence of Graves' disease in 21 of 42 pregnancies in which Graves' disease was in remission prior to conception [13]. Jansson et al. performed the first study evaluating the potential connection between de novo Graves' disease and the postpartum period [14]. Ninety-three consecutive Swedish women between the ages of 20–40 with new-onset Graves' disease were evaluated in respect to the temporal proximity to the postpartum. The unadjusted relative risk of women developing Graves' disease postpartum was 5.6, which increased to 6.5 when adjusted for parity and age. Tada et al. retrospectively evaluated the records of 289 consecutive women with Graves' disease who presented to their clinic in Osaka Japan. Of the 92 women of childbearing age, 37 (40)% had their initial presentation in the postpartum [15].

Rochester and Davies reported similar findings in a study based in New York City [16]. A review of the temporal relationship between pregnancy and onset of Graves' disease was performed in 152 women between the ages of 18 and 39 and compared to a predicted rate of postpartum Graves' disease based on New York City population data. Forty-five percent of the 152 women who developed Graves' disease did so within 1 year postpartum. This resulted in a significant increase in the relative risk which peaked in the older age group (35–39) at a relative risk of 5.6.

The most recent study investigating a temporal relationship between new-onset Graves' disease and the postpartum was published by Rotondi et al. in 2008 [17]. In their study of 215 consecutive Italian women with Graves' disease, no association was found between the occurrence of de novo Graves' disease and the first year postpartum. Specifically, only 9.8 % of the 215 women between the ages of 20 and 80 with a minimum of one successful pregnancy developed Graves' disease in the first postpartum year. When only women who developed Graves' disease during their childbearing years were evaluated, 21 out of 105 women (20 %) developed Graves' disease in the initial year following delivery. As over half of the 21 women had a family history of autoimmune thyroid disease, the authors concluded that the postpartum period serves as a precipitating event in women who are genetically predisposed to Graves' disease but does not cause Graves' disease in women without a genetic predilection.

Diagnosis of Graves' Disease in Pregnancy

The signs and symptoms of Graves' disease during pregnancy are identical to the signs and symptoms of Graves' disease in nonpregnant women. However, many of these symptoms (such as tachycardia, insomnia, and heat intolerance) may accompany a pregnancy uncomplicated by thyroid disease, making the clinical diagnosis difficult. In cases of a prominent goiter with a bruit or exophthalmos, the diagnosis is straightforward. However, these signs are not present in the majority of the cases. In fact, the presence of mild enlargement of the thyroid, especially in areas of iodine deficiency, is not uncommon in pregnancy and, in and of itself, is not indicative of Graves' disease. As heart failure has been associated with Graves' disease in pregnant women, thyroid function testing should be performed in all women who develop congestive heart failure [11, 18].

The diagnosis of Graves' disease during pregnancy requires laboratory evaluation. The combination of a suppressed TSH and elevated free thyroxine in a woman who tests positive for thyroid-stimulating immunoglobulins (TSI) is pathognomonic for Graves' disease. Both a solitary toxic nodule and a toxic multinodular goiter can present as thyrotoxicosis during pregnancy but can usually be differentiated from Graves' disease by the detection of nodules (on either physical or ultrasound examination) and the absence of TSI. Other causes of thyrotoxicosis during pregnancy are rare but need to be considered in the setting of TSI-negative thyrotoxicosis and included hydatidiform mole, choriocarcinoma, subacute thyroiditis, struma ovarii, and self- or overmedication with thyroid hormone.

The entity most commonly mistaken for Graves' disease is gestational transient thyrotoxicosis (GTT). GTT is caused by the thyrotrophic effect of the placental hormone human chorionic gonadotropin (hCG) on the TSH receptor resulting in an increased release of thyroid hormone. Both hCG and TSH are comprised of two subunits, alpha and beta. The alpha subunits are identical, and although the beta subunits are unique, they possess sufficient homology to result in hCG functioning as a weak TSH agonist. Prospective studies have documented an inverse relationship of increasing hCG levels in early pregnancy concomitant with declining TSH values (see Fig. 12.1) [19]. Human chorionic gonadotropin peaks in the first trimester and decreases rapidly thereafter. Women with GTT can present with many of the symptoms of Graves' disease. Laboratory evaluation however reveals a suppressed TSH with a normal or elevated free thyroxine, in the absence of TSI. Glinoer et al. found that 2.4 % of women between the 8th and 14th gestational week had a TSH <0.2 mIU/L and an elevated free thyroxine of >26 pmol/L [20]. Individuals with suspected GTT had an hCG level performed which was elevated in all cases. In a study by Yeo et al., the prevalence of GTT was as high as 11 % [21]. Women with

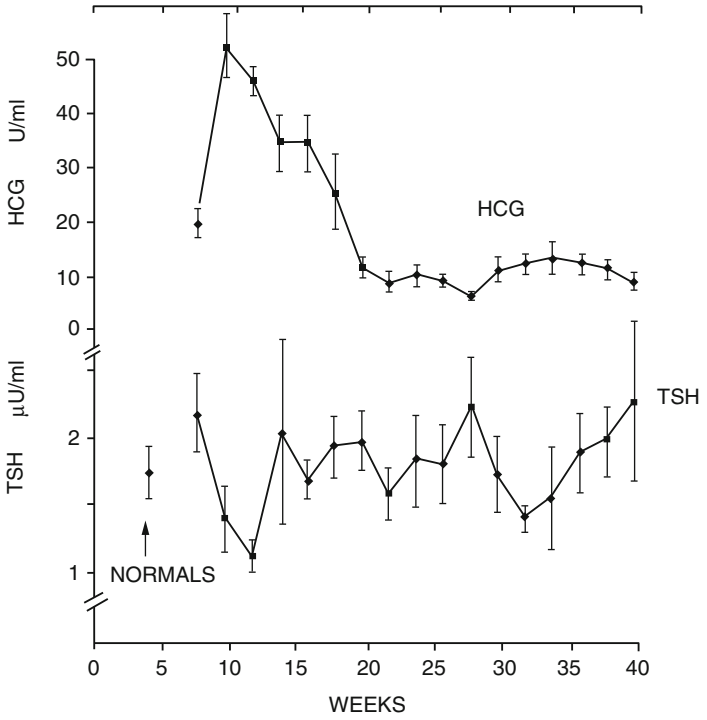

Fig. 12.1 Figure illustrates the reciprocal relationship between hCG and TSH in 339 women. Levels of TSH were lowest between 9 and 12 weeks and hCG levels peaked between 9 and 18 weeks [19] (Permission obtained from Wolters Kluwer Health. Goodwin TM, Hershman JM. Hyperthyroidism due to inappropriate production of human chorionic gonadotropin. *Clinical Obstetrics & Gynecology*. 1997;40(1):32–44)

twin pregnancies are more prone to GTT as the peak hCG is higher and lasts longer than seen in singleton pregnancies [22]. Lockwood et al., in a retrospective analysis, identified 69 specimens, from 15,597 samples, in which the hCG level was above 200,000 IU/L [23]. TSH testing revealed a suppressed TSH (TSH<0.2 mIU/L) in 67 % of the samples in which the hCG level was above 200,000 IU/L and in 80 % of the samples with a hCG that exceeded 400,000. In its most severe presentation, GTT presents as an entity called hyperemesis gravidarum, characterized by nausea, vomiting, ketonuria, and a weight loss in excess of 5 kg. Antithyroid therapy is not needed to treat hyperemesis gravidarum and thyroid function tests typically normalize in the second trimester in response to declining levels of hCG [24].

Fetal/Neonatal Thyrotoxicosis Secondary to Maternal Graves' Disease

Fetal and neonatal thyrotoxicosis is due to the transplacental passage of TSI, an IgG immunoglobulin. The majority of fetal IgG is maternal in origin. As pregnancy progresses, the level of IgG in the fetus increases from under 10 % at 4 months to 40 % at the end of the second trimester and approaches adult levels at delivery [25]. Consequently, fetal thyrotoxicosis, when it does occur, is found in the later part of the second trimester and third trimester. Given the decrease in IgG titers which occurs as pregnancy progresses, and the fact that fetal IgG levels are relatively low until the third trimester, it is only in cases of high maternal TSI, typically levels which exceed three times the upper limit of normal, that fetal/neonatal thyrotoxicosis may occur [26]. Consequently, fetal thyrotoxicosis is rare, occurring in less than 5 % of all women with Graves' disease [27]. Signs of fetal thyrotoxicosis due to Graves' disease include persistent fetal tachycardia, intrauterine growth restriction, fetal hydrops, accelerated bone growth, premature delivery, and intrauterine death. Fetal ultrasound is useful in monitoring for fetal thyrotoxicosis in women with high titers of TSI. Cordocentesis should be considered in TSI-positive mothers treated with antithyroid drugs when a fetal goiter is present but the thyroid status of the fetus cannot be determined.

Neonatal thyrotoxicosis occurs in less than 1 % of all women with Graves' disease during pregnancy [28]. Presentation of thyrotoxicosis may occur at birth or 1–2 weeks postpartum if the mother was on antithyroid medicine at the time of delivery. The delayed onset of thyrotoxicosis reflects the time taken for ATDs to clear the neonatal system. Presenting signs and symptoms of neonatal thyrotoxicosis include irritability, weight loss, diarrhea, goiter, tachycardia, hepatosplenomegaly, and hyperexcitability [27, 29]. As noted earlier, maternal Graves' disease resulting in neonatal thyrotoxicosis is caused by transplacental passage of TSI from the mother to the newborn. It is therefore not surprising that Matsuura et al., in an analysis of 56 pregnant women with Graves' disease, reported that TSI were present in all women whose children developed neonatal thyrotoxicosis [30]. Neonates in which maternal TSI levels in the third trimester exceed three to five the upper limits of

normal have the highest risk of developing neonatal thyrotoxicosis [31–33]. Given the half-life of the IgG immunoglobulin, neonatal thyrotoxicosis will spontaneously resolve within 2–4 months [25]. Treatment for symptomatic neonates with thyrotoxicosis is critical as complications of neonatal Graves' disease include neonatal mortality and heart failure. However, many neonates with Graves' thyrotoxicosis do not require intervention. In a series of 96 neonates born to mothers with Graves' disease, the prevalence of overt neonatal Graves' was 4 % [34]. The majority of the neonates were asymptomatic with peak free thyroxine levels at day 5. TSH levels however remained suppressed for as long as 3 months.

Complications of Untreated Thyrotoxicosis in Pregnancy

Graves' disease during pregnancy is associated with multiple adverse maternal and fetal adverse outcomes. Predominating the literature from over 50 years ago is the link between Graves' disease and first trimester spontaneous pregnancy loss. An evaluation of the literature for the last 20 years shows consistent findings of preterm delivery, low birth weight, gestational diabetes mellitus, pregnancy-induced hypertension, maternal cardiac failure, preeclampsia, and neonatal morbidity and mortality [35–40]. Graves' disease has also been linked to neonatal dysplasia of the hip [41].

Management of Graves' Disease in Pregnancy

Treating maternal Graves' disease is a delicate balance between the interests of the mother and fetus. Intervention should be sufficient so as to prevent the maternal morbidities associated with thyrotoxicosis. Simultaneously, the impact of treatment on the developing fetus needs to be carefully assessed as both TSI and antithyroid drugs cross the placenta and affects the developing fetus. The concerns needed to be addressed differ between mothers who had been successfully treated prior to conception and mothers who are thyrotoxic during gestation.

The major issue in women successfully treated for Graves' disease preconception is the presence of maternal TSI which, despite the mother being euthyroid, can cross the placenta and cause fetal/neonatal thyrotoxicosis. Both the American Thyroid Association and the Endocrine Society recommend measurement of TSI in the second trimester [42, 43] (ATA recommendation is between 20 and 24 weeks and Endocrine Society recommendation is by week 22). The absence of TSI at this point in pregnancy provides reassurance that fetal or neonatal thyrotoxicosis will not occur and no further TSI testing is required. On the other hand, women who are TSI positive, especially if the titer exceeds three times the upper limit of normal, will require close fetal monitoring for the development of fetal thyrotoxicosis and goiter by fetal ultrasound [44]. In rare cases, maternal administration of antithyroid drugs may be needed to treat fetal thyrotoxicosis [45]. In those cases, as the mother

was euthyroid prior to the administration of antithyroid drugs, concomitant administration of levothyroxine should be given.

Clinical management of Graves' thyrotoxicosis in pregnancy is complex and should be undertaken by a clinician with expertise in this area whenever feasible. Radioactive iodine is contraindicated and should never be administered during pregnancy. Surgery should be limited to circumstances in which antithyroid drugs cannot be tolerated and are ineffective or the patient is noncompliant [46]. Surgery, when needed, is best performed in the second trimester in order to minimize the risk of fetal loss. Consequently, the treatment of choice is antithyroid drugs. The choice of which antithyroid drug to administer during pregnancy has evolved over the last 5 years. The present recommendations are based on a desire to avoid the side effects of propylthiouracil (PTU) and the congenital anomalies associated with methimazole (MMI). Both PTU and MMI are effective in treating Graves' disease. Both agents cross the placenta and are associated with agranulocytosis. The major concern regarding PTU is its association with severe liver failure resulting in death or necessity of liver transplantation. Cooper and Rivkes have calculated that if all pregnant women in the United States with Graves' disease were treated with PTU, there would be four cases of severe liver toxicity annually [47]. On the other hand, MMI has been linked to an entity called MMI embryopathy which consists of a constellation of genetic anomalies including aplasia cutis, omphalomesenteric duct anomalies, omphalocele, and choanal atresia [48]. Consequently, both the ATA and ES thyroid and pregnancy guidelines recommend PTU as the treatment of choice in the first trimester. The Endocrine Society guidelines recommends that PTU be discontinued at the end of the first trimester and MMI be initiated. The ATA guidelines recommend that switching to MMI be considered in the second trimester and that the decision to switch antithyroid drugs should take into account the potential impact the switch might have on control of the thyrotoxic state.

The goal of antithyroid drug therapy during pregnancy is to achieve a free thyroxine level at, or slightly above, the upper limit of normal. Lower levels of maternal free thyroxine have been associated with fetal goiter and fetal hypothyroidism and therefore should be avoided [49]. TSH levels may remain suppressed throughout the entire pregnancy and should not be used to titrate the dose of antithyroid medication. Once antithyroid therapy is initiated, monitoring should occur every 2–4 weeks until the target free thyroxine level is achieved. At that point, monitoring should occur no less frequently then every 4–6 weeks. Once the target free thyroxine level is achieved, the dose of antithyroid medication will typically decrease as pregnancy progresses given decreasing TSI titers. It is not unusual to be able to wean the patient off of all antithyroid medications prior to delivery.

Recurrent Graves' Disease in the Postpartum Period

Immunologic changes associated with pregnancy results in a natural experiment that reflects the etiology of Graves' disease. In essence, Graves' disease activity mirrors the immunologic suppression which occurs during pregnancy and is followed

by the immunologic rebound that accompanies the postpartum. Therefore, women frequently experience a lessening of Graves' thyrotoxicosis as pregnancy progresses independent of the use of antithyroid drugs. This effect is directly related to the immunosuppressive effect of pregnancy resulting in decreased TSI titers. However, the TSI titer rebounds postpartum, frequently to levels that exceed prepregnancy values, and is accompanied by clinical relapse of Graves' disease activity.

The postpartum increase in TSI values may also impact women who were in remission prior to pregnancy resulting in the postpartum recurrence of Graves' disease. Rotondi et al. evaluated Graves' disease in women treated with methimazole for at least 1 year prior to pregnancy and who had been in remission for a minimum of 6 months following methimazole discontinuation [50]. Logistic regression analysis revealed a significantly higher disease relapse rate in women who had a pregnancy after MMI withdrawal as compared to women who had no subsequent pregnancies (84 % vs. 56 %, respectively, $p<0.05$). Given the high rate of Graves' disease relapse postpartum, Yoshihara et al. performed a retrospective study of women who were successfully treated for Graves' disease prior to pregnancy with either ATDs, radioactive iodine (RAI), or subtotal thyroidectomy [51]. Preconception, 110 of the 188 RAI-treated women were on levothyroxine, 74/148 women treated with subtotal thyroidectomy were on levothyroxine, and none of the 107 women treated with ATDs were on levothyroxine. Thyrotoxicosis recurred postpartum in 4/188 women treated with RAI, 35/148 treated with surgery, and 59/107 of women treated with ATDs.

The best predictor of Graves' disease relapse postpartum is the presence and titer of TSI at the end of pregnancy. A unique method of predicting recurrence is measurement of the peak systolic velocity (PSV) of the inferior thyroid artery (ITA). In a prospective study of 42 women with Graves' disease, measurement of the PSV/ITA postpartum revealed that the PSV/ITA ratio at delivery, compared to the value obtained each month postpartum, was predictive of recurrent Graves' disease 1 month prior to either clinical or biochemical thyrotoxicosis recurrence [52].

Preconception Counseling in Women with Graves' Disease

Women with Graves' disease, either active or in remission, should undergo preconception counseling [53]. Women who are thyrotoxic should be counseled to delay pregnancy until euthyroid. The pros and cons of the three treatment modalities for Graves' disease should be thoroughly explained to each patient. Thyroid surgery is the quickest way to render the patient euthyroid. Negatives of surgical intervention include the perioperative risks associated with surgery and the presence of a surgical scar. Radioactive iodine (RAI) therapy typically requires a couple of months to achieve euthyroidism and has been associated with a post-RAI increase in TSI titer which lasts for over a year [54]. Antithyroid drugs have the complications discussed earlier and are curative in only 50 % of women. Irrespective of treatment modality, euthyroidism should be achieved prior to attempting conception, and thyroid function tests should be obtained as soon as pregnancy is confirmed. Women who are

TSI positive should be made aware of the possibility of fetal and/or neonatal thyrotoxicosis despite the fact that they are euthyroid. Furthermore, the possibility of postpartum recurrence of active Graves' disease should be discussed.

Conclusion

Graves' disease during pregnancy requires careful monitoring and treatment to ensure a successful outcome for both mother and fetus. Women with Graves' disease diagnosed preconception should be rendered euthyroid prior to conception. The goal of treatment of Graves' thyrotoxicosis during pregnancy is to prescribe the lowest dose of antithyroid drugs feasible to attain a free thyroxine level at, or slightly above, normal. As both TSI and antithyroid drugs cross the placenta and impact the fetal thyroid, ultrasound monitoring of the fetus is recommended. Neonates born to mothers whose TSI levels exceed three to five times the normal range are at risk for thyrotoxicosis and should be carefully monitored.

Conflicts of Interest The authors have no potential conflicts of interest to declare.

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Chapter 13
Pathogenesis of Graves' Orbitopathy

Rebecca S. Bahn

Introduction

Graves' orbitopathy (GO), also known as Graves' ophthalmopathy or thyroid eye disease, is an inflammatory autoimmune disorder that primarily affects patients with a current or past history of Graves' hyperthyroidism [1]. While the onset of GO occasionally precedes or follows that of hyperthyroidism by several years, these conditions most commonly occur simultaneously or within 18 months of each other [2]. These clinical observations led clinicians early on to suspect that GO and Graves' hyperthyroidism share a common pathophysiology. Countering this concept appears to be the occasional finding of GO in euthyroid or hypothyroid individuals. However, with the advent of sensitive assays for circulating thyrotropin receptor antibodies (TRAb), the proximate cause of Graves' hyperthyroidism, it has been shown that at least minimally elevated levels of TRAb can be detected in essentially every patient with GO [3]. In addition, levels of TRAb correlate with the severity and clinical activity of the disease [4, 5] and higher titers of these antibodies in early disease portend a worse prognosis [6]. These clinical and laboratory observations point towards the orbital thyrotropin receptor (TSHR) as an autoimmune target that may play a central role in development of the ocular manifestations of Graves' disease. This chapter will discuss current concepts regarding the pathogenesis of GO.

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Mechanistic Explanation for Signs and Symptoms

Signs and symptoms of GO variously include proptosis (forward displacement of the globe), conjunctival and eyelid swelling and erythema, diplopia, and ocular pain. From a mechanistic standpoint, these features derive largely from enlargement of the orbital adipose tissues and extraocular muscles within the confines of the bony orbit. As the resulting orbital pressure increases, proptosis may develop and venous drainage may be impaired, facilitating the accumulation of inflammatory mediators within the orbit. This inflammation appears to be initiated by the migration of T-helper cells into the orbit [7]. This sets in motion the local production of cytokines, including interferon-γ (IFN-γ), interleukin-1 (IL-1), IL-6, as well as TRAb, although the latter may also reach the orbit via the circulation. In addition, chemoattractant cytokines, including interleukin-16 (IL-16), regulated upon activation, normal T cell expressed and secreted (RANTES), and CXCL10, may enhance mononuclear cell infiltration into the orbit [8]. Extraocular muscle dysfunction in early disease appears to result from active inflammation within the enlarged and edematous extraocular muscles. Diplopia encountered in late, inactive disease is likely due to fibrosis and may be impacted by local transforming growth factor-β production [1].

Histologic Underpinnings

Underlying the extraocular muscle and orbital adipose tissue remodeling characteristic of GO is an accumulation of hyaluronic acid (HA) with its attendant edema and the development of new fat cells, a process termed adipogenesis [9]. Additionally, within these orbital tissues can be found a perivascular and diffuse infiltration of CD4+ and CD8+ T cells, B cells, plasma cells, and macrophages. Several lines of evidence suggest that fibroblasts investing the extraocular muscle fibers and residing within the orbital connective tissues are the autoimmune target cells in GO [10–13]. These cells are heterogeneous and may be classified based on the presence or absence of the cell surface glycoprotein CD90, also known as thymocyte antigen-1 (Thy-1) [14]. Fibroblasts expressing this antigen are capable of copious HA production and are abundant in the extraocular muscles. In contrast, most fibroblasts found within the orbital connective tissues are Thy-1 negative and characteristically undergo adipogenesis under appropriate conditions.

The Role of TSH Receptor Activation

Insight into an important link between the thyroid and the orbit was gained by the demonstration that orbital fibroblasts, like thyrocytes, express the thyrotropin receptor (TSHR) [15, 16]. As such, this receptor could serve as a common autoantigen

allowing the pathogenic antibodies in hyperthyroidism to also impact the orbit. While orbital fibroblasts and tissues from both normal individuals and patients with GO express TSHR, significantly higher levels of the receptor are measured in GO tissues [17]. Further, ocular tissues from patients with active GO express higher levels of the receptor than do tissues from patients with inactive disease [4]. It has been shown in vitro that the expression of TSHR in these cells increases as they differentiate into mature adipocytes, perhaps leading to propagation of the autoimmune process within the GO orbit [18].

Sera from individual patients with Graves' disease contain a mixture of TRAb with the ultimate clinical expression of the disease influenced by the levels, varieties, and affinities of the TRAb present [19, 20]. Most TRAb-mediated TSHR signaling in thyrocytes is mediated through the Gαs protein subunit which activates the adenylyl cyclase/cAMP signaling cascade. Both TSH and some TRAb also activate a cAMP-independent cascade that increases phosphoinositide 3-kinase (PI3K) activity with subsequent phosphorylation of Akt and activation of the serine/threonine kinase mammalian target of rapamycin (mTOR). Recent evidence suggests that Forkhead box O-1 (FoxO-1) protein, a transcription factor and target of PI3K, may act as a downstream effector of both TSH and IGF-1 in thyrocytes [21]. In addition to these pathways, each Gα effector is impacted by growth factors that signal via MAPK pathways to regulate thyrocyte proliferation, differentiation, and survival [22].

TSHR signaling in orbital fibroblasts appears to be similar to that found in thyrocytes with TSH and TRAb-induced activation of both adenylyl cyclase/cAMP and PI3K/pAkt pathways [23]. In order to implicate TRAb as a proximate cause of the characteristic orbital tissue remodeling seen in GO, it would be necessary to show that activation of TSHR signaling in orbital fibroblasts enhances adipogenesis and/or HA production by GO orbital fibroblasts. The impact of TSHR activation on adipogenesis was studied by Zhang and colleagues using orbital fibroblasts into which an activating mutant TSHR was introduced [24]. This transfection led to an increase in adipocyte differentiation, as shown by two- to eightfold elevations in levels of early to intermediate adipocyte markers. Our laboratory similarly demonstrated pro-adipogenic effects of TSHR activation using a stimulatory monoclonal TRAb (termed M22) or bovine TSH as receptor ligands. Treatment with these agents resulted in increased expression of late adipocyte genes (adiponectin and leptin) and accumulation of lipid in GO orbital fibroblasts [25]. The adipogenesis promoted by M22 was inhibited by treatment with the PI3-kinase inhibitor LY294002, suggesting that this effect may be mediated via PI3K activation. While the cell systems used in the two studies differ, both suggest that TSHR activation may directly enhance adipogenesis in GO.

The Potential Role of IGF-1 Receptor Activation

The insulin-like growth factor-1 receptor (IGF-1R) has emerged as another receptor that might be activated within the GO orbit [26, 27]. While convincing evidence for the presence of elevated levels of autoantibodies against IGF-1R in GO is lacking, increased expression of IGF-1R and of IGF-1 itself has been shown in orbital cells from patients with GO [26]. The laboratory of Smith and colleagues studied the possible direct effects of human recombinant TSH (hrTSH) and purified IgG from patients with Graves' disease (GD-IgG) on HA synthesis in GO orbital fibroblasts. While they demonstrated IgG-induced HA synthesis, they found no increase in HA production following treatment of cultures with TSH [28]. Further, they showed that the stimulation of HA by GD-IgG was neutralized by a potent IGF-1R blocker (termed 1H-7) and that transfection of fibroblasts with a dominant-negative mutant IGF-1R inhibits GD-IgG-induced activation of T cell chemoattractant expression [29]. They concluded that these effects of GD-IgG on orbital fibroblasts were not due to TRAb, but rather to antibodies against IGF-1R that might be present in GD-IgG. The group of van Zeijl similarly found that GD-IgG, but not hrTSH, stimulates HA synthesis in GO fibroblasts using cells that had undergone adipocyte differentiation [30]. In contrast, Zhang and colleagues showed increased HA production in cultures treated with bovine TSH, or with two different monoclonal TRAb, in normal undifferentiated orbital fibroblasts, but not in GO fibroblasts [24]. We performed studies using undifferentiated GO orbital fibroblasts and found both bovine TSH and a potent stimulatory TRAb (termed M22) to increase cAMP production, phosphorylation of Akt, and HA production in these cells [31]. We also demonstrate that these effects can be abrogated by either 1-H7 or a small molecule inhibitor of TSHR activation [23], suggesting that HA synthesis resulting from TSHR activation in these cells may involve IGF-1R.

Direct interaction between TSHR and IGF-1R in orbital fibroblasts has been suggested in studies showing immunoprecipitation of both receptors using specific monoclonal antibodies directed against either receptor [26]. In these studies, the receptors appeared to be co-localized in the perinuclear and cytoplasmic compartments of the cells, suggesting physical and/or functional relationships between the receptors. In addition, both TSH and IGF-1 have been shown in thyrocytes to inactivate Forkhead box O-1 (FoxO-1) transcription factor by promoting its exclusion from the nucleus in an Akt-dependent manner [21]. Similarly, IGF-1 produced locally within the orbit may complement the effects of TSHR autoantibodies within the orbital tissues through modulation of downstream effectors, such as FoxO1. The combined effects of ligation of both receptors by their respective ligands may thus lead to full expression of the clinical features of GO [32]. A proposed model for the pathogenesis of GO is shown in Fig. 13.1.

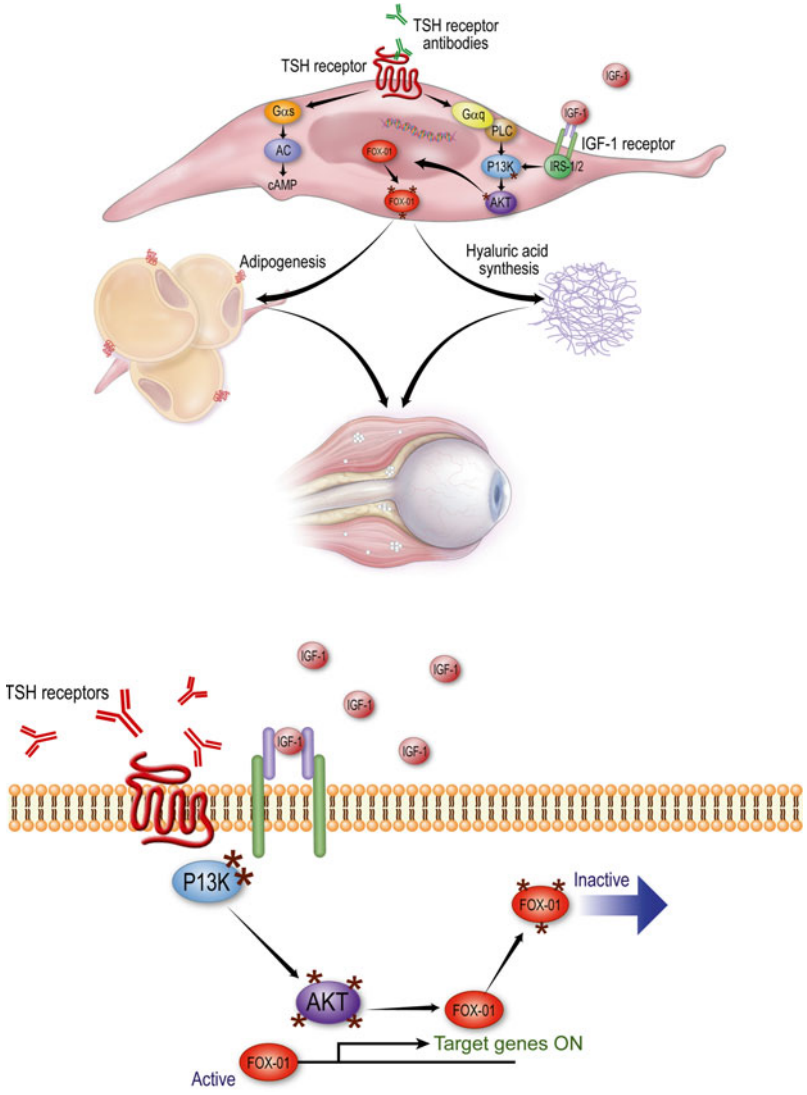

Fig. 13.1 Proposed model for pathogenesis of GO. (*Top*) Autoantibodies directed against the TSH receptor found in the sera of patients with GO engage this receptor on orbital fibroblasts while the IGF-1 receptor may be activated by locally produced IGF-1. Ligation of the TSH receptor activates the adenylyl cyclase/cAMP and the phosphoinositide 3-kinase (PI3K)/Akt signaling cascades. This may be augmented by IGF-1 receptor activation via physical and/or functional relationships between the receptors. This could involve the formation of receptor complexes and/or modulation of common downstream effectors, such as the transcription factor Forkhead box O-1 (Fox-01). This process results in increased production of hyaluronic acid, enhanced adipogenesis, and orbital infiltration of mononuclear cells with secretion of inflammatory cytokines. These cellular processes would lead to variable extraocular muscle enlargement, expansion of the orbital adipose tissues, and the inflammatory signs and symptoms of GO. (*Bottom*) Ligation of TSHR and IGF-1R in GO orbital fibroblasts by their respective ligands may lead to the inactivation of FoxO-1 by promoting its exclusion from the nucleus in an Akt-dependent manner. Inactivation of this known inhibitor of adipogenesis would be expected to enhance adipogenesis and may in addition augment hyaluronic acid production in these cells

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Chapter 14
Combined Thyroid–Eye Clinics in the Management of Graves' Ophthalmopathy

Wilmar M. Wiersinga

Rationale of Combined Thyroid–Eye Clinics

Graves' ophthalmopathy (GO) or thyroid eye disease is one of the extrathyroidal manifestations of Graves' disease. The diagnosis of GO is usually straightforward as it is typically a bilateral rather symmetric ophthalmopathy in a patient with Graves' hyperthyroidism. Diagnosis can be more difficult in unilateral cases which occur in 5–10 % of all GO patients, albeit Graves' disease is the most common cause of unilateral exophthalmos. Furthermore, although 85–90 % of GO patients have past or present Graves' hyperthyroidism, in 10–15 % the ophthalmopathy presents itself in patients who are euthyroid or hypothyroid. Thus, in a sizable proportion of GO patients a close cooperation between internists/endocrinologists and opthalmologists/orbital surgeons is needed to arrive at the proper diagnosis of GO.

A multidisciplinary approach to GO becomes even more compelling when it comes to treatment. The outcome of GO depends to a certain extent on restoration of the euthyroid state and how this is accomplished. Amelioration of eye changes is seen in hyperthyroid patients upon treatment with antithyroid drugs and achieving euthyroidism [1]. Recurrent hyperthyroidism after discontinuation of antithyroid drugs may cause a flare-up of GO. Radioactive iodine therapy of Graves' hyperthyroidism carries a risk of about 15 % of developing or worsening of GO, which can be mostly prevented by a course of steroids [2]. The occurrence of hypothyroidism after 131I therapy is an independent risk factor for GO worsening [3]. How to restore euthyroidism in the presence of GO in hyperthyroid patients, thus remains a challenge [4]. On the other hand, restoration of visual functions and appearance in GO patients frequently requires immunosuppression with steroids, retrobulbar irradiation or other disease-modifying treatments when the disease is still active.

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Each of these treatment modalities has contraindications, and specialists in internal medicine are frequently required for selection of patients. Delivery and supervision of disease-modifying drugs likewise needs the expertise of internists. In later stages of GO when the disease has become inactive, most patients will still require rehabilitative surgery to restore the premorbid state. Close cooperation between orbital surgeons and internists is also required at this late stage: one does not want to risk partial loss of the obtained surgical results because recurrent hyperthyroidism causes a flare-up of GO.

From these examples it is clear that a multidisciplinary approach to the patient with GO can be useful at every stage of the disease. A close cooperation between specialists from the field of internal medicine and ophthalmology is required to solve diagnostic problems, which do occur especially in unilateral ophthalmopathy and euthyroid cases. Mutual consultation is required to coordinate selection and timing of treatment for hyperthyroidism and treatment for the ophthalmopathy itself. A comorbidity like glaucoma and diabetes has to be taken into account and frequently complicates the management plan. A multidisciplinary approach is most effectively realized in combined thyroid–eye clinics.

Organization of Combined Thyroid–Eye Clinics

Starting combined thyroid–eye clinics requires a dedicated internist/endocrinologist and ophthalmologist/orbital surgeon, who should have a good working relationship between each other. I myself being an endocrinologist have been fortunate in meeting a very creative and dedicated orbital surgeon, Leo Koornneef. Returning from fellowships abroad to Amsterdam at about the same time, we discovered our mutual interest was GO. We decided to work together closely in order to improve patient care and try to advance knowledge about this disfiguring and frequently invalidating disease. We decided to refer all GO patients routinely to each other, and then see each patient together at combined thyroid–eye clinics. We started in the mid 1980s with the following schedule:

- First, separate consultations with endocrinologist and ophthalmologist
- Then appointments for lab tests, orthopsy, visual fields, orbital imaging
- Approximately 6 weeks later visit to the monthly combined thyroid–eye clinics

The schedule worked fine, but patients still had to travel to the hospital four to six times. Therefore we introduced in the mid 1990s a so-called “high-speed track” for GO patients (Table 14.1). The patient needs to travel only once to the hospital, and is occupied for the whole day. During that day the patient is seen separately by an endocrinologist and ophthalmologist (usually residents in training to become a specialist), blood tests are taken, and orthopsy and orbital imaging are done. The results of all these investigations are available in the desk-top computer as of 1600 h. The consultants in endocrinology and ophthalmology see the patient at 1630 h, together

Table 14.1 Combined thyroid–eye clinics: example of a high-speed track for patients with Graves' ophthalmopathy

08.00—Venipuncture for routine chemistry and TSH, FT4, TPO-Ab, TSHR-Ab
08.30—Consultation with internist/endocrinologist
10.00—Orthopsy
COFFEE
11.00—Visual fields (optional)
12.00—Orbital imaging (CT or MRI)
LUNCH
14.00—Consultation with ophthalmologist/orbital surgeon
15.00—Patient support group (optional)
TEA
16.00—All test results available in computer
16.30—Consultation in combined thyroid–eye clinics
17.00—Patient leaves hospital with diagnosis and management plan

with the residents who have investigated the patient earlier that day. At 1700 h the patient leaves the hospital with a diagnosis and management plan.

The scheme has been received with much enthusiasm by the patients themselves. Their only complaint has been that the day is very tiresome. We have this "high-speed track" for GO patients now every Tuesday, accommodating two patients each week. In about 5 % of cases the diagnosis at the end of the day is not clear or more information is required for delineating the most appropriate management plan. Among patients referred to the "high-speed track" the diagnosis of GO has to be rejected in about 2–3 %. In 95 % of cases a proper diagnosis and management plan is available when the patient returns home at the end of the afternoon.

The difficulties in starting a "high-speed track" should not be underestimated. Arrangements must be made with the endocrinology lab in order to have the results of all thyroid tests available in time; it means that all these assays should be run on Tuesdays. Some of these assays (especially those for TSH receptor antibodies) are not done routinely every day, but just once every week or fortnight depending on the work load. Agreement with the radiology department is also crucial: they should reserve two slots in their program for orbital CT or MRI. If the slots are not filled because the patient is not there, the manager of the radiology department will complain to you. It thus may take up to 6 months before you may have convinced everyone that the "high-speed track" has significant advantages especially because it is patient friendly, and all agenda's have been adjusted to this new track.

Local conditions will determine to a large extent how combined thyroid–eye clinics are best arranged. An essential part of combined clinics in my view is that the two consultants in endocrinology and ophthalmology are sitting simultaneously in front of the patient, and discuss together with the patient the results of all investigations, engage in shared decision-making and construct the most appropriate management plan.

Effect of Combined Thyroid–Eye Clinics on Patient Care

The question arises whether introduction of combined thyroid–eye clinics increases the quality of care given to GO patients. Although the setting is less critical than the expertise of clinicians, one is inclined to think so. Randomized clinical trials in other clinical disciplines have provided firm evidence that a dedicated multidisciplinary clinic results in better outcomes [5, 6]. Such studies have not been done in GO, but questionnaire studies among members of two thyroid patient support organizations in the UK strongly suggest added value of combined thyroid–eye clinics [7]. Patients who had attended a specialist GO clinic were (in comparison to those who had not):

- More often satisfied with treatment: 67 % vs. 52 % ($p<0.05$)
- More often informed on GO course and outcome: 72 % vs. 57 % ($p<0.05$)
- More often informed on different treatment options: 80 % vs. 65 % ($p<0.05$)
- More often informed on rehabilitative surgery: 70 % vs. 48 % ($p<0.05$)

This postal survey was performed in 2008; only 25 % of the 264 responders reported attending a specialist clinic. Another questionnaire study has been done in 2006 among members of the European Thyroid Association, European Association for Nuclear Medicine and European Society for Ophthalmic, Plastic and Reconstructive Surgery [8]. Although 96 % of respondents valued a multidisciplinary approach, only 32 % participated in or referred to a multidisciplinary team. The European Group on Graves' Orbitopathy (EUGOGO) has recommended to refer all GO patients except mildest cases to combined thyroid–eye clinics [9].

The timetable of the high-speed track in Table 14.1 also contains a time slot for contact with fellow GO patients. Thyroid patient associations have been established in many countries by now, and representatives might be asked to be present at the same time as the combined thyroid–eye clinics. The physicians may inform the patient about the existence of thyroid patient associations, and the possibility to talk with fellow patients in an adjacent room. Many patients appreciate this opportunity. After all, fellow patients are experts by experience. E.g., if a patient is offered orbital surgical decompression, the orbital surgeon will provide information about the expected results, the efficacy and safety of the procedure. However, to hear the story from a patient who himself has undergone surgical decompression, adds another dimension to the information. It may give a realistic picture of what is going to happen, and may alleviate feelings of anxiety. A wide array of informative brochures is available as well.

Numerous studies testify the negative impact GO may have on quality-of-life (QoL) [10]. The physical consequences of GO could have a negative and lasting impact on patients' employment, hobbies and psychosocial function. A German study among consecutive GO patients attending a combined thyroid–eye clinic, reports significant occupational disability: 36 % were on sick leave, 28 % were disabled, 5 % had gone into early retirement, and 3 % had lost their jobs [11]. GO is frequently associated with psychosocial morbidity [12]. It is against this background that actual measurement of QoL might have added value. A well-validated

disease-specific QoL questionnaire is available, the so-called GO-QoL [13]. It is available in 12 languages, and can be downloaded for free from the EUGOGO website (www.eugogo.eu). It has been used as primary outcome measurement in randomized clinical trials. Whether routine application of the GO-QoL in daily clinical practice results in better outcomes has not been studied formally. Systematic QoL assessments may have value by increasing awareness of a wide range of issues, possibly increasing detection of psychosocial morbidity, social problems, and changes in physical status [14]. Incorporating standardized QoL assessments in daily oncology practice improved care as evident from a RCT [15]. The same might be true in GO: incorporating the GO-QoL in the routine of combined thyroid–eye clinics may identify patients in whom further psychological support is needed [10, 13].

Effect of Combined Thyroid–Eye Clinics on Teaching

Combined thyroid–eye clinics provide ample opportunities for bedside teaching. I have learnt a lot from my ophthalmology colleagues over the years, e.g., that it is possible to have double vision when looking with just one eye. Conversely, I think the ophthalmologists have become very adroit in diagnosing pretibial myxedema as another extrathyroidal manifestation of Graves' disease. Thus combined clinics are a learning experience for all, and its educational value is appreciated by students, residents, fellows, and consultants alike. These teaching opportunities of combined clinics should not be underestimated. After all, GO is a rather rare disease, and not many physicians are familiar with this disease. It may be one of the reasons why in one quarter of GO patients it takes more than 1 year before the correct diagnosis has been established (Table 14.2) [7]. It is in fact rather common that initially the eye changes are attributed to conjunctivitis or allergy. GO is diagnosed in 41 % of cases by ophthalmologists, in 33 % by endocrinologists, and in the remaining 26 % by a wide variety of other care providers (Table 14.2). It could well be that the diagnosis

Table 14.2 Diagnosis of Graves' ophthalmopathy[a]

Who made the diagnosis?
• 41 % Ophthalmologist
• 33 % Endocrinologist
• 14 % General practitioner
• 5 % Opticians
• 2 % Emergency staff
• 4 % Others: neurologist, allergy specialist, self-diagnosis
Delay in diagnosis
• 58 % Initially wrong diagnosis (mostly conjunctivitis, allergy)
• 26 % Delay > 1 year

[a]Data compiled from ref. [7]

of GO would have been made at an earlier point in time if physicians in general are more familiar with GO and how the ophthalmopathy may present itself. In this regard the combined thyroid–eye clinic offers a golden opportunity. If the students and residents in training would attend the combined thyroid–eye clinics just a couple of times, they most likely will become acquainted with the phenotypic appearance of GO. Once you have seen the classical phenotype of rather symmetrical bilateral exophthalmos with swelling and redness of the eyelids and conjunctiva, you will probably remember the picture for the rest of your life. If our students join the weekly combined clinics for 1 month, they will have seen on average eight GO patients, allowing a reasonable case mix as well. It is hoped that this imprint of GO in their student time may result in early recognition of the disease when they come across a patient with red and/or protruding eyes later in their career.

Effect of Combined Thyroid–Eye Clinics on Research

The introduction of combined thyroid–eye clinics creates a favorable environment for research. In view of the many unresolved issues surrounding GO, there is an obvious need for more basic and clinical research to clarify its pathogenesis and improve outcomes by more efficacious and better tolerated treatment modalities. Most clinical trials in the field of GO suffer from a too restricted sample size. In our own experience and that of others, the availability of combined thyroid–eye clinics is attractive to patients and results in more referrals [16]. Many clinical studies are hampered by missing data. Combined thyroid–eye clinics are likely to do better on this point as well: patients undergo a structured investigation, facilitating completeness and validity of the dataset. Combined thyroid–eye clinics leads to multidisciplinary discussion of each GO patient, which is likely to generate new ideas. At one of our combined clinics we wondered why asymmetric involvement of both eyes is frequently observed despite the ophthalmopathy being clearly bilateral. We hypothesized that sleeping position might be involved: when for example the preferred sleeping position is on the right side, retrobulbar pressure might be somewhat higher in the right than in the left orbit, resulting in more severe eye changes in the right eye. Although the idea may be a little bit naïve and the hypothesis had to be rejected in a subsequent study among 75 consecutive untreated GO patients [17], the point here is that our combined thyroid–eye clinics with its steady flow of patients allowed us to test our hypothesis in a prospective study within a reasonable period of time.

The stimulating effect of combined thyroid–eye clinics on clinical research is illustrated by the number of randomized clinical trials (RCT) in GO patients performed in the last 25 years. There were 25 RCTs from Europe (where combined thyroid–eye clinics have become rather prevalent), and just 3 RCTs (all from Mayo Clinics, Rochester, MN) in the USA (where combined thyroid–eye clinics are rare).

Concluding Remarks

Institution of combined thyroid–eye clinics is likely to improve the quality of care delivered to GO patients, and it creates a favorable environment for teaching and research in this area. EUGOGO consequently recommends referral to combined clinics of all patients with GO except mildest cases [18]. The number of combined thyroid–eye clinics has been steadily increasing over the last 15 years worldwide, especially in Europe but less so in the USA.

Against the background of identified deficiencies in the management of GO patients [7, 8], international experts on GO, representatives of professional organizations, and patient representatives met in Amsterdam in October 2009, and unanimously agreed on the following [19, 20]. Health care providers and professional organizations should recognize the need to improve the care of people with GO and support plans for implementing better care and prevention. The general objectives are to minimize the morbidity associated with GO and improve the patients' experience and quality of life, and to prevent development of GO in people at high risk. The so-called "Amsterdam Declaration on Graves' Orbitopathy" was signed by 31 endocrinological and 30 ophthalmological societies, and 24 thyroid patient associations. The 5-year targets are:

- Halfing the time from presentation to diagnosis
- Halfing the time from diagnosis to referral to a center of excellence
- Appropriate management of thyroid dysfunction
- Vigorous antismoking measures
- Improvement of existing research networks
- Development of international collaborative research.

The Amsterdam Declaration International Steering Group (composed of EUGOGO, International Thyroid Eye Disease Society, and Thyroid Federation International members) was established to track progress on the targets. Combined thyroid–eye clinics could contribute greatly to reach targets.

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Chapter 15
Thyroid Dermopathy and Acropachy

Vahab Fatourechi

Introduction

Thyroid dermopathy and acropachy are extrathyroidal manifestations of autoimmune thyroid disease, in particular Graves' disease [1]. Thyroid dermopathy is also called pretibial myxedema because of its usual presentation in the pretibial area, although it can also less commonly occur in the upper body particularly if exposed to repeated trauma [2], and in surgical and burn scars and vaccination sites [3]. Since it is a systemic autoimmune manifestation of Graves', it can be present independent of status of thyroid function. Over 90 % of cases have either current or past history of hyperthyroidism [1]. The remainder may have been euthyroid [4, 5] or hypothyroid [6] and have had previous diagnosis of Hashimoto thyroiditis [7, 8]. Basic pathogenic process is similar to Graves' ophthalmopathy [9, 10] [11]. Occurrence in the lower extremity is best explained by dependent position and mechanical factors [12, 13]. Diagnosis is based on typical clinical skin features and ubiquitous presence of ophthalmopathy [1].

Thyroid acropachy is manifested by clubbing of fingers and toes and fusiform thickening of fingers and toes and occasional periosteal reaction of distal bones. It is considered an advanced form of dermopathy [14]. Thyroid dermopathy and acropachy, except for rare cases, almost never occur without evidence of ophthalmopathy [14].

Epidemiology

Four out of 100 patients with ophthalmopathy in a midwestern community study had dermopathy [15] and one out of five patients with dermopathy has acropachy [14]. In cases with severe ophthalmopathy 13 % have dermopathy [16].

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Dermopathy of Graves' occurs in all ethnic groups and many cases have been reported in Japanese population [17].

Although dermopathy without ophthalmopathy has been reported in rare cases [1, 18], presence of resolved prior ophthalmopathy or subclinical form in these cases cannot be excluded [1].

Chronology of Dermopathy and Acropachy

Since for development of dermopathy longer duration and more severe immune process are required, it usually occurs in the second year or later after diagnosis of hyperthyroidism and after development of ophthalmopathy [19]. However, it can occur many years later after diagnosis of Graves' disease [1, 20]. Rare cases of dermopathy as a presenting manifestation of Graves' disease or in the absence of ophthalmopathy have been reported [18, 21–23].

Pathogenesis and Histology of Dermopathy and Acropachy

Similar activation of immune process as described in the section on ophthalmopathy is involved in dermopathy [10]. TSH receptor as a source of antigen and subsequent production of TSH receptor antibodies seem to be the starting point [10]. Serum of patients with pretibial myxedema stimulates fibroblasts in vitro [24]. A role for IGF-1 antibodies in sustaining the immune process has been proposed [12, 25–27]. Similar to orbital fibroblasts, the presence of TSH receptor in dermal fibroblasts has been demonstrated [10, 28–31]. The cascade of immune process that involves T-cells and B-cells and interleukin-1 and interferon-gamma and TNF results in fibroblast proliferation and production of excess glycosaminoglycans [32] and subsequent local fluid retention and edema [9, 10, 33]. Later obstruction of microlymphatic structures results in further aggravation of the process [34, 35]. Although there is recruitment of T-cell and B-cell lymphocytes, lymphocytic infiltration is less pronounced than in ophthalmopathy [1, 36]. In ultrastructural studies many fibroblasts show dilated rough endoplasmic reticulum containing abundant amorphous material which indicates a significant role of fibroblasts in the pathogenesis of this disease [37]. Histology of the lesions shows abundance of mucin and fragmentation of collagen fibers in the dermis [1]. Quantitative and qualitative defects of dermal elastic fibers are also present [38].

Pathogenesis of Pretibial Localization

There is indirect and direct evidence that thyroid dermopathy is a systemic process and subclinical disease may be present in the upper parts of body [39]. Yet some biopsy studies in the upper extremity have not shown fibroblast proliferation in the

upper extremity biopsies in Graves' disease [40]. Dermopathy can develop in any location in the upper or lower extremity or trunk, if subjected to mechanical factors such as trauma [2, 41, 42]. The more common localization in the lower extremity in the form of pretibial myxedema can be explained by either difference in fibroblast subtypes in different areas of the skin [43, 44] or mechanical factors [12]. However, mechanical factors seem to be the dominant factor [45]. In favor of mechanical theory is the fact that thyroid dermopathy can occur in the upper extremity when exposed to trauma [2, 42] or in the surgical scars, in vaccination sites, and in burn scars [3]. Also when skin is grafted from upper extremity to lower extremity, dermopathy can develop in both the original site and donor site [45–47]. Thus pretibial localization is most likely a result of mechanical factors and dependency of the lower extremity.

Clinical Features of Dermopathy and Acropachy

Pretibial Myxedema

Thyroid dermopathy usually presents in pretibial areas, hence the name pretibial myxedema [1]. It can also be present as dermopathy of toes [48, 49] and feet [50]. Lesions are usually asymptomatic and may not be a source of complaint by patients and can be missed in early stages. Thus pretibial areas and feet should be carefully examined in patients that have ophthalmopathy. Mild cases present only as a cosmetic problem but severe cases may create functional problems such as difficulty wearing shoes or neurologic deficit as a result of entrapment neuropathy. Pain is usually not a complaint except in cases associated with acropachy and periosteal involvement. The lesions may be pruritic. Burning and numbness and occasional foot drop because of entrapment neuropathy can be seen [51].

The lesions have appearance of orange skin because of effect related to prominent hair follicle openings (Fig. 15.1). They may present as waxy, or flesh or reddish colored indurated plaques [17]. The lesions are often raised and firm and are non-pitting. Pigmentation and hypertrichosis may be present [1]. Localized hyperhidrosis may also be present in some lesions [52, 53] presumably related to local stimulation of sympathetic nerve fibers [54]. Exuberant tumoral lesions in dorsum of the feet may be present in advanced cases [55]. The lesions usually do not ulcerate [1].

Pretibial and lower extremity dermopathy can present in several clinical forms. The most common form is non-pitting edema (Fig. 15.2) [1]. Plaque form and nodular form [56–58] are also relatively common. Mixed forms of nodular and plaque forms also may be present [22] The extreme form is elephantiasis (Fig. 15.3) [59] that is less common and occurs in 5 % of cases [1]. The elephantiasis form clinically is similar to lymphedema [1].

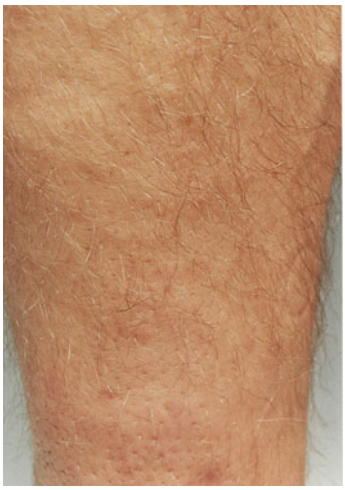

Fig. 15.1 Thyroid dermopathy in pretibial area of a patient with Graves' disease. Note *orange* skin appearance in the lower part of the image

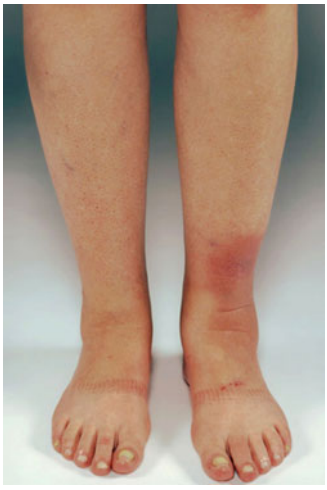

Fig. 15.2 This is a non-pitting edema type of thyroid dermopathy involving pretibial areas. Note the red color of the skin. Some asymmetry of the lesions in this patient is not a usual feature

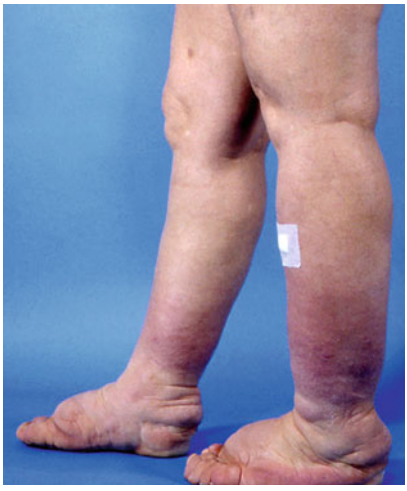

Fig. 15.3 Elephantiasis form of thyroid dermopathy involving tibial areas and feet and toes

Atypical Presentations and Involvement of Upper Body Skin

Spontaneous involvement of the upper extremity can occur in advanced cases, but is uncommon. Upper body dermopathy can occur in sites of vaccination, surgical scar, scar tissues [60], and in areas subject to trauma in particular if trauma is repetitive [2, 13]. Dermopathy of forehead [61], and cheeks associated with ophthalmopathy have been reported [62]. Rarely cutis gyrata [63] can occur. Combined elephantiasis of upper and lower extremity can occur in rare severe cases [42]. Involvement of a single index finger has been reported [64]. Skin lesions of shoulder in carriers of yolk, involvement of site of laparoscopy, and involvement of thenar area as a result of repetitive trauma have been reported [2]. When there is acropachy of upper extremity, it can be associated with dermopathy of entire hand. In one case vascular compromise resulted in amputation of a hand [11].

Acropachy

Acropachy is almost always associated with dermopathy and is a less common but more advanced manifestation. Most common presentation is asymptomatic clubbing of fingers and toes that happens in 20 % of dermopathy cases and may not be noticed by patients [14]. Clubbing is similar to other types of clubbing with other etiologies. Clubbing may be associated with fusiform soft tissue swelling of digits and toes with thickening of skin (Fig. 15.4) [14]. In its complete form, that happens in 3 % of dermopathy cases, there is periosteal reaction of distal bones that can be detected by X-Rays (Fig. 15.5) or bone scan. Acropachy sometimes is associated with significant pain mainly in patients with periosteal involvement [14, 65].

Punch biopsies of digits in patients with autoimmune thyroid disease have suggested a subclinical form of acropachy [66], but it appears that it could indicate subclinical dermopathy rather than acropachy.

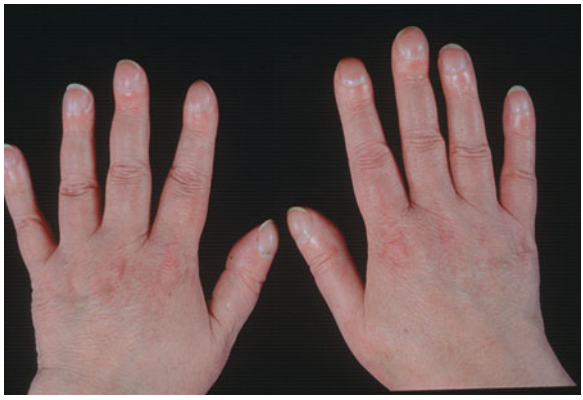

Fig. 15.4 Thyroid acropachy in a patient with dermopathy and acropachy. Note digital clubbing. There is moderate fusiform thickness of the digits

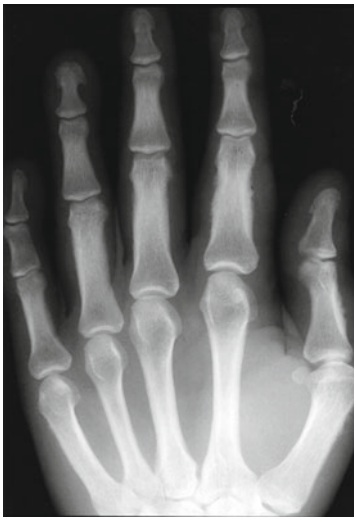

Fig. 15.5 Radiograph of a hand in a patient with thyroid acropachy. Note subperiosteal reaction best evident in the thumb and index finger

Diagnosis of Dermopathy and Acropachy

Diagnosis of Dermopathy

Diagnosis in patients with previous Graves' disease and in the presence of ophthalmopathy is based on clinical features. Skin biopsy is usually not needed but will confirm diagnosis in questionable cases [1]. In all cases thyroid-stimulating antibodies (TSI) or TSH receptor antibodies are positive, and if serology is negative diagnosis of active dermopathy should be excluded.

Presentation of pretibial myxedema without clear history of ophthalmopathy is of rare occurrence, and diagnosis in the absence of ophthalmopathy should be considered doubtful. In a large series of 178 patients with thyroid dermopathy, all had Graves' ophthalmopathy except four cases [1]. For follow-up and documentation of the status of dermopathy, digital infrared thermal imaging and high-resolution ultrasonography have been suggested [67].

Certain skin condition associated with mucinosis and lymphedema with other etiologies may have clinical and histologic similarities [68], but absence of positive serology for Graves' disease and lack of ophthalmopathy are helpful in differential diagnosis [69–76]. Chronic edema and subsequent secondary skin changes may also mimic the non-pitting edema type of dermopathy [77]. Mucinosis as a result of venous insufficiency or stasis, generalized myxedema, chronic or lichenified dermatitis, hypertrophic lichen planus, and mucinosis associated with morbid obesity [73] are other conditions with apparent similarities on clinical examination. Absence of ophthalmopathy, lack of history of Graves' disease, and, in particular, absence of elevated TSH receptor antibodies should exclude thyroid dermopathy [13]. It should be noted that in hyperthyroidism of Graves' disease with heart failure and sometimes without heart failure, because of vasodilation, pitting edema of the lower extremity may be present and should not be mistaken for pretibial dermopathy [78, 79].

Diagnosis of Acropachy

Since acropachy almost never happens in the absence of dermopathy and ophthalmopathy and never in the absence of elevated TSH receptor antibodies, clinical picture is the basis for diagnosis [14]. The differential is pulmonary osteoarthropathy and other causes of clubbing including occult malignancy [80]. Radiologic studies in thyroid acropachy show periosteal reaction [65] that has a frothy, leathery, or lacy appearance more characteristic to thyroid acropachy and somewhat different from pulmonary osteoarthropathy. The involvement is usually limited to metacarpals, the proximal middle phalanxes of the fingers, and metatarsal and proximal phalanxes. Findings are more prominent in the midportion of diaphysis. Long bones are less likely to be involved and joints are not usually involved although one case has been reported [14]. Radiographs show a periosteal reaction that tends to be bilateral and generally symmetrical involving the tubular bones of the hands and feet [81]. Periosteal reaction in the long bones of the lower extremities is unusual in thyroid acropachy, and when it occurs, it is more likely to be associated with considerable pain [65]. Bone scan shows abnormal accumulation of radio nucleotides in the periosteal areas [82]. In some cases radiographs may be normal but bone scan may be abnormal [82, 83]. Although MRI features also have been demonstrated in acropachy and dermopathy, it is not needed for diagnosis [84]. Only one histologic study is available showing nodular fibrosis of periosteal area [85].

Measures for Prevention of Development or Worsening of Dermopathy and Acropachy

All of the preventive measures for ophthalmopathy are applicable to dermopathy and acropachy [86]. The role of environmental risk factors for occurrence and progression of ophthalmopathy has been well defined in the chapter on ophthalmopathy. Tobacco use is the most studied risk factor for extrathyroidal manifestations of Graves' disease [87–89]. It is also the best modifiable risk factor for dermopathy and acropachy. Among patients with dermopathy 75 % have a history of tobacco use, many times more than the frequency of tobacco use among comparable population [13, 14]. It is hoped that with reduction in tobacco use the frequency of ophthalmopathy and dermopathy will be reduced. It is advisable to have tobacco cessation counselling for all patients with Graves' disease even before development of extrathyroidal manifestations [14].

Rapid normalization of thyroid function is likely beneficial for improvement of immune process. The mode of therapy of hyperthyroidism also may influence extrathyroidal manifestations [90, 91]. There are reports of development of aggressive dermopathy after radioiodine therapy [59], but isolated case reports cannot be relied on. However, randomized studies have shown that radioactive iodine therapy may aggravate ophthalmopathy in 15 % of cases if not accompanied by concomitant corticosteroid therapy [92–94]. In support of this finding is the evidence to show

that TSH receptor antibodies are increased after radioactive therapy, whereas surgical thyroidectomy and to a lesser extent antithyroid therapy will reduce antibody levels [95]. It is thus reasonable to recommend concomitant one month prednisone therapy with taper in 2–8 weeks in high risk cases or if there is evidence of ophthalmopathy or current tobacco use. Some authors recommend that most (if not all) patients treated with radioiodine should receive low-dose oral prednisone (so-called steroid prophylaxis) to prevent radioiodine-induced *de novo* occurrence or progression of existing ophthalmopathy [96, 97]. The same may apply for prevention of development of de novo dermopathy and acropachy and worsening of existing dermopathy. Although there is no clear evidence, it is possible that early systemic therapy for ophthalmopathy may prevent dermopathy and acropachy. American Thyroid Association recommends thyroidectomy for some cases of Graves' hyperthyroidism with severe ophthalmopathy with the intention of rapid normalization of thyroid function and also for most efficient way of reducing TSH receptor antibody levels [98]. It is conceivable that this approach may also be helpful in preventing development of dermopathy. Avoidance of multiple radioactive therapies and early management of treatment-induced hypothyroidism are also important [91, 99].

The recent evidence for benefits of selenium in mild Graves' ophthalmopathy is of interest and it may be applicable to prevention of dermopathy. In this European multicenter randomized study of patients with mild Graves' ophthalmopathy, 100 μg of selenium twice daily for 6 months was shown to be associated with improvement of ophthalmopathy [100]. Accordingly, selenium supplementation should be regarded as a preventive measure in Graves' patients particularly if there is ophthalmopathy.

After total ablation of thyroid antibodies gradually disappear in, 3 years, follow-up [101]. Theoretically total ablation of thyroid by either surgery, radioiodine, or a combination of both, because of elimination of source of antigen, may also be an empiric preventive measure with possible long-term benefit [102–104]. Available data are, however, inconclusive.

Preventive measures that are specific for dermopathy include avoidance of trauma, unnecessary surgery in the lower extremities, and appropriate shoes to avoid pressure to toes and feet [11]. Obesity is a risk factor since it aggravates mechanical factor of dependency [105]. Weight management thus is essential since it is also reported to be associated with mucinosis in none Graves' patients [13, 73, 105, 106].

In most patients with dermopathy, there is severe ophthalmopathy and systemic immunotherapy may be used for ophthalmopathy. Thus some cases of dermopathy may be prevented [11].

Therapy of Thyroid Dermopathy and Acropachy

Mild asymptomatic cases of dermopathy in the pretibial areas can be covered by clothing, and some patients may not request therapies other than management of thyroid dysfunction and management of more vexing ophthalmopathy [1].

However with increased duration dermopathy lesions may undergo secondary lymphatic obstructive changes and in severe cases fibrosis may develop and lesions may become irreversible [11]. Our practice is, other than preventive measures described above, to initiate local corticosteroid therapy early in the course of disease [11]. To reduce the effect of dependency of the lower extremity and mechanical pressure in patients with increased BMI, weight management is not only a preventive measure but also a part of management of existing disease. Support stockings and appropriate shoes to avoid repetitive trauma to the foot are also recommended [11].

Local Therapies

Corticosteroid therapy should be directly applied to involved skin and covered with occlusive dressing [107, 108]. After application, the area should be covered with plastic films such as Saran Wrap (S.C. Johnson and sons, Inc). Early treatment is essential since longstanding lesions may not respond well to local therapy [109]. Fluocinolone acetonide or high potency clobetasol propionate or triamcinolone cream base 0.1 % can be used. Application can be kept for 12 h/day usually overnight and be continued up to 6–10 weeks depending on response [1]. After improvement of the lesions, maintenance local therapy 2–4 times per month may be needed [1]. Skin should be observed for adverse reaction of chronic local corticosteroid therapy such as skin atrophy, telangiectasia and ecchymosis, or infection. In one reported case of acropachy of upper extremity with dysfunction of fingers, application of fluorinated topical steroids under an occlusive dressing, using one hand as a control, resulted in a substantial decrease in hand circumference and volume and increased finger mobility in the treated hand [83].

Use of compression stocking or Jobst stocking during the day after overnight corticosteroid application will prevent fluid retention and reduce dependency effect on the lower extremity [1, 11]. Athletic wraps or compression stockings with 20–40 mmHg of pressure are also helpful. In severe cases therapies similar to lymphedema with intermittent pump can be used [110]. Complete decompressed physiotherapy, manual lymphatic drainage, massage, and compressive bandages in elephantiasis cases are recommended [110, 111].

Topical clobetasol propionate cream and tacrolimus ointment 0.1 % for about 7 months were reported to be of benefit in one patient [112].

Surgical excision although reported in some cases [113, 114] should be avoided because of risk of exuberant scarring.

Although previous reports of local corticosteroid injection had indicated adverse pitting of the skin and cosmetic issues [114], recent use of mesodermic needles in two reports has indicated excellent results. One patient was treated with triamcinolone acetonide by multipoint subcutaneous injections in a combined dose of 20 mg in each lower extremity administered every 25–28 days. The injection was started from the border of the lesions and normal skin by selecting 4–5 points per leg for

each course and then moving to other parts in subsequent courses of treatment. The depth of mesodermic needle insertion was 0.5–1.0 cm. The reported patient had complete remission after 6 months of therapy [115]. In another report similar benefit was noted in five treated patients, one with elephantiasic and four with diffuse pretibial myxedema. Patients had local injection of a mixed solution of dexamethasone lidocaine and saline in the subcutaneous tissue using 4 mm long needles employed for mesotherapy, delivering the medication within the dermis or the first layer of the subcutaneous fat. Pretibial myxedema plaque and the area surrounding the lesions were injected once a week for three consecutive weeks. All patients reportedly showed improvement of pretibial myxedema at clinical assessment and a reduction of the thickness of the lesions at ultrasound [116]. These two reports are of interest but further studies are needed to recommend their routine use.

Systemic Therapies

There are no randomized studies of systemic immunotherapies focused on thyroid dermopathy. It is unlikely that such therapies will be feasible because of rarity of the condition. Thus any therapy proven by randomized therapies to be of benefit for ophthalmopathy empirically can be applied to dermopathy.

It should be considered that since thyroid dermopathy is a risk factor for severe ophthalmopathy, majority of patients with dermopathy may receive systemic corticosteroid therapy for their ophthalmopathy. When these two extrathyroidal manifestations are present, it is a judicious practice to have a low threshold for systemic immunosuppressive therapy.

Intravenous pulse prednisolone has shown mild superiority to oral corticosteroid therapy for ophthalmopathy [117]. And oral prednisone has been proven to be superior to cyclosporine and combination has been superior to either one for Graves' ophthalmopathy [86] and may thus be considered for severe cases of dermopathy.

Although some case reports have shown benefit of octreotide therapy for ophthalmopathy, therapy of two cases with severe dermopathy did not show any benefit [118]. Moreover, in randomized studies long-acting release octreotide has not been shown to be beneficial for ophthalmopathy [119, 120]. Thus octreotide also cannot be recommended for dermopathy.

Reports of therapy with plasmapheresis [121–124] and intravenous immunoglobulin for dermopathy [125] have indicated benefit. These reports are limited to isolated cases and benefits cannot be confirmed. There are reports of Rituximab therapy directed at dermopathy with some positive results [127, 128]; however recently conducted randomized studies for ophthalmopathy have had conflicting results. One randomized study of 12 patients with moderately severe ophthalmopathy has shown no superiority to placebo (Stan, M. et. al, personal communications) and another study of 16 patients compared to IV corticosteroids has shown superiority of Rituximab to IV corticosteroid pulse therapy (Salvi, M. et al, personal communications). Before this biotherapy can be applied to dermopathy, more randomized studies for ophthalmopathy are needed.

Potential Future Therapies

There are other potential agents that can block the cascade of immune process involved in pathogenesis of ophthalmopathy and dermopathy [10]. Some agents such as IGF-1 receptor blocking antibodies IGF-1 receptor [129] and mycophenolate [130, 131] are actively undergoing randomized therapies for ophthalmopathy and results soon will be available. There are other agents that have shown potential promise in in vitro studies of orbital fibroblasts and thus deserve to be used in trials. A small molecular ligand (SML) antagonist of TSHR inhibits thyrotropin receptor antibody-induced orbital fibroblast functions involved in the pathogenesis of Graves' and ophthalmopathy [132]. Similar molecules or antibodies may also be potential therapeutic candidates for extrathyroidal manifestations of Graves'. There are other agents that from pathogenic standpoints may be targets for future therapies for ophthalmopathy and if proven of benefit can be applied to dermopathy and acropachy [10, 133]. These agents include small molecule antagonists of TSH receptor [132], Enalapril [134], thalidomide [135], inhibitors of IL-1 ((gevokizumab) [136], blockers of CD28-mediated costimulatory pathways (Abatacept) [10], human anti-B-cell activating factor monoclonal antibody (Belimumab) [10, 137], TNF inhibitors (infliximab) [138, 139], TGF-beta blocking antibodies (lerdelimumab) [10, 140], interleukin-6kin- 6 blockade therapy (tocilizumab) [141, 142] and Interleukin-1 receptor antagonist (Anakinra) [143], and etanercept [144].

Long-Term Outcome

Long-term outcome of thyroid dermopathy and acropachy has not been well studied. Spontaneous resolution associated with reduction in TSH receptor antibodies in one case despite minimal therapy has been recently reported [127]. In the only available long-term follow-up of a large cohort of 178 patients with dermopathy, approximately 46 % with mild dermopathy did not receive any specific therapy for dermopathy [1]. A 17-year follow-up of the untreated patients suggested 50 % complete remission. However after 25 years 58 % of treated patients with local therapy and 75 % of milder cases without treatment had either partial or complete remission [1]. However these results should be interpreted with caution. Although it appears that severe cases despite treatment fared worse than mild cases without therapy, this should not be interpreted as a reason for not initiating therapy for mild cases. The author believes that all cases of pretibial myxedema even early cases should receive local corticosteroid therapy to avoid vicious cycle of pathologic process.

Conclusion

Between 4 and 13 % of patients that have ophthalmopathy of Graves' disease will develop dermopathy and 20 % of dermopathy patients will have acropachy, predominantly in the form of digital clubbing. Pathogenesis of dermopathy is

similar to ophthalmopathy. TSH receptor antibodies react with TSH receptors present in the fibroblasts resulting in fibroblast proliferation and hyaluronic acid and mucin production. Localization of thyroid dermopathy to lower extremity can best be explained by mechanical factors such as dependency of the lower extremity since low level dermopathy is likely a systemic process and dermopathy can develop in upper body if skin is traumatized.

Measures for prevention and treatment of dermopathy are similar to ophthalmopathy. They include optimal and rapid normalization of thyroid function and early local corticosteroid therapy for existing pretibial myxedema.

First-line systemic therapy includes corticosteroids. Other systemic therapies used in ophthalmopathy can be tried in refractory cases not responding to local corticosteroid therapy. At the present time evidence for specific effectiveness in dermopathy is lacking. In future any systemic therapy proven to be beneficial for ophthalmopathy can be used empirically for refractory cases of dermopathy.

For thyroid acropachy no specific therapy has been reported and management should be preventive and local therapy for associated dermopathy of hands and feet. In severe cases of acropachy with painful periosteal reaction, pain management will be needed.

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Chapter 16
Treatment of Hyperthyroidism in Patients with Graves' Orbitopathy

Luigi Bartalena

Introduction

Graves' disease is the main form of hyperthyroidism in iodine-replete countries [1], and Graves' orbitopathy (GO) is its main and most frequent extrathyroidal manifestation [2]. A recent prospective study indicates that its prevalence in newly diagnosed Graves' hyperthyroidism is around 25 %, and GO is mild in most of these cases [3]. Thus, recent figures suggest that incidence and prevalence of GO are probably decreasing: a recent registry-based study from Denmark reported an incidence of moderate-to-severe GO of about 21 cases/million/year [4]. Likewise, it is apparent that progression of initially mild or absent GO to more severe forms is infrequent, whereas spontaneous improvement of mild forms may occur [3, 5]. Several explanations for this trend can be offered, but effective actions on modifiable risk factors for de novo development or progression of GO play a major role [6]. Some of these actions are related to modalities of treatment for hyperthyroidism and are outlined in the following paragraphs; others are independent of treatment for hyperthyroidism. Smoking is a well-established risk factor for GO [7], and quitting smoking has been associated with a decreased risk of developing exophthalmos and diplopia [8]. Oxidative stress plays a major role in both Graves' hyperthyroidism and GO [9, 10]. Thus, a course of selenium, a trace element with antioxidant and immunomodulating properties, has been shown to improve mild GO and prevent its progression to more severe forms [11].

In many instances onset of hyperthyroidism and onset of GO are temporally linked and usually occur within 12–18 months of each other [12]. GO may however develop even years before hyperthyroidism or may follow it. In the latter situation there might be a relation between treatment for hyperthyroidism and occurrence of GO.

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In this chapter I briefly review the effects of currently available treatment modalities for hyperthyroidism [antithyroid drugs (ATDs), radioiodine (RAI), thyroidectomy] on GO and discuss the therapeutic approach to hyperthyroidism in patients with associated GO.

Effects of Treatment Modalities for Hyperthyroidism on GO

Antithyroid Drugs

ATD treatment represents the first-line treatment for Graves' hyperthyroidism in Europe and Japan [1], although an increased use of this treatment modality has recently been observed also in United States [13, 14]. Methimazole (or carbimazole in the UK) is now generally preferred to propylthiouracil, except for the first trimester of pregnancy [15]. There is no evidence that ATDs have direct effects on GO (Table 16.1). However, circumstantial evidence indicates that restoration of euthyroidism associated with ATD treatment is associated with an improvement of preexisting GO [16]. Furthermore, in a Dutch study uncontrolled hyperthyroidism appeared to be associated with a greater likelihood of severe GO [17]. Thus, earlier diagnosis of hyperthyroidism and institution of ATD treatment probably represent a key factor affecting the low rate of progression of GO discussed above. In the Consensus Statement of the European Group on Graves' Orbitopathy (EUGOGO), prompt restoration and stable maintenance of euthyroidism is a fundamental recommendation and should be included among preventive actions [18].

RAI Treatment

RAI treatment is a well-established therapy for Graves' hyperthyroidism (15, 19). In the USA it still is the first-line treatment [1, 14]. Several reports, including randomized clinical trials and a meta-analysis, have clearly indicated that RAI bears a

Table 16.1 Effects of various treatments for hyperthyroidism on Graves' orbitopathy

Treatment	Effect on orbitopathy
Antithyroid drugs	• Neutral, possible amelioration related to restoration/maintenance of euthyroidism and/or decrease in TSH-receptor antibody levels
Radioiodine	• Possible deterioration and/or de novo appearance related to exacerbation of autoimmune reactions after RAI-induced cytolysis • Most likely in the presence of risk factors (particularly smoking) • Undue effect can prevented by low-dose oral steroid prophylaxis
Thyroidectomy	• Neutral, possible amelioration due to removal of thyroid antigens and intrathyroidal autoreactive T-lymphocytes

low but definite risk for de novo occurrence or progression of mild GO [20–23]. This deterioration occurs in about 15–20 % of cases and is permanent in 5 % (Table 16.1) [21]. It is most likely in smokers [23, 24]. Late correction of post-RAI hypothyroidism is an important risk factor for RAI-associated exacerbation of GO [25, 26]. Thus, a strict follow-up of patients after RAI treatment is mandatory.

The untoward effect of RAI treatment on GO can be prevented almost always by a short course of low-dose oral prednisone, the so-called steroid prophylaxis [21, 27, 28]. This is particularly important if other risk factors for progression of GO, such as cigarette smoking or high levels of TSH-receptor antibodies, are present [18]. In my clinical practice, in view of the negligible risk of using very low doses of steroids for a few weeks, I give steroid prophylaxis to almost all patients submitted to RAI treatment.

Thyroidectomy

Surgical treatment is less frequently used than ATDs and RAI for the management of Graves' hyperthyroidism, but is especially indicated in large goiters or when associated malignancy is suspected [1]. In recurrent hyperthyroidism, thyroidectomy is a valid alternative to RAI according to patient choice [29]. Thyroid surgery should be performed by skilled and experienced surgeons to minimize the risk of related complications, namely, hypoparathyroidism and laryngeal nerve paralysis [30].

Conflicting results have been reported in the literature concerning the effects of thyroidectomy on GO, with uncontrolled studies reporting improvement, deterioration, or no change of GO [31]. In general, thyroidectomy is believed to be neutral to the outcome of GO [31]. A variant of a pure surgical approach is the so-called total thyroid ablation (TTA). This consists of a combination of total thyroidectomy followed by RAI remnant destruction. The rationale is that, if GO results from autoimmune reactions directed against antigen(s), total antigen removal (not achievable by either thyroidectomy or RAI alone), as well as removal of autoreactive intrathyroidal T-lymphocytes, might be beneficial for GO. Some studies have indeed suggested that TTA may provide better GO outcome, at least in the short term, compared with surgery alone, in patients with moderate-to-severe GO treated with immunosuppressive therapy [32–35], but the problem is still unsolved owing to paucity of randomized control trials.

Choice of Treatment for Hyperthyroidism in Patients with Associated GO

GO is characterized by an initial phase of florid inflammation of different severity (active disease), followed by a period of stabilization (plateau phase) and a subsequent, progressive remission of inflammation until complete inactivation (burnt-out disease) [36]. Duration of the whole cycle is variable, but it is commonly believed to last 18–24 months. Spontaneous complete regression, except for mild cases, is

almost impossible. Treatment of GO depends on assessment of disease activity and severity [18]. Assessment of GO activity and severity still is somehow difficult. A simple yet admittedly imperfect method to define activity is based on the calculation of the Clinical Activity Score (CAS) [37]. This is composed of seven items (eyelid/periorbital swelling, eyelid erythema, conjunctival erythema, chemosis, caruncle edema, spontaneous ocular pain, pain with eye movements) which reflect inflammatory status. By giving one point to every item, when present, a score ranging from 0 (no activity) to 7 (highest activity) is obtained. Arbitrarily, a CAS $\geq$3 identifies patients with active GO [18]. Objective definition of severity is also difficult and should result, in addition to assessment of inflammatory changes, from an overall evaluation of different components of the disease (exophthalmos, extraocular muscle dysfunction, secondary corneal abnormalities, optic nerve involvement) [18]. In addition, assessment of changes in the quality of life by disease-specific questionnaires [38] should be included to define severity of the disease, because what appears to be objectively mild to the physician may be perceived as severe by the patient, because cosmetic (exophthalmos, swollen eyes) and functional (diplopia) ocular changes heavily interfere with daily activities. Thus, GO may be mild and inactive or active, moderate-to-severe and active or inactive, or sight-threatening (due to dysthyroid optic neuropathy or corneal breakdown) [18]. Immunosuppressive treatment (usually high-dose systemic glucocorticoids with or without orbital radiotherapy) is first-line treatment for moderate-to-severe and active GO [39, 40], while most patients with mild GO usually do not need any specific treatment except for local treatments (eye drops and ointments, dark glasses) and preventive measures (particularly quit smoking) [18]. As previously mentioned, selenium supplementation is an important measure for mild orbitopathy [10, 11]. Occasionally, patients with mild and active GO may require immunosuppressive treatment if the impairment in GO-related quality of life is relevant [18]. Dysthyroid optic neuropathy requires immediate high-dose intravenous glucocorticoid treatment followed by emergent orbital decompression if response to medical treatment is absent-to-poor within 2 weeks [18, 41].

Irrespective of, but strictly related to, management of GO, most patients need to be treated for the associated hyperthyroidism. The optimal treatment for thyroid hyperfunction in patients with GO and the question whether the severity and activity of GO influence the choice of treatment for hyperthyroidism remain unsolved problems owing to the limited evidence coming from randomized clinical trials [31].

Mild GO

Management of hyperthyroidism in these patients is not influenced by the presence of mild orbital disease (Fig. 16.1). The choice among ATDs, RAI, and thyroidectomy is based standard criteria, including age, first episode versus recurrence, goiter size, patient preference, presence of suspicious nodules [42], or regional differences [1, 14]. Solid and convincing evidence supporting the superiority of the conservative

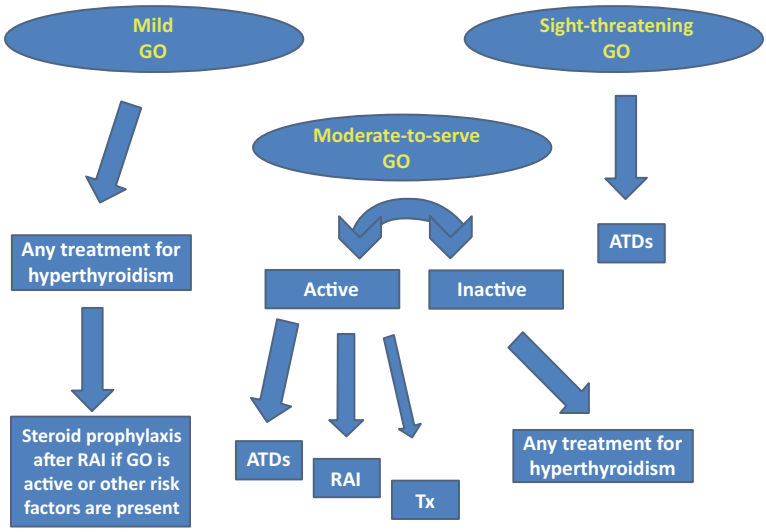

Fig. 16.1 Treatment for hyperthyroidism in patients with associated Graves' orbitopathy (GO). In patients with moderate-to-severe and active GO, different widths of arrows and different positions of treatment boxes indicate a hierarchy in the preference for either treatment. *ATDs* antithyroid drugs, *RAI* radioiodine, *Tx* thyroidectomy

approach (ATDs) over a more radical approach (RAI, thyroidectomy, total thyroid ablation) or vice versa is missing [32–35, 43, 44]. It is certainly true that ATD treatment is associated with a very low rate of progression of GO to more severe forms and may be accompanied by a substantial remission of ocular involvement [3, 5], but rapid control of hyperthyroidism and stable maintenance of euthyroidism are more important than the method used to achieve these goals [18]. The latter can be obtained also with RAI and surgery. If RAI is the treatment of choice, steroid prophylaxis should be given to most patients if *mild and active* GO shows some signs of activity, because the benefits (prevention of RAI-associated GO development or exacerbation) outweigh the risks associated with a short course of low-dose oral prednisone (Fig. 16.1) [2, 18]. This is particularly true if other risks for GO progression or de novo occurrence (smoking, high levels of TSH receptor antibodies) coexist [18]. Selenium administration for 6 months is a valid adjuvant treatment for mild and active GO given ATDs and to prevent its deterioration [10, 11]. Whether this treatment is effective for a better/prompter control of hyperthyroidism or to reduce the risk of relapse of hyperthyroidism after a course of ATDs is unproven. Likewise, there is no current evidence that selenium may be useful in addition to or as a substitute for steroid prophylaxis in patients with mild and active GO receiving RAI treatment.

Patients with *mild and stably inactive* GO may need rehabilitative surgery for cosmetic or functional residual manifestations (exophthalmos, extraocular muscle dysfunction, eyelid malposition). In these patients treatment for hyperthyroidism is unlikely to affect GO. Accordingly, patients can safely be submitted either to a

course of ATDs or to total thyroidectomy, as indicated, without any detrimental effect for GO [31, 45]. There is no universal agreement on whether steroid prophylaxis should be used also in these patients, if RAI is the selected treatment for hyperthyroidism [26, 46]. The presence of risk factors for GO progression other than RAI, e.g., smoking or high TSH receptor antibody levels, may support the choice of using steroid prophylaxis also in these patients [18].

Moderate-to-Severe GO

Patients with *moderate-to-severe and active* GO should be treated with high-dose systemic glucocorticoids [39, 47] with or without orbital radiotherapy [18, 48]. Other treatments, particularly rituximab [49] or other biologics [50], are presently under investigation, but studies of randomized clinical trials are not available [50]. Treatment should be given as early as possible in the course of GO to increase the chances of a favorable outcome [36]. In these patients optimal treatment for hyperthyroidism (conservative therapy vs. thyroid ablative therapy) is controversial and a matter of argument (Fig. 16.1). ATDs offer the advantage of a prompt and, usually, stable restoration of euthyroidism, frequently associated *per se* with an improvement of ocular involvement [3, 16, 17]. Patients can be treated for a long time (even several years) [43, 44] while their orbitopathy is inactivated or cured. The drawback of ATD treatment is the high rate of hyperthyroidism recurrences [51]. The latter might potentially be associated with a flare-up of eye disease, although in a retrospective study it has been reported that subsequent RAI treatment is safe for GO after this approach (long-term ATDs for hyperthyroidism and treatment for GO) [43]. Choice of thyroid ablative therapy in patients with moderate-to-severe GO is supported by the concept that, ideally, removal of intrathyroidal autoreactive T-lymphocytes and thyroid antigens likely involved in the pathogenesis also of GO (shared antigen hypothesis) [52] might be beneficial to the orbital disease [53]. Some, but not conclusive, evidence indeed shows that this approach may be associated with a better outcome of immunosuppressive treatment [32–34] or, at least, with a faster achievement of the best possible result [35]. In summary, evidence is limited to make one prefer either the conservative approach or the ablative approach. In practical terms, moderate-to-severe GO should be promptly treated and, at the same time, euthyroidism should be promptly restored by ATDs (if the thyroid has not been ablated previously) (Fig. 16.1). One possible way to reconcile the two approaches, which I frequently use in clinical practice to my satisfaction, is to start intravenous glucocorticoids (with or without orbital radiotherapy), to treat patients with RAI after the first 6 of 12 weekly glucocorticoid infusions, and to continue then, until completion, the immunosuppressive treatment. Admittedly, this approach is not based on evidence, but rather reflects wide experience.

Selection of treatment for hyperthyroidism in patients with *moderate-to-severe and inactive GO* is far less critical or controversial (Fig. 16.1). Patients have no signs of inflammation; their residual manifestations are exophthalmos, strabismus, eyelid malposition, to be corrected surgically. In these patients any modality of

treatment for hyperthyroidism can be chosen, based on standard criteria. As for mild and inactive GO, the use of steroid prophylaxis, if RAI is selected, is debated. In this regard, the high indirect (loss of productivity) and direct (treatment, hospitalization etc.) costs of a reactivation of GO [54] should be considered, also in view of the very low risks associated with a short course of low-dose prednisone [28].

Sight-Threatening GO

This is an emergent, although it is fortunately rare, situation, due to dysthyroid optic neuropathy (DON) and/or corneal breakdown. There is no doubt that management of GO with very high doses of intravenous glucocorticoids and/or orbital decompression has an absolute priority [18]. In these patients hyperthyroidism should be controlled with ATDs, and definitive treatment, if needed, should be postponed until DON has improved and GO has become inactive or has been cured [18].

Conclusions

Many patients with Graves' disease have no ocular involvement at diagnosis [3] and infrequently develop GO during the course of the disease [5]. In patients who have GO, optimal treatment for hyperthyroidism represents a dilemma. All of established therapies for hyperthyroidism (ATDs, RAI, thyroidectomy) can be used safely in patients with mild GO, and their choice is based on established criteria independent of GO, but, if RAI is selected, steroid prophylaxis is advisable in the majority of cases, especially when some signs of activity of GO and/or other risk factors for RAI-associated progression of GO are present [31]. In patients with sight-threatening GO, ATDs are the treatment of choice while GO is being treated. In patients with moderate-to-severe GO, the optimal treatment remains a matter of discussion.

A final consideration is that the established treatments for hyperthyroidism as well as for GO are imperfect because they do not target pathogenetic mechanisms of either hyperthyroidism or GO [55]. Thus, future efforts should be directed to identify novel therapies acting simultaneously on pathogenetic mechanisms causing thyroid disease and orbital disease. These treatments should cause permanent remission of hyperthyroidism without causing hypothyroidism, prevent occurrence or progression of preexisting GO, cure GO without the need for rehabilitative surgery, and have low cost and low risk of side effects/complications. For the time being, such medications are not available, and translation of promising basic research into clinical practice is beyond the horizon.

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Conflicts of interest none to declare.

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Chapter 17
Assessment and Management Plan for Graves' Orbitopathy

Peter J. Dolman

Introduction

Graves' Orbitopathy (GO), or Thyroid Eye Disease (TED), is an autoimmune disorder affecting orbital fat, extraocular muscles, and lacrimal gland, causing inflammation, tissue expansion, and fibrosis [1, 2].

It is the most common orbital disease worldwide, with an annual incidence in females of approximately 15 per 100,000 and approximately one-fifth that for males. It occurs in all races and is most common between the second and sixth decades [3]. Although TED is self-limited, it may cause permanent cosmetic and visual morbidity, impacting quality of life more than diabetes mellitus or chronic pulmonary disease [4].

The most frequent clinical presentation results from orbital fat expansion with proptosis, upper lid retraction, and resultant ocular exposure (Fig. 17.1a, b). Approximately one-third of patients with TED develop a more severe presentation from significant extraocular muscle involvement, with periocular soft tissue redness and swelling, restricted ocular motility and double vision, and occasionally vision loss from compressive dysthyroid optic neuropathy (DON) (Fig. 17.2a, b) [5]. This spectrum of clinical changes is graded as "*disease severity*".

TED follows a biphasic course, with a progressive or active phase lasting up to 18 months, followed by a stable or inactive phase. Rundle first described this

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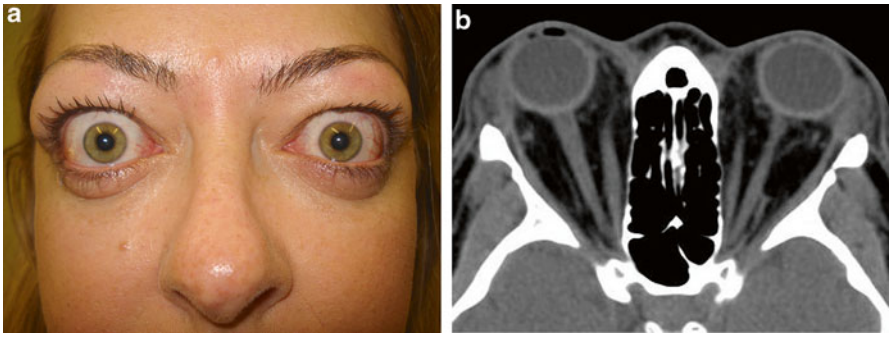


Fig. 17.1 (**a**) A 32-year-old female with insidious onset of progressive bilateral proptosis and upper lid retraction and right lower lid retraction. (**b**) Axial CT Scan demonstrates proptotic globes with fat expansion and prolapse of enlarged lacrimal glands but no significant extraocular muscle involvement

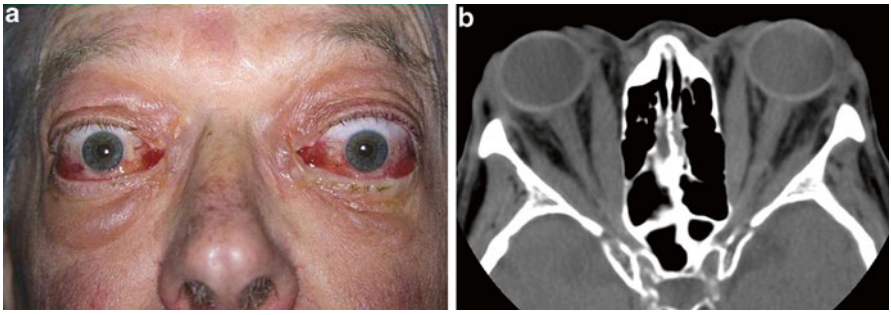


Fig. 17.2 (**a**) A 73-year-old male with progressive, rapid onset of severe inflammatory features with restricted ocular movements. (**b**) Axial CT Scan demonstrates enlargement of horizontal recti muscles bilaterally, corresponding with areas of redness and swelling on the bulbar conjunctiva. There is probable crowding of the optic nerve at the apex

progression using a graph of orbital disease severity against time (Fig. 17.3) [6, 7]. A steeper slope in the active phase reflects a more precipitous onset with the likelihood of more serious sequelae [8]. During the early progressive phase, immunomodulators and radiotherapy may limit the destructive consequences of the immune cascade [9, 10]. Once the disease has stabilized, surgery may be considered to improve orbital cosmesis, comfort, and function. Occasionally surgery is required urgently during the active phase to prevent visual loss from DON or severe corneal exposure. The course and phases of the disease are graded as "*clinical activity*."

This chapter reviews methods for evaluating and grading both the severity and activity of TED, and describe the use of the VISA classification to predict the disease course, plan management, and assess response to therapy.

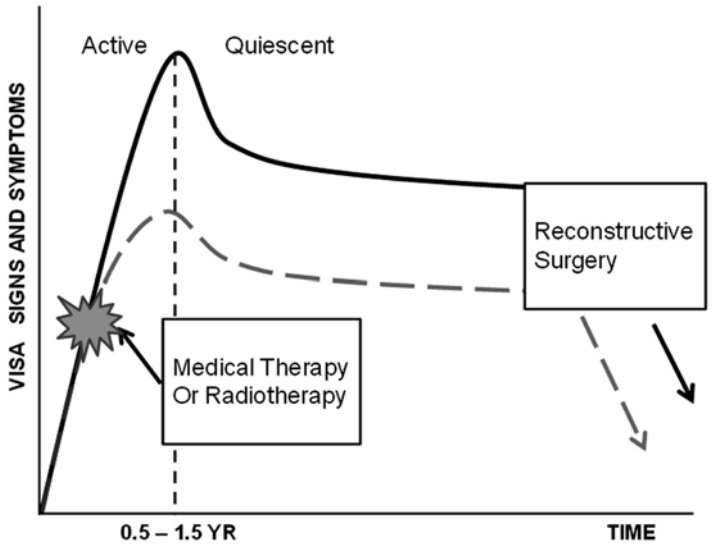


Fig. 17.3 Rundle's curve shows the biphasic course of myopathic Thyroid Eye Disease with a progressive (active) phase followed by a quiescent (inactive) phase. Medical therapy and radiotherapy are offered during the early progressive phase to prevent more serious complications of disease such as ocular motility restriction and optic neuropathy. Rehabilitative surgery is delayed until the quiescent phase. Occasionally surgery is required emergently during the active phase for vision threatening conditions such as compressive optic neuropathy or corneal ulceration

Diagnosis

Early diagnosis of TED allows appropriate evaluation and treatment that might prevent more serious complications. The primary physician may recognize early ocular clinical features, identify those at risk for developing serious disease, and arrange prompt referral to a dedicated center for appropriate intervention. This disease is best managed by a collaborative effort of experienced specialists, including ophthalmologists, endocrinologists, rheumatologists, and radiation oncologists.

The diagnosis is usually made clinically based on presenting ocular symptoms and signs described in the next section.

Abnormalities in thyroid function tests (T3, free T4, and TSH) and/or the presence of thyroid specific autoantibodies (anti-TSH receptor, anti-thyroid peroxidase) help support the diagnosis, although they may be negative.

Orbital imaging may be indicated if the clinical features alone are not diagnostic, or for monitoring progression or planning surgical intervention. Magnetic resonance imaging (MRI) may show increased edema in the muscles during the active phase [11] but is less helpful in surgical planning since it does not show bone structure. CT Scan is the most useful modality, allowing volume measurements of orbital fat and individual extraocular muscles [12], as well as identifying orbital apical crowding in optic neuropathy and the structure of the surrounding bone and sinuses for possible surgical decompression (Fig. 17.2b).

Clinical Features and Grading Severity

Appearance and Exposure

Over 80 % of patients with TED develop upper eyelid retraction, often with an insidious onset that is first recognized by others [13]. The "thyroid stare" has a characteristic lateral flare (Fig. 17.4a) that is accentuated with emotion or fixation giving the patient an angry look. It is associated with lid lag on down-gaze and incomplete lid closure while asleep (lagophthalmos). A careful review of CT images at our center has identified a strong correlation between enlarged levator muscle and upper eyelid retraction, suggesting that this muscle is the most common orbital muscle targeted by autoantibodies (Fig. 17.4b, c).

The lower lid typically rests at or slightly above the inferior corneal limbus. Lower lid retraction is present when sclera is visible inferiorly, and is associated with increasing proptosis (Fig. 17.1a).

Proptosis is the second most common finding in TED, resulting from expansion of the orbital fat and/or muscles. It may be less apparent in East Asians with tight eyelids limiting forward protrusion. Complete subluxation of the globe beyond the lids is a rare but troubling complication that may lead to visual loss if repositioning of the eye is delayed [14]. Proptosis is measured with the exophthalmometer and documented with photographs and orbital imaging (Figs. 17.1a and 17.2a).

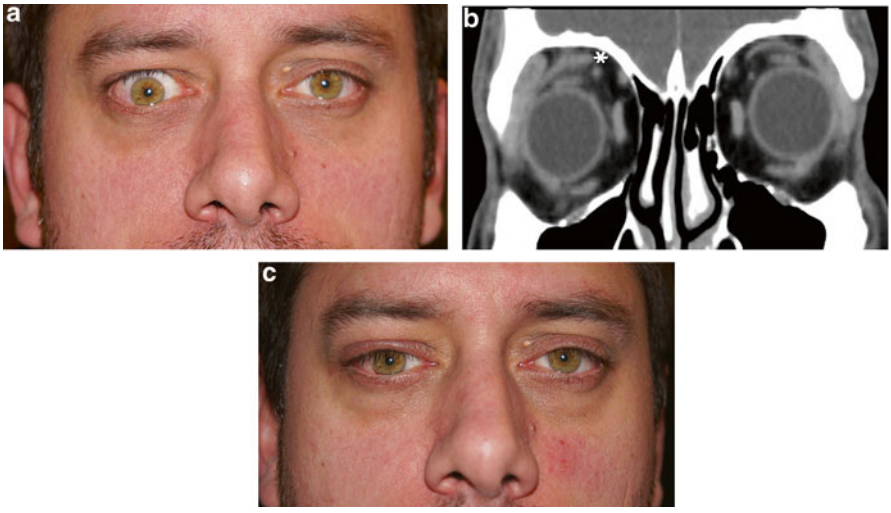


Fig. 17.4 (**a**) Isolated right upper lid retraction, the most common sign in thyroid eye disease. The patient was bothered by his altered appearance as well as dryness and photosensitivity. (**b**) Coronal CT Scan demonstrates the thickened levator muscle aponeurosis near its insertion point into the lid. The other extraocular muscles are not enlarged and this patient has a low risk of developing more serious complications of TED. (**c**) Right upper lid symmetry immediately following a surgical disinsertion of the levator muscle from a posterior lid approach

The combination of lid retraction and proptosis increases corneal exposure and may lead to symptoms of irritation, photophobia, and secondary epiphora. Signs of exposure are best assessed with the slit-lamp microscope and may range from corneal epithelial erosions to ulcerations with risk of perforation. The latter complications are most likely with significant lagophthalmos combined with absence of the normal protective Bell's phenomenon because of a tight inferior rectus muscle.

Periorbital Soft-Tissue Inflammation and Congestion

Symptoms and signs of periorbital soft-tissue inflammation include orbital ache at rest or with movement, conjunctival and caruncular injection and edema, eyelid redness and edema, and diurnal variation (worse with the head dependent after sleeping).

Assessment is subjective although reliability can be improved using precise verbal descriptors or by reference to an atlas of standardized photographs [15]. Eyelid redness may be challenging to assess in those with darkly pigmented skin, while lid edema may be hard to distinguish from orbital fat prolapse. Orbital discomfort must be distinguished from ocular surface irritation; the latter typically resolves with topical anesthetic.

Various grading schemes have been described for each of these features. The simplest binary scale (present/absent) has good reproducibility, but is insensitive at documenting change, while more sensitive scales may have poorer inter and intra rater reliability.

While these soft tissue changes may be an indicator of active inflammation, they are also seen in patients with non-progressive disease but with chronic congestion. They often reflect significant involvement of orbital muscle and should alert the physician to be vigilant for onset of more serious disease complications.

Restricted Ocular Motility and Strabismus

While the levator muscle is commonly involved in TED, the extraocular muscles become clinically involved in only a third of patients, often in an older population [16]. The onset of muscle involvement may be heralded by aching with eye movement and with conjunctival redness and edema overlying the insertion of the involved muscle. During the active inflammatory phase, progressive restriction of motility develops, initially intermittent or with gaze. Later motility restriction may be due to secondary fibrosis.

The symptoms for strabismus are best graded using the Bahn–Gorman scale: 0 = no diplopia, I = intermittent diplopia (present with fatigue), II = inconstant

diplopia (with vertical or horizontal gaze), III = constant diplopia in straight gaze, correctable with prisms, IV = constant diplopia, not correctable with prisms.

Ocular ductions can be graded from 0° to 45° in four directions using the Hirschberg principle: the patient is asked to gaze as far as possible in four directions while the observer points a bright light at the eye and studies the reflected light off the ocular surface. If the light reflex hits the edge of the pupil, the eye has rotated 15°, between the pupil edge and the limbus, 30° and at the limbus, 45°. This technique is as reliable as the "gold standard" perimetry technique with a coefficient of reliability of 12° [17].

Strabismus can be measured objectively by prism cover testing in different gaze directions and is used for planning surgical alignment.

A field of single binocular vision provides a plot of area where the patient sees single versus double because of ocular restriction.

Orbital CT Scan identifies which muscles are enlarged and with contrast may show enhancement and fat stranding around the affected inflamed muscles. In later stages, lucent zones within the enlarged muscles are thought to be hyaluronate deposition (Fig. 17.5). T2 weighted MR Scans may show enhancement of muscles thought due to edema during the active, inflammatory phase.

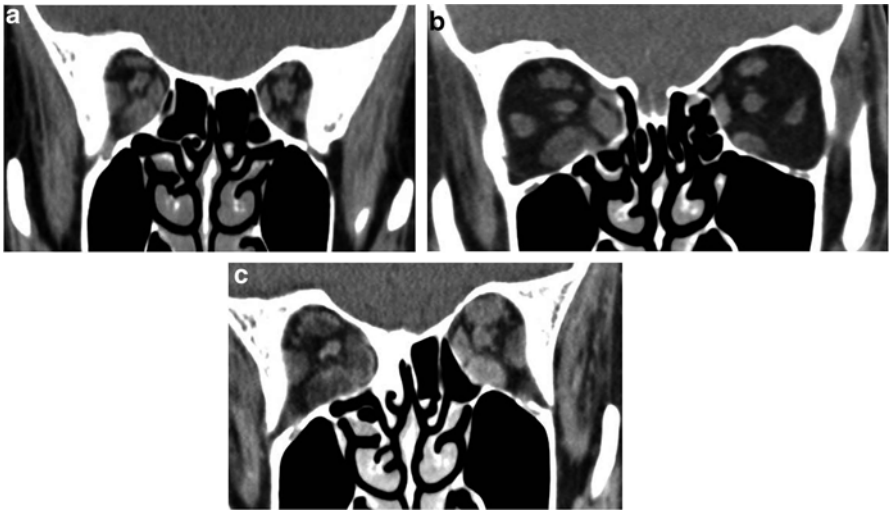


Fig. 17.5 (**a**) A 65-year-old male with progressive onset of right visual deterioration with right compressive optic neuropathy. (**b**) Immediately following decompression, his right color and central vision improved. The medial floor and wall have been expanded into the adjoining sinuses, reducing compression on the central optic nerve. (**c**) Five years later he developed a sudden onset of left congestive features with a drop in color and central vision. CT Scan shows interval enlargement of the left extraocular muscles with optic nerve crowding; the contrast enhancement suggests active inflammation in the muscle. The right muscles remain enlarged but the clear zones represent hyaluronic acid deposition and are typical in longstanding quiescent disease. He was treated successfully with left orbital decompression and adjuvant steroid/radiotherapy

Dysthyroid Optic Neuropathy (DON)

DON is a potentially reversible optic nerve dysfunction seen in 5–7 % of all cases of TED. Most cases are caused by direct compression of the nerve by swollen muscles in the narrow confines of the boney orbital apex, presumably impairing axoplasmic flow (Fig. 17.5). In rare cases with severe fat expansion, vision loss has been reported from optic nerve stretch [18].

Symptoms typically consist of desaturation of colors and blurring of central vision. This is usually confirmed on clinical examination, although a EUGOGO (European Group on Graves' Orbitopathy) survey of its members found that 20 % of patients with diagnosed DON had Snellen visual acuity better than 6/9 [19]. An afferent pupil defect is a specific sign of DON but is not detected in 50 % of patients because of symmetric loss of vision. Disc edema is also a specific sign when present, but is absent in over 40 % of patients with DON [19].

DON usually presents during the active phase of TED, since the onset of visual loss provokes the patient or clinician to investigate further. However, it may also develop insidiously, sometimes with little other clinical findings of TED.

Most cases are associated with muscle enlargement, with resultant subjective diplopia and motility restriction. Congestive and inflammatory features are typically present, but may be subtle. Likewise, proptosis is not typically a striking finding associated with DON, and some argue that this is commonly seen in patients with tight eyelids, limiting anterior decompression of the orbit.

Patients who develop DON are more likely to be male, older, and diabetic compared with their non-DON counterparts.

Coronal CT Scans demonstrate the enlarged extraocular muscles crowding the optic nerve at the orbital apex and causing effacement of the surrounding fat [20].

Ancillary tests include visual field testing, which demonstrates paracentral scotomas or generalized loss in 70 % of DON cases. Visual evoked potentials show abnormal latency in 75 % [19], but are not available in many centers.

In spite of these clinical findings and investigations, the diagnosis of DON may be uncertain in its early stages, necessitating close follow-up in high-risk groups.

Grading Severity

Several classification systems have been devised to grade severity of these clinical manifestations.

Dr. Werner's NO SPECS Classification grades TED-related symptoms and signs and assigns a global severity score (Table 17.1) [21]. The acronym reminds one of the different features of TED but the grades are loosely defined and are often based on only one variable, such as Snellen visual acuity for sight loss (ignoring other more sensitive variables such as color vision). Summary scores also tend to hide

Table 17.1 Werner's NO SPECS classification

Class	Grade
0	***N***o physical signs or symptoms
I	***O***nly signs [eyelid retraction]
II	***S***oft tissue involvement [0: absent, a: minimal, b: moderate, c: marked]
III	***P***roptosis [0: absent, a: minimal, b: moderate, c: marked]
IV	***E***xtraocular muscle signs [0: absent, a: limitation in extremes of gaze, b: evident restriction, c: fixation of globe(s)]
V	***C***orneal involvement [0: absent, a: stippling, b: ulceration c: clouding, necrosis, perforation]
VI	***S***ight loss (optic nerve compression) [0: absent, a: VA: 0.63–0.5, b: VA: 0.4–0.1, c: VA<0.1–NLP]

details about how the patient is specifically affected and make it difficult to assess disease progression or response to therapy. It does not assess clinical activity.

EUGOGO grades TED broadly in three categories from mild to very severe [22]. Mild disease is defined as minimal eyelid swelling, lid retraction or proptosis with little or no extraocular muscle dysfunction. Moderate to severe disease implies some form of active disease with or without ocular motility dysfunction with diplopia and inflammatory features interfering with ability to function. It may also include significant proptosis >25 mm. Very serious disease refers to sight threatening conditions such as DON or serious exposure resulting in corneal ulceration or scarring.

This classification separates the disease into management categories with mild disease requiring no intervention, moderate to severe disease often requiring immunomodulation, and very severe disease requiring urgent surgical intervention. A weakness of this classification is that a patient might be in the moderate class for different reasons (inflammation, motility disturbances, or severe proptosis), providing a heterogeneous group for any research trial. Also, there is an implied rank order for severity that may disagree with the patient's perception of their disease. For example, an individual with early optic neuropathy may be unaware of their mild color desaturation but would be graded as "very severe," while another individual with disabling torsional diplopia would be graded with "moderate" disease.

Course of Disease and Grading Activity

Rundle's Curve

While severity grades indicate the disease state on a particular visit, a plot of Rundle's curve based on subjective or objective data allows one to determine the course of disease (onset and progression) and activity.

In cases with primarily fat expansion or lid retraction, the disease onset may be gradual and distinguishing active from quiescent phases may be difficult.

These cases often present in a stable phase when surgery can be offered on a non-urgent basis.

Individuals with extraocular muscle involvement tend to have a more obvious progression through the active and inactive phases (Fig. 17.3). The acuter the onset and the rapider the deterioration, the higher the chance of serious orbital consequences and the greater the urgency for intervention. Inflammatory and congestive periocular changes are commonly noted during this progressive phase and alert one to the disease's activity.

Disease Duration and Rate of Progression

Individuals affected by TED are keenly aware of their condition and in progressive cases may remember the duration since onset and the recent disease course (deteriorating, stabilizing, or improving). They can also report on the rate of onset (the slope of Rundle's curve), helping define the urgency of intervention [8]. In general, immunosuppressive medical therapy and radiotherapy are likely to be most effective early in TED and when the disease is progressive, and careful questioning may identify such cases even on the first encounter.

Accurate documentation of ophthalmic signs on each visit allows the clinician to determine onset and progression objectively. An observed change can only be considered significant if it is greater than the known coefficient of reliability for the measurement [17]. For each measurement, a sensitive and reliable scale is needed to document change accurately.

Clinical Activity Score (CAS)

The Clinical Activity Score was introduced in 1989 by Mourits and colleagues as a global scale of soft tissue inflammation, to help identify active TED patients who are likely to respond to immunosuppressive therapy [23] (Table 17.2). This uses a binary scale with a single point for seven periocular soft tissue inflammatory symptoms and signs as surrogate markers of disease activity. On follow-up visits, additional points are given for increased proptosis (2 mm or more), decreased ocular motility (8° or more), or decreased visual acuity over the previous 3 months. The scale is relatively easy to score and a CAS score of 4 or higher has been shown to have an 80 % positive predictive value and a 64 % negative predictive value in predicting response to corticosteroid therapy.

The CAS was intended to identify active disease, but has not been shown to correlate with risk of developing significant complications such as diplopia or DON. Limitations of this binary scale are that each clinical feature carries equal weight, (development of optic neuropathy is scored equally to the onset of conjunctival redness), and that positive or negative changes are documented only when they appear or resolve.

Table 17.2 Clinical activity score

First visit (score 0–7)
• Painful feeling behind globe
• Pain on attempted gaze
• Redness of eyelids
• Redness of conjunctiva
• Chemosis
• Inflammatory eyelid swelling
• Inflammation of caruncle or plica
Follow-up visits (3 additional points: total score 0–10)
• Increase of 2 mm or more in proptosis in last 1–3 months
• Decrease in visual acuity in last 1–3 months
• Decrease in eye movements of 8° or more in last 1–3 months

While these inflammatory periocular soft tissue symptoms and signs may reflect underlying TED activity, severe disease complications such as DON can develop with low CAS scores, and patients with high CAS scores may have long-standing congestive changes that are unresponsive to any immunotherapy but that respond best to mechanical surgical decompression.

Laboratory and Imaging

Several potential serum markers for TED activity have been studied with the hope of monitoring change in activity more accurately. These include urine and serum glycosaminoglycans (GAG) [24] and thyrotropin (TSH) receptor antibodies. Imaging techniques have included assessing vascularity within and around extra-ocular muscles with contrast CT Scans, assessing edema on T2 weighted or STIR sequenced MRI scans, and monitoring inflammation using gallium or octreotide scintigraphy [25]. Facial thermography, PET Scans, and Doppler ultrasonography have also been studied, but none appear better than the clinical assessment tools.

Trial of Therapy

In some cases, determination of activity is uncertain based on an equivocal history of progression and borderline inflammatory changes. A trial of therapy using a 3-day course of oral prednisolone 50 mg can determine whether clinical features show improvement and if responsive, permit choice of more definitive therapy such as intravenous corticosteroids or radiotherapy.

VISA Classification, Planning Management, and Predicting Outcomes

Overview

The VISA classification [26] is a clinical recording form that permits grading of both clinical severity and activity based on both subjective and objective inputs and that guides overall management planning. It separates the various clinical features of TED into four discrete parameters: V (vision, DON); I (inflammation, congestion); S (strabismus, motility restriction); A (appearance, exposure).

The basic follow-up visit form (Appendix) is divided into four sections recording specific symptoms on the left and standardized signs for each eye on the right. After each section is a progress row (better, same, worse) for both the patient's and clinician's impression of the course of that parameter since the last visit. The clinician determines progress on the basis of defined interval changes (i.e., 2 mm change in proptosis, 12° change in ocular ductions) rather than on global scores.

The layout is based on the natural order of the ocular examination as well as in descending order of priority for therapy. It is designed to simplify data recording and possible later research data collation.

The end of the form lists a summary grade for the severity and progress for each of the four disease parameters. The severity grades are used as a capsule summary for the patient but not for determining progression. Rather than grading TED severity based on a rank order of the four parameters, each feature is considered and graded independently.

Activity is determined on the basis of deterioration in any one of the four parameters. An elevated VISA inflammatory score is interpreted that the extraocular muscles are likely inflamed or enlarged and alerts the clinician that the disease may follow a more serious, progressive course.

On the first visit, the date and rate of onset as well as historic progress of both the systemic and orbital symptoms is recorded, helping define characteristics of the disease activity. Additional questions also determine risk factors for more serious TED outcomes including smoking, family history, and diabetes.

A downloadable first visit form (2 pages) and follow-up form (1 page) is available through the International Thyroid Eye Disease Society (ITEDS) website: www.thyroideyedisease.org. An associated quality of life form (TED-QOL) allows patient feedback concerning the effect of the disease on their overall quality of life, satisfaction with appearance, and ability to function [27]. This is also available through the same website.

VISA Classification and Risk Factors for Serious Disease

Because TED can present with a wide spectrum of orbital manifestations and activity levels, it is important to identify those most likely to progress to more serious complications such as strabismus or DON before they develop, so that they can be followed more closely and preventive therapy offered earlier.

Risk factors for developing TED include smoking, life stressors, poorly controlled hypothyroidism following radioactive iodine, and a positive family history of orbitopathy [2].

Predictive variables for developing more serious consequences of TED, (specifically those 30 % of affected individuals with significant extraocular muscle involvement), include male gender, increasing age, smoking, and a rapid onset of orbitopathy [16, 18]. Diabetics may have a higher risk of developing DON.

Cigarette smoking has been shown by numerous studies to be correlated strongly with the development of TED and a progressively higher incidence of smoking is seen with more severe disease [28, 29].

Reactivation of disease is fairly uncommon [30], occurring in less than 5 % of individuals, and is sometimes associated with a major life stressor such as a family death, divorce, or loss of job.

Specific VISA Sections and Planning Management

V: Vision/DON and Corneal compromise: The focus of this section is to identify vision threatening processes such as DON or corneal breakdown.

DON is recognized by the combination of central and color vision loss combined with possible afferent pupil defect and/or optic nerve head changes. Ancillary tests to confirm the diagnosis include visual fields, VEP, and coronal CT Scans (Fig. 17.5).

As a summary grade, VISA lists DON as present or absent since therapy is usually offered if the condition is suspected.

Most cases are identified during the progressive phase with the patient aware of the date of onset and the rate of recent deterioration; occasionally the onset may be insidious and the findings subtle.

Initial therapy is a trial of systemic corticosteroids (oral prednisone 1.5 mg/kg/day or iv methylprednisolone 1 g for three doses). The response to this trial of therapy often helps predict whether benefit will be gained from subsequent external beam radiotherapy or surgical decompression. Complete lack of response or the presence of a pale optic nerve head signifies a poorer prognosis.

Most cases do show at least partial response to corticosteroid, but this may be incomplete or refractory to repeated doses. Some authors have found external beam radiotherapy (2000 Rads divided over 10 days by lateral port to the posterior orbits) may avoid surgery [31]. Surgical decompression near the orbital apex by removing the medial orbital wall and medial floor into adjoining sinuses may significantly

restore even severe vision loss, sometimes even months after onset of the optic neuropathy (Fig. 17.5). Adjuvant radiotherapy is often offered to prevent continued postoperative expansion of muscle and recurrence of visual loss.

Corneal exposure may occur from severe lid retraction combined with proptosis and in severe cases may result in corneal ulcers, perforations or scars. This may be recognized by an opacity or a disruption of the light reflex on the corneal surface and is often associated with ocular surface redness and edema. The patient must be referred urgently to an ophthalmologist who may protect the cornea with topical antibiotics, patching, temporary suturing of the eyelids, or even emergent decompression.

I: Inflammation/congestion: VISA records features of orbital soft tissue inflammation or congestion as a separate parameter which can be graded and followed for progression. Symptoms include orbital ache at rest or with movement and diurnal variation while signs include injection and edema of the ocular surface or eyelid. These are summed to form a VISA Inflammatory Score based on the worst score for either eye or eyelid. This differs slightly from the CAS by widening the grade for chemosis and lid edema from 0 to 2 [26].

Unlike the CAS, the VISA inflammatory score is not interpreted as proof of disease activity, but rather as a marker for extraocular muscle involvement (either acute inflammation or chronic congestion) and the chance that more serious sequelae such as diplopia or DON may develop.

Mild soft tissue inflammatory changes may be treated with cold compresses and head elevation.

Those with recent onset and worsening scores may be treated medically with oral or intravenous corticosteroids (CS), with several studies demonstrating that soft tissue inflammation is reduced in 60 % of cases with oral therapy and in 85 % of cases with intravenous (iv) therapy (Fig. 17.6) [32]. Fewer side-effects are encountered with iv CS, but cumulative dosages less than 8 g solumedrol are recommended to avoid possible hepatic complications [33]. We recently reviewed 144 patients who had received monotherapy iv CS and found that 35 % still developed strabismus and 15 % developed dysthyroid optic neuropathy in spite of adequate iv CS therapy [34].

Refractory cases may respond to combination therapy (including cyclosporine, azathioprine, or newer monoclonal antibody biologic agents).

External beam radiotherapy (XRT) has been used for over 50 years for active thyroid orbitopathy and retrospective studies have shown 60 % efficacy in reducing soft tissue inflammation and stabilizing strabismus, possibly by targeting lymphocytes and fibrocytes that play an important role in disease evolution. Three randomized controlled trials have demonstrated XRT to be as effective as oral CS therapy and that it has benefit in reducing strabismus and soft tissue inflammation [35–37]. A recent retrospective review at our institution of 258 patients found that there was 0 % incidence of new onset DON in those treated with XRT/CS, compared with 17 % for those treated with iv CS alone [34].

In chronic cases refractory to medical therapy with no other signs of progression, the high VISA inflammatory score may represent chronic orbital venous congestion, rather than true inflammation, from enlarged extraocular muscles; in these cases, surgical decompression should be considered (Fig. 17.7).

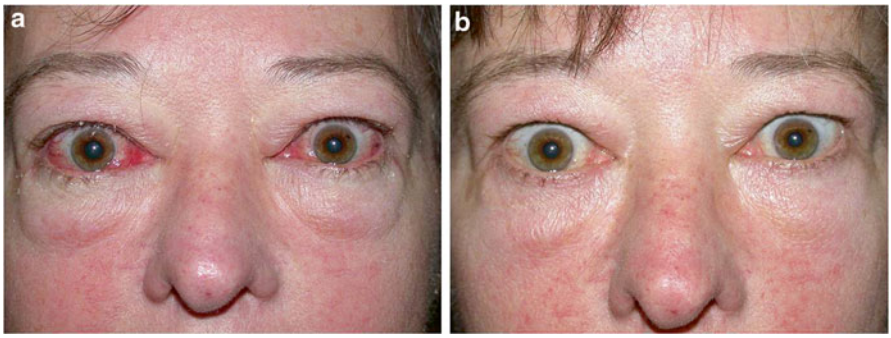


Fig. 17.6 (**a**) A 47-year-old female with relatively rapid and recent onset of inflammatory changes (CAS Score 7/10, VISA inflammatory score 9/10). The recent onset and history of progression indicate *active disease* while the congestive changes indicate extraocular muscle enlargement (and the risk for serious sequelae) based on the VISA classification criteria. (**b**) She was treated with combination corticosteroid and radiotherapy for control of the inflammatory changes and to prevent onset of motility disruption and optic neuropathy. Notice that the inflammatory soft tissue changes have resolved but the upper lids remain retracted, suggesting levator scarring has already occurred

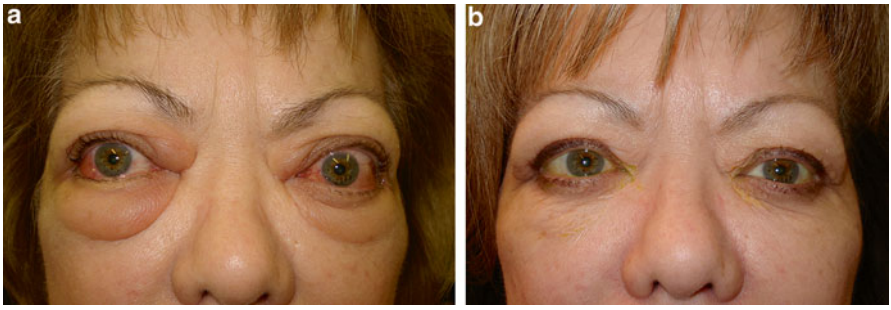


Fig. 17.7 (**a**) This lady had a high VISA inflammatory score (and high CAS Score) based on her soft tissue changes. However, she had been on combination oral corticosteroids and cyclosporine for over a year with no history of progression, and was *inactive* following the VISA Classification guideline (although her CAS score would have been interpreted as active). (**b**) One month following bilateral orbital decompression and upper lid lowering, her congestive features had resolved and her medications were tapered off. Both the VISA inflammatory score and CAS scores were reduced to zero

S: Strabismus/motility restriction: Three aspects are documented. Symptoms of diplopia are recorded using a modified Bahn-Gorman scale and can be graded from 0 to 3. Ocular ductions are measured to the nearest 5° in four directions using the corneal light reflex technique described above. Ocular restriction can be graded from 0 to 3 based on the range of ductions (0–15°, 15–30°, 30–45°, >45°). Strabismus can be measured objectively by prism cover testing in different gaze directions to plan surgical alignment.

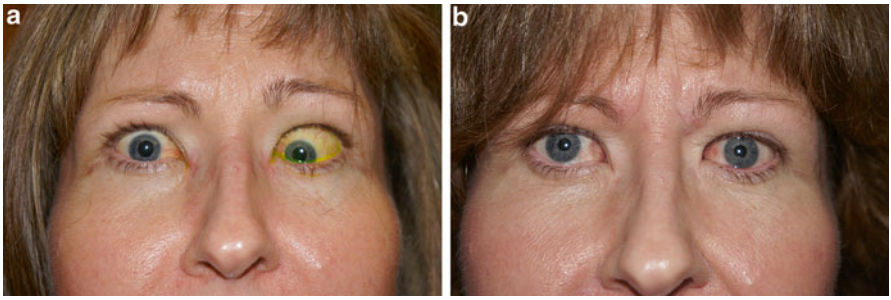


Fig. 17.8 (**a**) Progressive disease with bilateral upgaze restriction and constant diplopia. (**b**) Quiescent disease following combined iv corticosteroids and radiotherapy and subsequent ocular alignment surgery and upper lid lowering surgery

Diplopia is treated with prisms or patching during the active phase, and systemic CS and XRT are considered to limit ocular restriction. Once a stable phase is documented, alignment surgery or prisms may be offered (Fig. 17.8).

A: Appearance/exposure: This section records features relating to appearance and exposure including lid retraction, exophthalmometry, and corneal exposure changes. Photographs document appearance changes.

Exposure changes are treated with lubricant drops and patching during the active phase. Rarely a tarsorapphy or even an orbital decompression may be required for corneal breakdown or ulceration to prevent vision loss as mentioned above.

Once the disease is non-progressive, surgery may be offered to deal with proptosis, eyelid retraction, and orbital fat prolapse.

Referrals

In patients with a low-risk profile (nonsmoking, younger females with slow onset of ocular changes), with milder clinical features, and with no history of recent progression, referral to an ophthalmologist is recommended on a non-urgent basis.

Individuals undergoing radioactive iodine therapy for hyperthyroidism should be referred for ophthalmologic evaluation to help decide on prophylactic corticosteroid therapy.

Individuals in a high-risk group (older, male, diabetic, or smoker), with a recent history of progression, or with any moderate inflammatory changes, should be referred and seen by the ophthalmologist within a few weeks to consider therapy to avoid onset of diplopia or DON.

Cases with reported color or central visual loss, progressive diplopia, rapid deterioration in symptoms, or significant inflammatory scores should be seen within a few days. In all cases, a close communication between all involved physicians is essential [2].

ITEDS: VISA Follow-Up Form

Date: Visit #:

Patient Label:

Date of birth: Age:
Gender:

ORBITOPATHY
Symptoms:

THYROID
Symptoms:

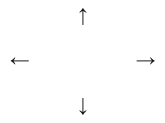
GENERAL
Smoking:

Meds:

Progress: Status:

Therapy: Therapy:

QOL: ☹ - - - - - - - - - - ☺

SUBJECTIVE	OBJECTIVE	OD	OS	
VISION				**Refractions** Wearing _____ + _____ X _____ _____ + _____ X _____ Manifest _____ + _____ X _____ _____ + _____ X _____
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___	
	with manifest	20/___	20/___	
Color vis: n / abn	Color vision plates (HRR) / 14			
	Pupils (afferent defect)	y / n	y / n	
	Optic nerve: Edema	y / n	y / n	
	Pallor	y / n	y / n	
Progress: s / b / w	Macular/ lens pathology	y / n	y / n	
INFLAMM^N/ CONGESTION				**Inflammatory Index (worst eye/eylid)** Caruncular edema (0-1): Chemosis (0-2): Conj redness (0-1): Lid redness (0-1): Lid edema (0-2): Retrobulbar ache (0-2): Diurnal Variation (0-1): **Total**: (10):
Retrobulbar ache	Caruncular edema (0-1)			
At rest (0-1)	Chemosis (0-2)			
With gaze (0-1)	Conjunctival redness (0-1)			
Lid swelling: y / n	Lid redness (0-1)			
Diurnal variation: (0-1)	Lid edema Upper (0-2)			
	Lower (0-2)			
Progress: s / b / w				
STRABISMUS/ MOTILITY				Prism Measure:
Diplopia:	Ductions (degrees):			
None (0)				
With gaze (1)				
Intermittent (2)				
Constant (3)	Restriction > 45°	0	0	
Head turn/ tilt: y / n	30-45°	1	1	
	15-30°	2	2	
Progress: s / b / w	< 15°	3	3	
APPEARANCE/EXPOSURE				Fat prolapse and eyelid position:
	Upper lid position: MRD	mm	mm	
Lid stare y / n	Scleral show (upper)	mm	mm	
	(lower)	mm	mm	
	Levator function	mm	mm	
Light sensitivity y / n	Lagophthalmos	mm	mm	
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm	
Tearing y / n	Corneal erosions	y / n	y / n	
Ocular irritation y / n	Corneal ulcers	y / n	y / n	
	IOP -straight	mmHg	mmHg	
Progress: s / b / w	-up	mmHg	mmHg	

DISEASE GRADE			Grade	Progress / Response	DISEASE ACTIVTY
V	(optic neuropathy)	y / n	/ 1	s / b / w	
I	(inflammation/congestion)	0-10	/ 10	s / b / w	Active
S	(diplopia)	0-3	/ 3	s / b / w	
	(restriction)	0-3	/ 3	s / b / w	Quiescent
A	(appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT **FOLLOW-UP INTERVAL:**

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Chapter 18
Natural History, Risk Factors, and Management of Patients with Mild GO

Marius N. Stan

Natural History

The diagnosis of Graves' orbitopathy (GO) is closely related to the diagnosis of Graves' disease (GD). The temporal relationship between the two entities has been evaluated by a number of studies: data from Olmsted County, Minnesota, suggests they are diagnosed simultaneously in 20 % of cases [1] while European data puts that number at 40 % [2]. A smaller number of GO cases are identified before the thyroid dysfunction, with 8 % in the Dutch study [2] and 18 % in the study from Olmsted County. Therefore, the majority of the patients are diagnosed after development of hyperthyroidism, most of them within the first 6 months after GD diagnosis. This distribution remains valid if one looks only at the cases of moderate-to-severe GO as described by Laurberg et al. [3]—7.5 % prior to, 29.3 % simultaneous with, and 63.2 % after the diagnosis of thyroid dysfunction. The association of GO with hypothyroidism or with normal thyroid function is also consistently described in epidemiological studies with roughly 5 % of GO cases in each category [4, 5].

When observed without intervention the disease follows a course that for many years now has been simply described as Rundle's curve (Fig. 18.1; [6, 7]).

As stated by Rundle [8]: the curve "is an attempt to sketch diagrammatically the behavior of the principal ocular changes during the dynamic phase of protrusion and recession. They are ideal and theoretical curves in the sense that relatively few patients have been, or could be followed through the complete cycle." The curve is still accepted today as accurate and depicts the natural history of GO as one of deterioration, usually more rapid, followed by a slow, gradual improvement that though fails to reach the baseline in the majority of cases. On a historical note, the recent

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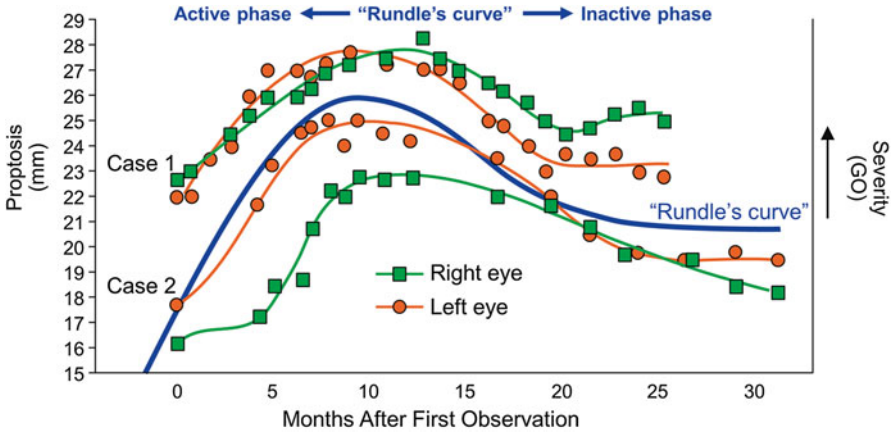

Fig. 18.1 Development of Rundle's curve. The original data by Rundle [6] depicts the evolution of proptosis in two patients (each eye separately) over 30 months of follow-up. Superimposed on that is the idealized curve created by Kallmann and Mourits [7] depicting the change in disease severity over time. The "active" and "inactive" phases of the disease are indicated at the *top*. Modified from Rundle and Wilson [6] and Kalmann and Mourits [7]

editorial by Bartley [9] presents also the context in which Rundle generated his work along with emphasizing Rundle himself, the man that has charted so much of the modern GO map. A more recent description of the natural history of GO is presented by Perros [10] in the series of 65 GO patients that have been rendered euthyroid and followed for 5 years. They were included based on the absence of a need for specific GO treatment at presentation. In this series the majority of GO patients (64.4 %) improved spontaneously, 22 % did not change their clinical status and 13.5 % deteriorated. Prior to this study a number of smaller studies have reported on GO patients having very variable and divergent outcomes from group to group [11–14] but all these reports have followed patients while still hyperthyroid. Perros and colleagues noted that improvements in disease occur even over short periods of time like 2 months, and therefore the recommendation that patients be followed frequently during the first 6 months of GO, as that period is likely to define the trend of the disease. Since in the study by Perros et al. the patients were referred to this tertiary care center it is possible that an element of selection bias towards more severe cases is likely to be at play and one could hypothesize that the number of patients with GO that will improve with observation alone is likely to be larger.

The most recent view of the natural history of the eye disease is provided by the study of Tanda et al. [15]. They have elected to look at GD cases with or without mild GO, mainly treated with ATDs, eliminating the cases of moderate-to-severe GO, as they required GO-specific therapy. In this cohort of 346 patients they report on GO changes or the progression towards GO. This is a population study by virtue of the fact that their center is not a tertiary referral center, thus eliminating referral bias. The GO presence at the GD diagnosis was consistent with other studies with 20 % having mild and inactive GO, 6 % having moderate-to-severe GO and only 1

case (<1 %) having sight-threatening GO. Looking at the cases of mild GO that were followed for 18 months, they report that almost 2/3 (58 %) were GO free at the end of the observation period, 40 % still had mild and inactive GO and 1 case (2 %) progressed to moderate-to-severe GO. It is also interesting and reassuring to consider the evolution of their patients without GO at baseline where 87 % continue to be GO free after 18 months of follow-up while 10 % of patients did develop mild GO and only 5/194 patients (2.6 %) developed moderate-to-severe and active GO during follow-up. These results suggest a positive trend in GO development and progression by comparison with the data from Perros described earlier. It is likely that this is a real trend as the impact of a number of risk factors known to impact GO development and progress have evolved over the last few decades—the incidence of smoking has declined [16], the use of radioactive iodine (RAI) for GD therapy has declined [17] and thyroid dysfunction overall is likely to be identified and managed at an earlier stage.

Thus, it is apparent that if GO is not present at GD diagnosis it is unlikely that it will develop later on for the majority of the ATD-treated patients. If GO is present, it is likely to be mild in severity and, if the modifiable risk factors are controlled, the eye disease quite likely will improve during follow-up. Deterioration does occur though in a small minority of cases and that is where ongoing research is needed for identifying predictive markers for disease progression and effective therapeutic agents with acceptable adverse effect profile.

Risk Factors

There are a number of risk factors associated with development or worsening of GO (Table 18.1), some which are modifiable (e.g., thyroid dysfunction, smoking) and some which are not (e.g., advanced age, male gender, and high TSH receptor antibody titer). We review them here individually.

The role of gender in autoimmunity is well known. Women are more likely to be affected by GD, and therefore by GO [1, 2]. Fortunately women's risk for GD, quantified in women-to-men ratio of 5:1, remains essentially the same for GO based on data on moderate-to-severe GO presented by Laurberg et al. [3, 18]. In terms of severity though multiple studies (not population-based) found men to be at higher risk for the more severe forms of the disease [19, 20].

Advanced age was also identified as being a risk factor for more severe GO. Tanda and colleagues [15] in a population-based study found that moderate-to-severe disease occurred in subjects on average 10 years older than those with mild GO (53.7 ± 13.6 vs. 43.9 ± 12.2, $p < 0.004$) and 8 years older than those without GO at GD diagnosis (45.6 ± 13.6, $p < 0.001$) and that patient with mild GO that experienced improvement in their disease were younger than their counterparts with stable or worsening disease (42.9 ± 12.1 vs. 51.4 ± 10.0 years, $P < 0.02$). Looking at the impact of iodine fortification in Denmark, Laurberg et al. [3] also noted that <2 % of moderate-to-severe GO cases where found in the young population group of

Table 18.1 GO risk factors

Risk factor	Amenable to intervention	Comments
Age	No	Advanced age—risk for more severe GO
Gender	No	GO is more frequent in women; more severe in men
Genetics/ancestry	No	Highest prevalence of GO in Caucasians, lowest in Asians. Immunomodulatory genes likely involved
Mechanical factors	No	Noted wider lateral wall orbital angle in GO
TSH receptor antibody	No[a]	Predicts GO risk and GO therapy response
Smoking	Yes	Increases GO progression and decreases therapy efficacy. Smoking-cessation clinics favored for intervention
Thyroid dysfunction	Yes	Need for expeditious control of hyperthyroidism and prevention of hypothyroidism post GD therapy
RAI therapy	Yes	Risk is additive to smoking; preventable by glucocorticoids 6–12 weeks post RAI

[a]Decreased TRAb noted with methimazole therapy yet available data is unable to separate that change from the natural history of GO with improving TRAb [27]

<40 years of age but that risk increases significantly between 40 to 60 years of age. This is consistent with data from most studies [19, 21, 22] but not all [20]. The differences are likely related to the variations in the definition of clinical GO and its degrees of severity.

The therapy for GD is considered by most to have an impact on the risk for GO. The use of antithyroid drugs and thyroidectomy are deemed to be relatively neutral towards GO outcome, while radioactive iodine (RAI) has the potential to lead to deterioration of GO, in patients with active disease. This was noted in the randomized clinical trial (RCT) conducted by Tallstedt and colleagues [23] and demonstrated most conclusively by Bartalena et al. [24] in another RCT that enrolled patients into three groups: therapy with methimazole, therapy with RAI, and therapy with RAI plus prednisone. The group that received methimazole had at trials' conclusion 3 % of patients with new or worse GO (three with and one without preexistent GO), while the group that received RAI had 24 % (17/72) of patients with preexistent GO that deteriorated and 8 % (6/78) that developed new GO. The group that received the combination of RAI with steroids did not experienced GO development or deterioration arguing that the negative impact of RAI can be prevented with the use of glucocorticoids (see management section). The negative impact of RAI was also noted in the recent RCT conducted by Traisk et al. [25] where new GO cases were more common in the RAI-treated group as opposed to medical therapy group. On the other hand RAI therapy for GD in patients with inactive GO is unlikely to lead to any deterioration of the eye disease, as documented be Perros [26]. He followed 72 patients, most with moderate-to-severe GO, after RAI therapy without concomitant glucocorticoids use. 95 % of them had a clinical activity score (CAS) <3, a marker of inactive disease. In this population no patient had deterioration of GO yet it is pertinent to mention that hypothyroidism was carefully

prevented throughout the study. The mechanism that is probably at work in the negative impact of RAI on GO is the autoimmune stimulation induced by the thyroid destructive process associated with RAI. RAI is known to be associated with increase in TRAb titers [27] and that could lead to amplification of the orbital pathophysiology.

Both hypothyroidism and hyperthyroidism are known to increase the risk for GO development or deterioration. The active Amsterdam group, led by Mark Prumell, M.P. Mourits, and Wilmar Wiersinga, has reported [28] along with their colleagues on a large retrospective series of GO cases, from which they excluded ¼ of the cohort that had euthyroid GO, noting that the group that had moderate-to-severe GO had more thyroid dysfunction, as a percent of patients, than the group that had mild GO with an OR of 2.8 (95 % CI 1.2–6.8). They also noted in a separate series followed prospectively that restoration of euthyroidism was followed by GO improvement while the cases that had stable euthyroidism also had stable GO [29]. Furthermore, in patients treated with RAI it was reported that if multiple such treatments were necessary to control hyperthyroidism the OR for GO development or progression was 2.8 [30]. A limitation for this study remains the fact that the negative role of repeat RAI therapy on GO has not been addressed as a confounder to the risk calculation. The impact of hypothyroidism on GO development of progression was described well by Tallstedt and colleagues when they compared the patients treated with levothyroxine after radioactive iodine (RAI) in a preventive fashion so as to preserve euthyroidism as opposed to a cohort that got treated only when hypothyroidism was biochemically present [31]. The relative risk for GO development/progression was 1.64 in the latter group as compared with the patients treated with levothyroxine in a preventive fashion. In addition, they also noted that in the hypothyroid group the severity of GO was increased as measured by the number of patients requiring GO-specific therapies for their disease (relative risk for therapy requirement at 2.3 with 95 % confidence interval 1.1–2.6). These results were confirmed by Kung and colleagues in an Asian population [32], while we reached similar conclusions in a North American cohort [33]. We have found that patients initiated on levothyroxine when already hypothyroid after RAI therapy had an OR of 3.3 for development/progression of GO compared to those that were euthyroid by the time of their post-RAI clinical reassessment.

Mechanical factors are clearly at play in GO considering that up to 14 % of the cases in some series [34] are presenting with unilateral disease. There is evidence for differences in orbital anatomy between GO and non-GO patients from Baujat and co. [35] who described a wider lateral wall orbital angle in GO patients, arguing for the limited to absent clinical benefits of a lateral wall decompression. The variations in orbital anatomy are likely to play a role in altering the venous and lymphatic drainage, subsequently affecting the concentrations of inflammatory cytokines in the local milieu and thus the risk for clinical GO. These circulatory alteration have been reported to play a role in a disease associated with GO and having likely a very similar pathophysiology—pretibial dermopathy. Rappaport and colleagues have reported a case of severe dermopathy that deteriorated significantly with periods of prolonged standing yet the patients' feet were clearly spared, with a line of demarcation at the

edge of the shoe, speaking to the role of local mechanical forces on the development of these changes [36].

Smoking is the best documented risk factor for GO with a number of studies ascribing an increased risk for GO development or deterioration in smokers. There are many studies that have looked at this association, and a meta-analysis on the subject has been published in 2002 [37]. The risk for GD development is increased by smoking with an odds ratio of 3.3 (95 % CI: 2.1–5.2), with a higher impact in women than men. In ex-smokers that risk disappeared (OR = 1.41, 95 % CI: 0.77–2.58). The smoking-associated risk for GO appears to be even higher with OR of 4.4 (95 % CI: 2.88–6.73). When Pfeilschifter and colleagues [38] looked at the correlation between number of cigarettes smoked per day and markers of GO severity they found a direct correlation with the risk for diplopia: relative risk 1.8 for patients smoking 1–10 cigarettes/day, 3.8 for 11–20 cigarettes/day and 7.0 for >20 cigarettes/day. In one of the most recent studies that evaluated the impact of smoking on GO [25], a post hoc assessment that tried to use the most objective criteria for GO development or deterioration found smoking to increase the odds for this negative outcome by a factor of 9.8. Furthermore, there is evidence that second-hand smoking has the same negative impact on GO. This was documented by Krassas [39] when he looked at GO development in children and found a higher prevalence in those that grew in an environment with a higher percentage of smokers. The authors found that in countries with a high prevalence of smoking (>25 %) young children (<10 years of age and presumably nonsmokers) suffering from GD had a very high GO prevalence of 52 % as opposed to a GO prevalence of 19 % in similar age children with GD residing in countries with lower smoking prevalence. If GD is treated with RAI there is evidence that smokers will have a fourfold higher rate of developing or worsening of preexistent GO [25]. The additional negative impact of smoking on GO is reflected in the response to GO therapy: in smokers there is a lower likelihood of benefit from glucocorticoids and external radiation therapy, as opposed to nonsmokers with 61 of 65 nonsmokers having a favorable response to treatment (94 %) vs. 58 of 85 smokers (68 %), for $p < 0.001$ in this retrospective review by Bartalena and colleagues [40]. Another group that looked at the response to GO therapy in smokers has described it as less effective, delayed and in an inverse relationship with the number of cigarettes smoked per day, as compared to their nonsmoking counterparts [41].

Why would smoking have this negative impact on GO? There is good basic research data to explain the negative role of smoking on GO. Both local hypoxia and generation of oxygen-free radicals are induced by smoking and they are proven to stimulate proliferation of orbital fibroblasts along with increased synthesis of glycosaminoglycans [42, 43]. In a separate study where cultured human orbital fibroblasts from GO patients and normal controls were exposed to cigarette smoke the authors confirmed that smoke exposure initiated increased hyaluronic acid production in a dose-dependent manner (with an impressive correlation coefficient of 0.978) as well as stimulated adipogenesis, an effect that was synergistic with the one induced by IL1 exposure [44].

Both triiodothyronine (T3) and thyroxine (T4) levels before therapy for GD have been suggested as predictive markers for GO development. High T3 level was first

proposed by Talsstedt et al. [23] as a GO risk predictor. Thereafter same group found high T4 levels to play that role [25] while many more studies failed to identify either T3 or T4 levels as having a predictive role in GO course [15, 33, 45]. Presently the data is inconclusive in order to make recommendations for GO management based on T3 or T4 levels.

Different ethnic groups present different risks for GO which were summarized quite nicely in a recent review by Chng [46]. Tellez and colleagues were one of the first groups to described a significantly higher prevalence of GO in Caucasians as compared with Asians and a 6.4 times higher incidence for GO developing in a Caucasian population [47]. The severity of GO also appears to be lower in the Asians (particularly with less extraocular muscle dysfunction) with the exception that sight-threatening disease with dysthyroid optic neuropathy (DON) is likely to occur more readily in Asians. The explanation for this finding is likely to be in part the anatomical variation that includes a shallower orbit in Asians [48] combined with lower normative exophthalmometry values in this population group. In general normal ranges for exophthalmos measurement are increasing from Asians to Caucasians and increasing even further in African-Americans [49]. These ethnic differences in normal values for proptosis measurement are important for practicing clinicians in order to avoid the risk of both underestimation as well as overestimation of the prevalence of this abnormality in different groups. There are also anatomical differences between Caucasian and Asian patients regarding the appearance of the eyelids. As described by Doxanas and Anderson [50] the basic distinction is the anatomical rapport between the orbital septum and the levator aponeurosis. In Asians as a result of this relationship the eyelid appears fuller and the lid crease is positioned much lower. This is speculated to play a role in the ethnic variations in GO presentation [46]. In looking at genetic susceptibility factors for GD and GO many authors have focused on the HLA genes. Those that have revealed the most interesting signature in Asians are entirely different from those identified in Caucasians. TSH-receptor and CTLA-4 genetic differences have also been sought to explain GO predisposition, but no polymorphism has been consistently associated with GO in various populations [46]. Few TNF-alpha gene polymorphisms have been found to be associated with GO with different locations in different populations (T-1031C and C-863A in Asians and G-238 in Caucasians) and these findings might have a role in explaining the ethnic variation in this disease. An interesting difference between ethnic groups consists of the different GO risk associated with the thyrotropin receptor antibodies. Thus, the thyroid stimulating immunoglobulin (TSI) titer is consistently associated with a higher GO risk in all groups; in contrast, while in Caucasians TSH binding inhibitory immunoglobulins (TBII) are directly related to GO risk [51, 52], the opposite is true in Asians, where TBII values are higher in GD patients without features of ophthalmopathy compared with GO patients [32, 53–55]. Needless to say, cultural differences between ethnic groups are impacting the presence of other risk factors for GO, like smoking. Thus, a complex interplay of cultural differences, anatomical differences, genetic differences and the different autoimmune antibody profile are responsible for ethnic differences noted in GO expression.

Genetic factors associated with increased GO risk are still being investigated. This topic is addressed separately in Chap. 4 of this book. Here it suffices to say that in order to understand the predisposition for GO in some of the GD patients as well as the GO predisposition of those that are euthyroid or hypothyroid the researchers have looked at a number of genetic polymorphisms, mainly at those present on genes encoding immunomodulatory components. Thus, there is data regarding various single nucleotide polymorphisms affecting HLA, CTLA-4, TSH-receptor, intercellular adhesion molecule-1, IL-23 receptor, and IL-1 genes to name few of the most important targets. This research has generated some interesting findings but the field is still working to separate GO risk from the GD risk and to verify the reproducibility of their findings in different populations.

TSH receptor antibodies (TRAb) are playing a role in disease pathogenesis as supported by multiple lines of evidence described in Chap. 13 of this book [56]. Therefore, it is no surprise that their titer is having an association with the risk for GO [15, 53, 55, 57]. Thus, for example the study by Khoo [57] found the prevalence of GO at 20, 36, 52, and 64 % in the first, second, third, and fourth quartiles of TSI, respectively. In a dichotomous fashion if the TSI was above median for that group the reported OR for GO presence was 3.6 (1.5–8.0). All this is strongly supportive of the direct relationship between the existence of these antibodies and GO development. However, the initial studies that looked at this issue were not consistent and some found the absence of such association. The likely explanation is the use in these studies of lower sensitivity assays like first-generation TBII assays or long-acting thyroid stimulator assays. Gerding et al. [52] looked at 63 patients with untreated moderate-to-severe disease in order to describe the relationship between TRAb and the stage of GO. They described the direct and strong correlation between clinical activity score and both TSI and TBII. A number of studies have addressed the impact of TRAb in predicting the response to GO therapy. An observational study by Eckstein et al. [58] found that that TRAb levels remained detectable in 93 % of patients that failed to respond to GO therapy while they became undetectable in the majority of those with a positive outcome. Kahaly et al. [59] also observed a decrease in TRAb with successful GO therapy, here intravenous glucocorticoids, which correlated with a decrease in clinical activity score. Using 159 patients followed for 24 months Eckstein and colleagues [51] were able to define TRAb cutoff values that are predictive of future course of GO. They identified both lower cutoffs bellow which the patients had 2.3–15.6-fold higher chance of a mild disease course as well as high cutoff values above which the patients had a 8.7–31.1-fold higher risk of a severe GO course. They were thus able to predict the clinical course of GO in approximately 50 % of the patients. A similar outcome was noted in the data presented by Tanda and colleagues [15] where patients with mild GO that improved during follow-up had a lower TRAb titer than those that progressed towards moderate-to-severe disease over the 18 months of the study (11.1 ± 7.7 vs. 18.1 ± 9.3 U/L, $P < 0.01$). While this parameter might be an interesting therapeutic target so far direct immunomodulatory intervention has not been able to significantly impact it. The role of long-term antithyroid drug therapy in that respect is debatable given that the natural course of TRAb is one of decline in most GO patients [27].

From a clinical perspective, despite the abundance of data supporting these risk factors, we have to acknowledge that there are a significant number of nonsmoking GO patients, of euthyroid or hypothyroid GO patients as well as patients that develop typical GO in the absence of detectable TSH receptor antibodies. These patients speak to the multifactorial process that is the GO development and progression as well as to possible additional risk factors for GO, yet to be identified and to the fact that no single risk factor is able to determine GO's clinical course.

Management of Mild GO

Management of GO is best performed by a team of endocrinologists and ophthalmologists, at times with the support of other specialties (e.g., ENT surgeons, optometrists, radiation experts). Their combined assessment will lead to an individualized approach for that patient that should consider both functional and cosmetic concerns. The European Group on Graves' Orbitopathy (EUGOGO) is using the model of combined thyroid—eye clinics where the patients are seen jointly by an endocrinologist and an ophthalmologist who then reach a joint decision about the management of the case [60]. All GO patients need to start their management with an assessment of the modifiable risk factors. As discussed above the presence of thyroid dysfunction, both hyper- and hypothyroidism, has been documented repeatedly to be associated with development or deterioration of GO. Therefore, therapy for restoration of euthyroidism is the first step. As discussed earlier the use of antithyroid drugs and thyroidectomy are deemed to be relatively neutral towards GO outcome, while radioactive iodine (RAI) has the potential to lead to deterioration of GO, in patients with active disease. In the trial by Bartalena et al. [24] one group received therapy with RAI plus prednisone. By protocol they received prednisone 0.4–0.5 mg/kg of body weight initiated within 48–72 h after RAI therapy. It was continued at that dose for 1 month and then tapered to off over the subsequent 2 months. In this group no patient experienced a deterioration of their GO and 67 % of those with preexistent GO experienced improvement in their eye disease. This trial supports the contention that patients with preexistent GO that are to be treated with RAI should be considered for therapy with glucocorticoids. This conclusion was also emphasized, particularly for patients who have other risk factors for GO progression, by the hyperthyroidism management guidelines sponsored jointly by the American Thyroid Association and the American Association of Clinical Endocrinologists [61]. More recently the use of much lower doses of prednisone has been reported with one group describing beneficial effects on GO with a dose of prednisone as low as 0.2 mg/kg of body weight [62]. The generalizability of the low-dose approach is yet to be verified in a clinical trial, and therefore, it should not be recommended as standard of care.

Prevention of hypothyroidism post RAI has also a beneficial impact on GO risk as documented by Perros [26]. As discussed earlier, in this study 72 GO patients, most with moderate-to-severe but mainly inactive GO, received RAI therapy without concomitant glucocorticoids and none of them suffered deterioration of

GO. Pertinent for the management part is that in all cases hypothyroidism was carefully prevented throughout the study by early initiation of levothyroxine at 2 weeks post RAI. This approach was tested earlier by Tallstedt and his colleagues [31] when they compared a cohort of patients treated with levothyroxine only when hypothyroidism developed (approximately 3 months after RAI therapy) and compared it with a group of patients that received LT4 as early as 2 weeks after RAI, at a dose of 50 mcg daily and then increased to 100 mcg by 4 weeks post RAI. They found that it prevented GO development or deterioration of preexistent GO while only 2/244 patients required discontinuation of levothyroxine due to resurgence of hyperthyroidism-like symptoms. The trial by Perros [26] described above has employed a very similar approach to prevention of hypothyroidism. Presently we are conducting a study to understand the feasibility of this approach to prevention of overt hypothyroidism post RAI in a North American population. While the approach with levothyroxine therapy 2 weeks post RAI might not be standard of care, attention should be given to prevention of overt hypothyroidism through close follow-up post RAI keeping in mind that 40 % of these patients are hypothyroid by 6–8 weeks after RAI administration [33].

Despite scant data on reversing GO progression, smoking cessation should be an essential step in preventing GO development or deterioration and in improving the likelihood that the disease will respond well to therapy. Physicians' counseling to that effect is important but unfortunately most of the time is not effective enough. It is apparent that professional smoking cessation clinics are more effective than individual practitioners at this task, and therefore, they should be utilized whenever possible. They are in a better position to provide behavioral therapy, appropriate pharmacotherapy, and psychological counseling to increase the chances of success [63].

After correcting the modifiable risk factors the clinician should consider the use of local measures that address the signs and symptoms of GO. Topical agents are quite effective at dealing with corneal dryness from exposure, thus helping with the symptoms of grittiness, excessive watering, photophobia and possible even some local pain [64]. During daytime it is best to use tear drops or gels (4–6 times per day) while at night it is best to use gels or ointments which have a longer biological action. For some patients with severe corneal exposure, particularly if the symptoms of dryness are prominent upon awakening, there is benefit from taping the eyelids shut at night or to use a moisture chamber. The corneal discomfort can also be helped by the use of glasses with lateral shield or goggles, particularly in dusty or windy environments. One can try to minimize the upper eyelid retraction by using guanethidine 2 % solution which has been proven effective in the majority of patients tested [65]. Photophobia is helped by the use of sunglasses which can also help the patient with the perceived social impact of the disease. The periocular swelling might be improved by having patients sleep with the head of the bed elevated, though this measure is not well tolerated.

For cases where the above measures have not lead to significant improvement in GO an additional step to be taken is consideration for selenium therapy. Selenium is a trace mineral and an essential nutrient that has antioxidant properties. It is incorporated in selenocysteine which is the building block for several selenoproteins,

where selenium forms the oxidation-reduction center. In both GD and GO there appears to be a state of increased generation of oxygen-free radicals [42, 66, 67]. In addition there is evidence to its impact on the immune system in HT and GD [68, 69]. This has led to the hypothesis that selenium therapy might have a positive role in GO. The hypothesis was tested in a large RCT reported by Marcocci et al. [70] in which patients were randomized into one of three groups: 6 months therapy with selenium selenite at 100 mcg twice daily, pentoxifylline, or placebo. After 6 months of therapy they were observed for an additional 6 months. The primary outcome was a composite overall ophthalmic score and, separately, quality of life measurements with the use of GO-QOL questionnaire [71, 72]. The use of this instrument as a primary outcome is laudable for an RCT in the GO field, given the lack of correlation between some of the physician as opposed to patient important outcomes. After 6 months of therapy the selenium-treated group had less eye involvement and less GO progression than the placebo group as assessed through the overall ophthalmic score. The quality of life was also significantly improved in the selenium group with positive results in both the appearance and the visual-functioning score. The authors proposed that this benefit reflects the amelioration of soft-tissue changes and improved eyelid aperture, which occurred in most of the patients who had improved GO-QOL scores. The benefits noted at 6 months persisted at 12 months for both the overall ophthalmic score as well as the quality of life. The drug was well tolerated, without any reported adverse events. In contrast, pentoxifylline was associated with a number of side-effects while being on par with placebo regarding GO outcomes. A concerned that was raised regarding the use of selenium relates to the risk of development of hyperglycemia. Fortunately the study authors have reported subsequently that none of the patients that had glucose testing developed such an adverse-effect [73]. In evaluating these results for generalizability to other patients we must be aware of the fact that most study patients came from populations with marginal selenium levels while the selenium levels in the study were not measured. Thus, we do not know if the impact of selenium is limited to patients with preexistent selenium deficit or not. That will hopefully be answered by a new RCT organized by ITEDS (International Thyroid Eye Disease Society) which is currently underway in multiple North American centers (US and Canadian).

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Chapter 19
Medical Treatment of Moderately Severe and Vision-Threatening Graves' Orbitopathy

Maarten P. Mourits

Introduction

Disease Severity and Disease Activity

Graves' orbitopathy (GO) has many different faces which range from eyelid changes to disfiguring proptosis, double vision, and blindness. For almost all patients, a large part of the disease burden consists of the psychological sequels of the detrimental changes of that part of the face that is most characteristic for the patient and plays a dominant role in social interaction. In addition, GO-patients suffer from ocular discomfort such as grittiness and watering, slight pain during eye movements, blurred vision, and diplopia. Next to reduced vision, which is only seen in a minority of patients, diplopia is the most debilitating expression of GO as it interferes with almost all daily activities. Based on the impact of the disease on the usual daily performance, the EUGOGO (European Group on Graves' Orbitopathy) has suggested to categorize GO-patients into three subgroups, namely, mild (hardly interfering with daily activities), moderate to severe (significant impact), and vision threatening [1, 2]. Hard criteria exist for vision-threatening GO: reduced visual acuity, reduced color vision, pupillary defects (in unilateral cases), disc swelling, and apical congestion of the extraocular muscles. Undoubtedly, patients with double vision should be categorized in the middle group, while patients with minimal eyelid swelling or retraction are placed in the group of mild GO. But what about patients with "only" proptosis? Hard criteria here are missing, because the way people cope with their problem differs immensely. The EUGOGO considers GO-patients to be moderately severe when there is no sight threatening orbitopathy, but an orbitopathy

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severe enough to justify immunosuppressive treatment or surgery. These patients have one or more of the following symptoms: more than 2 mm lid retraction, NO SPECS class II, grade II or III eyelid swelling, more than 3 mm proptosis above the upper limit of their reference group and inconstant or constant diplopia. This chapter deals with all GO-patients except for those, who consider themselves hardly handicapped by their affection.

While disease severity dictates the need for treatment, disease activity determines the choice of treatment. Already in the 1950s, the Australian internist F.F. Rundle [3, 4] showed that GO runs a course starting with increasing proptosis, retraction and motility impairment lasting several months until a plateau phase is reached followed by a phase of slow improvement and an incomplete decline of symptoms. This course has become known as the Rundle's curve. The time axis in this curve may vary from months to years. Recently, our group showed that Rundle's curve of disease severity is preceded by a similar curve of disease activity [5] (Fig. 19.1). Relating serial calculations of orbital tissue volumes to clinical parameters, we found that signs of clinical activity disappear over time while fat volume and proptosis increase.

> Disease severity dictates the need for treatment, whereas disease activity determines the choice of treatment.

Inflammatory signs such as pain, redness and edema of the eyelids and conjunctiva plus increasing proptosis and motility impairment (e.g., "functio laesa") usually herald the onset of GO. Based on these clinical signs, the Clinical Activity Score has been grounded, that helps to distinguish active from burn out orbitopathy, or in other words patients that are in the mounting part or in the descending part of

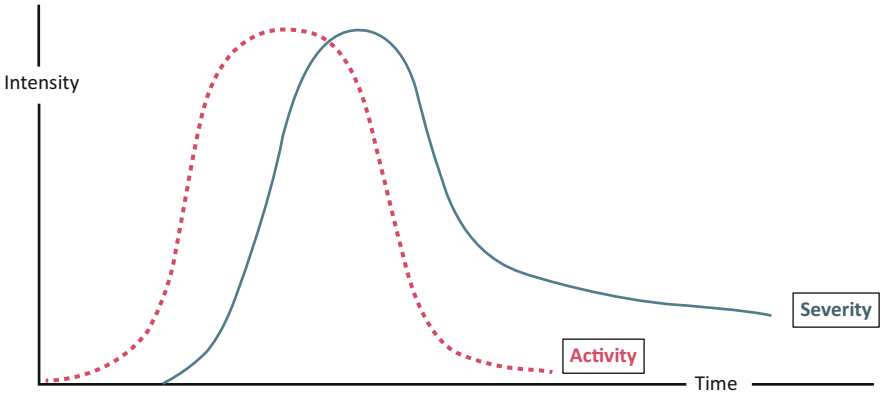

Fig. 19.1 Curves of disease activity (*red*) and of disease severity (*blue*) in patients with Graves' orbitopathy

Rundle's curve [6, 7]. This distinction is of paramount importance as the established treatment for patients with active GO is immune modelling or medical treatment, whereas surgical intervention must be postponed until the disease has become objectively quiescent.

Goals of Medical Treatment of GO

The discussion about the profit of medical treatment, in particular of glucocorticosteroids, for GO has been impeded by different expectations.

In GO orbitopathy eyelid swelling and proptosis are caused by an increase of muscle and fat volume, whereas retraction and motility impairment are caused by inflammatory changes leading to fibrosis in and around the extraocular muscles. Reduced vision, finally, is secondary to severe corneal exposure with corneal epithelial breakdown and ulceration, or more commonly to compression of the optic nerve in the orbital apex due to extensive swelling of the extraocular muscles. Recently, it has been shown that 70 % of patients with GO have an increase of their orbital muscle volume as compared to their reference group, whereas 13 % have an increase of their fat volume [8]. Moreover, fat volume increase is a relatively late phenomenon in the course of GO [5].

Immune modelling treatment of GO is expected to inhibit the function of immunocompetent cells and of inflammatory mediators such as cytokines, to influence orbital fibroblast that produce glycosaminoglycans and thus reduce edema and, finally, to inhibit orbital preadipocytes to turn into adipocytes. Thus, immune modelling agents prevent further worsening, but have little effect on eyelid swelling and proptosis caused by established muscle and fat increase. Indeed, the effects of oral and intravenous glucocorticosteroids or of orbital irradiation on proptosis are minimal and surgery is until present the only option to deal with disfiguring proptosis. But surgery cannot replace medical treatment. There is no evidence that surgery influences the autoimmune mediated inflammation in the orbit. In contrast, it has been demonstrated that patients having undergone orbital decompression continue to be active and need additional immune modelling treatment after surgery [9].

Therefore, the contribution of medical and radiotherapeutical treatment for many patients with moderately severe and GO is no more than to shorten the period of disease activity and in this way allowing rehabilitative surgery in an earlier stage of the disease than when its natural course had been awaited. The arrest of the inflammatory changes, however, may reduce eyelid edema and retraction and improve eye movements and even reduce compression of the optic nerve so much, that patients may be spared from immediate orbital decompression.

The aim of immunosuppressive treatment in GO is to deactivate the disease process and to allow surgery, if still necessary, in an earlier stage.

Evaluating 32 patients with moderately severe and active GO, i.v. methylprednisolone pulse therapy stabilized the orbitopathy in 85 % and reduced the severity of GO in 38 % of the patients [10]. A reduction of 0.5 surgeries per patient for responders was found. Four out of 32 patients needed additional immunosuppressive treatment. Although different outcomes were found for different outcome parameters, both the EUGOGO criteria and the clinical activity score (CAS) appeared to be good predictors for additional immunosuppressive treatment and additional rehabilitative surgeries.

Assessment of the Outcome of Medical Treatment of GO

Treatment of GO orbitopathy may selectively influence one or more signs or symptoms of the disease, while others remain unchanged or even worsen. How then should the overall outcome of the treatment be assigned? Several attempts have been done to overcome this problem. Based on the NO SPECS classification [11], an ophthalmopathy score or index has been defined as the sum of each NO SPECS class multiplied by the severity grade within that class [12]. In later studies, the overall outcome was based on a change in major and minor criteria [13]. Table 19.1 shows the present criteria as used by the EUGOGO. Next to this objective outcome (as viewed by the doctor), a subjective outcome measurement has been introduced based on quality of life questionnaires focused on GO [14, 15]. Basically two systems are used at present, the one developed in Amsterdam and accepted by the EUGOGO and the VISA-system, developed in Vancouver. The differences between both systems, however, are minimal and of little importance.

Table 19.1 EUGOGO criteria for assessing outcome of medical treatment of GO

a. **Improvement**, when at least two of the following outcome measures improved in one eye, without deterioration in any of these measures in either eyes:
1. Reduction in palpebral aperture by at least 3 mm
2. Reduction in any of the class 2 signs of NOSPECS by at least two grades
3. Reduction in exophthalmos by at least 2 mm
4. Improvement of >8 in motility in any duction or improvement in diplopia (disappearance or change in degree)
5. Improvement in CAS by at least 2 points
b. **Deterioration**, when DON or two of the following occurred:
1. Increase in palpebral aperture by at least 3 mm
2. Increase in any of the class 2 signs of NOSPECS by at least two grades
3. Increase in exophthalmos by at least 2 mm
4. Deterioration of >8 in motility or worsening of diplopia (appearance or change in the degree)
c. **No change**
When there were no changes or changes smaller than previously defined in any of the mentioned parameters

Glucocorticosteroid Treatment Modalities for Moderately Severe GO

Glucocorticosteroids Injected into the Orbit

The first, often anecdotic reports on the use of glucocorticosteroids appeared in the middle of the last century. These concerned injections of steroids into the orbit. Recently, the concept of intra-orbital or subconjunctival steroid injections by the group of Martin Devoto from Buenos Aires has added a breath of new life. He considered intralesional injections an alternative for i.v. pulse therapy in patients unable to stay in or near a specialized center for a longer time. Several studies [16–18] showed improvement of lid retraction, of proptosis, of motility impairment, and even of muscle size. These studies, however, did not fulfill the strict scientific criteria nowadays required: these were no double blinded randomized clinical trials and used no validated tools to quantify the muscle size. Moreover, this approach loses its advantage when repeated injections are needed. Robert Goldberg, in a comment on one of these publications [19], enumerated the risks of intraorbital injections. "In addition to the systemic complications of steroids, injection around the eye also poses the risk of local complications including globe perforation, intractable elevated intraocular pressure, conjunctival or corneoscleral melting, vascular occlusion from embolization or pressure induced optic nerve compression, proptosis or fat atrophy, depigmentation, and granuloma related to the methyl cellulose vehicle of the depot injection." Although these complications may be largely avoided by modified injection techniques, the question whether injected steroids are efficacious has not been answered. The Pisa group compared retrobulbar with orally given corticosteroids both combined with orbital cobalt irradiation and found the latter to be more effective [20].

Orally Administered Glucocorticosteroids

The efficacy and safety of oral prednisone have extensively been studied by several groups [12, 20–24]. The dosage used in these studies varied from 60 to 100 mg a day and the duration of treatment from 10 to 20 weeks. The reported response rates varied from 45 to 67 %. The frequency and severity of major (e.g., mental depression, osteoporosis) and minor (e.g., weight gain, hirsutism, osteoporosis, hypertension) side effects were impressive and tempted researchers to look for alternatives. The incidence of oral prednisone side effects is related to the duration steroids are prescribed. Clinicians in the past, expecting a full recovery of the orbitopathy using oral prednisone alone, were inclined to treat patients with oral steroids far too long or at any so-called recurrence, resulting in most horrible situations. A patient (Fig. 19.2) referred after 1 year of continuous oral prednisone of 60 mg a day had gained 30 k of weight. Her appearance had changed unrecognizably and she

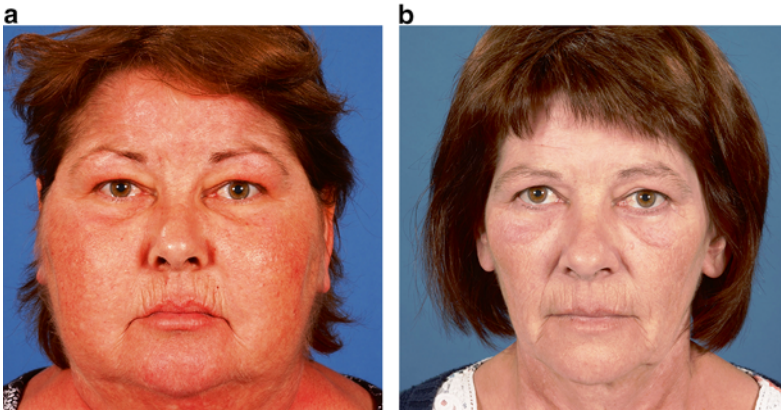

Fig. 19.2 A 51-year-old woman, treated with an overdose of oral prednisone, at entry (**a**) and 1 year after cessation of glucocorticosteroids (**b**)

suffered from a "spontaneous" Achilles tendon rupture apart from mental depression and dramatic osteoporosis. Such practices, ignoring the fact that steroids should be given to patients with active GO and only for a limited period of time, have given oral prednisone in the treatment of GO a bad reputation.

Intravenously Administered Glucocorticosteroids

Around the turning of the last century, the awareness grew that early and intense treatment of autoimmune diseases may yield better outcomes. A number of controlled studies for patients with moderately to sight-threatening GO showed that intravenously administered glucocorticosteroids are more effective than oral steroid and have less side effects [25–28]. The average reported response rate was 79 %.

In a single-blind study of Kahaly et al. [27], in 2005, 70 euthyroid untreated outpatients with active and severe GO were randomly assigned to receive either once weekly iv methylprednisolone (IVMP) (0.5 g, then 0.25 g, 6 week each) or oral prednisolone starting with 0.1 g/day, then tapering the dose by 0.01 g/week. At 3 months, 27 of 35 patients (77 %) in the iv group had a successful treatment response compared with 18 of 35 (51 %) in the oral group. Improvements over baseline values for disease severity (e.g., visual acuity) and activity (e.g., chemosis) and for quality of life were significantly greater in the iv group. TSH receptor antibody titers decreased during iv steroid administration ($P<0.001$). Additional treatment was required less frequently in the iv group.

To the best of my knowledge, we performed the only prospective randomized study so far [28], in which IVMP was compared to a placebo. Fifteen previously untreated patients with active, moderately severe GO participated in the study; six

patients received steroids and nine patients a placebo. Moderately severe disease was defined using the NO SPECS classification of clinical signs of GO. Activity was measured with the clinical activity score (CAS). A dose of 500 mg MP or only solvent was administered intravenously, over three consecutive days, in four cycles at 4 weekly intervals (6 g of IVMP in total). Qualitatively, a successful treatment outcome was defined as an improvement in one major and/or two minor criteria in the worst eye at week 48. The major criteria were: improvement in diplopia grade; improvement in eye movement; a decrease in CAS of three points. The minor criteria were: decrease of eyelid retraction; decrease of proptosis; improvement in grade of soft tissue swelling; a decrease in CAS of two points. The qualitative treatment outcome was successful at the end of the trial in five out of six (83 %) patients receiving prednisone and in one out of nine (11 %) patients given the placebo (relative risk = 7.5; (95 % confidence interval 1.1–49.3), $P = 0.005$). The treatment was well tolerated.

These and other studies show that inflammatory signs such as redness, eyelid edema, and chemosis, as well as motility impairment will regress, but the effect of IVMP on proptosis in general is irrelevant. Moreover, these trials do not provide data beyond the study period, and the number of relapses after three or more months is unknown. In a recent study, Vannuchi et al. [29] suggest that patients who do not respond within 6–8 weeks better refrain from further prednisone treatment, because a later response is not to be expected.

None of these studies reported major side effects. The infusion of glucocorticosteroids may cause transient hot flushes, palpitations, gastric burn, and hypertension. Sleeplessness is also reported. In addition, a weight gain of up to 3 kg is seen at the end of the treatment period. However, incidental cardiovascular events in patients receiving i.v. prednisone have been described [30, 31]. More importantly, i.v. steroid pulse therapy creates large cumulative doses, especially when oral prednisone is given after i.v. pulses in order to perpetuate the response, as is often been practiced. In a number of case reports, the risks of liver failure have been reported during IVMP resulting in fatal expiration in four patients so far [32–34]. These patients received a cumulative dosage of 10–24 g. Sanchez-Ortiga et al. [35] compared two dosing regimes of i.v. steroids and found the lower dose to be much better tolerated. The liver toxity of steroids seems therefore to be dose dependent. Further evidence suggests that an acute withdrawal of steroid treatment may also exacerbate underlying liver disease, as oral steroids, which are slowly tapered down, are not associated with acute liver dysfunction.

We performed a prospective observational study in 13 patients with dysthyroid optic neuropathy (group A) and in 14 patients with moderately severe GO (group B) who were treated with high-dose (group A) or low-dose (group B) IVMP [36]. Cumulative steroid doses were 8.45 g in group A and 4.5 g in group B, and follow-up time was 24 weeks. Slight increases in serum aminotransferases (in alanine aminotransferase [ALAT] more than in aspartate aminotransferase [ASAT]) were observed, in seven patients exceeding the upper normal limit of 40 U/L. These changes were more prominent in group A than in group B as was also evident from a decrease in ASAT/ALAT ratio in group A but not in group B. Changes in serum

aminotransferases occurred especially in the first 6 weeks of IVMP, becoming smaller thereafter with the decrease in steroid dosage. Pretreatment liver steatosis or diabetes was not related to liver damage, but preexistent viral hepatitis was. We concluded that IVMP in GO patients causes dose-dependent liver damage by a direct toxic effect of glucocorticoids on hepatocytes. Nevertheless, IVMP seems to be pretty safe if cumulative doses exceeding 8 g are avoided and liver function is checked before and at regular intervals during pulse therapy.

In a survey by the European Thyroid Association (ETA), Claudio Marcocci et al. evaluated the use and complications of IVMP among their members [37]. A response was obtained from 128 ETA members of which 115 used glucocorticosteroid therapy for GO. The majority of respondents (83/115, 72 %) used IVMP, with a relatively wide variety of therapeutic regimens. The cumulative dose of methylprednisolone ranged between 0.5 and 12 g (median 4.5 g) for IVMP and between 1.0 and 4.9 g (median 2.4 g) for oral GC. Adverse events were often reported during oral GCs (26/32, 81 %); most side effects were non-severe, but ten respondents reported severe adverse events (hepatic, cardiovascular, and cerebrovascular complications), including two fatal cases. Adverse events were less common in IVMP (32/83 respondents, 39 %), but mostly consisted of severe events, including seven fatal cases. All but one fatal event occurred in cumulative IVMP doses (>8 g) higher than those currently recommended. They concluded that both oral and IVMP may be associated with severe adverse effects, including fatal cases, which are more frequently reported in daily or alternate day IVMP. IVMP therapy should be undertaken in centers with appropriate expertise. Patients should be carefully examined for risk factors before treatment and monitored for side effects, which may be asymptomatic, both during and after treatment.

Intravenously administered methylprednisolone pulse therapy for patients with active GO is effective and save as long as cumulative doses of >8 g are prevented.

In order to find the optimal dose of methylprednisolone, the EUGOGO carried out a multicenter, randomized, double-blind trial to determine efficacy and safety of three doses of IVMP in 159 patients with moderate to severe and active GO [38]. Patients were randomized to receive a cumulative dose of 2.25, 4.98, or 7.47 g in 12 weekly infusions. Efficacy was evaluated objectively at 12 weeks by blinded ophthalmologists and subjectively by blinded patients (using a GO specific quality of life questionnaire). Adverse events were recorded at each visit. The 7.47-g dose provided short-term advantages over lower doses. However, this benefit was transient and associated with slightly greater toxicity. The use of a cumulative dose of 7.47 of methylprednisolone provided short-term advantage over lower doses. This may suggest that an intermediate-dose regimen be used in most cases and the high-dose regimen be reserved to most severe cases of GO.

Table 19.2 Protocol for treatment of moderately severe GO

Indication: moderately severe GO
Contraindications:
1. Any active inflammation
2. Ulcus ventriculi or duodeni
3. Unexplained liver enzyme abnormalities
4. Relative contraindication: diabetes mellitus, osteoporosis
Check before you start:
– Hb, leukocytes, creatinine, Na, K, glucose, AF, ASAT, ALAT, gammaGT, bilirubin, glucose. Start when levels are normal
– Blood pressure, pulse
– Echography liver
Treatment:
– Methylprednisolone 500 mg intravenous, once per week during 6 weeks
– Next: methylprednisolone 250 mg intravenous, once per week during 6 weeks administration:
– Methylprednisolone (500 of 250 mg) dissolved in 50 ml NaCl 0.9 %, intravenous
– Administration in 60 min
Adverse effects:
– In case of too fast administration: (500 mg in less than 10 min) arythmia of the heart, circulatory collapse, and heart arrest
– Nausea, vomiting
– Latent diabetes mellitus becomes manifest
– Hypertension, sodium and fluid retention
– Euphoria, sleeplessness, depression, and psychosis
Check:
– During administration—RR, pulse, glucose before infusion and immediately after infusion
– After 6 weeks and 12 weeks: AF, ASAT, ALAT,gammaGT, bili, glucose, T4, TSH, T3
Osteoporosis prophylaxis:
– Alendronaat (Fosamax) 70 mg 1× per week, calcium 1,000 mg 1dd1, cholecalciferol (Devaron) 400 IE 1dd1 from week 1–week 12

In conclusion, a series of six infusions of 500 mg, slowly administered during 1 or 2 h once every week during 6 weeks, followed by a second series of six infusions of 250 mg during 6 weeks, can be regarded as a safe and effective way to deal with patients with active and moderately severe GO (Table 19.2). In fact, this treatment is advocated by the EUGOGO as a first line treatment in these patients. One may expect the disease activity to slow down, inflammatory signs to disappear in up to 80 %, disease severity to decrease in up to 40 % and the number of subsequent operations to shrink. However, not all patients will respond and the long-term relapse rate has not been studied sufficiently. Non-responders should not be treated with new courses of steroids (as they apparently do not respond to steroids), but other treatment modalities should be applied. Before IVMP is given, patients should be thoroughly screened for diabetes and hypertension, gastric and liver disease, and

osteoporosis. Supportive treatment to prevent gastric complications (proton pump inhibitors) and osteoporosis (bisphosphonates) is required and during the course of treatment patient must be checked regularly.

Glucocorticosteroids for Vision-Threatening Orbitopathy

Dysthyroid Optic Neuropathy (DON) is an alarming situation and most clinicians will feel uncomfortable when no immediate action is undertaken. Orbital decompression, especially removal of the posterior part of the medial wall has shown to be very effective in restoring good vision [39], even after prolonged periods of reduced visual acuity (oral information). However, there is a role for i.v. steroids as well. Already in 1989, a French group [40] described five patients with severe dysthyroid optic neuropathy who were treated with intravenous methylprednisolone (1 g daily for 3 consecutive days). Before administration, visual acuity of the more severely affected eyes of each patient was counting fingers at 5 ft, 8/200, 20/400, 20/200, and 20/80. Immediately after completion of pulse therapy, visual acuity improved to 20/25 in four patients and 20/30 in one. Remissions were maintained with oral prednisone and external beam irradiation of the orbit. They concluded that pulse methylprednisolone therapy appears to be beneficial in the initial management of severe dysthyroid optic neuropathy.

In another, non-controlled, retrospective study [41], DON-patients were hospitalized and received four times 500 g methylprednisolone intravenously. Immediately afterwards they were treated with oral prednisone (maximal dose 60 mg) and/or orbital irradiation (ten times 2 Gy). Evaluation was done 1 day after the last bolus (T1) and when the orbitopathy had been stable for at least 6 months (T2). Visual acuity, proptosis, elevation and CAS all improved significantly at T1, whereas the lid aperture did not change. At T2, 24 out 62 (39 %) DON-patients were stable with normal vision. The other 38 (61 %) had undergone orbital decompression because of persistent or recurrent DON within 1 week to 6 months after methylprednisolone treatment. Final visual acuity in the whole group (121 eyes) was less than 0.1 in 3 eyes, between 0.1 and 0.5 in 17 and more than 0.5 in 101 eyes. Thus, one-third of DON-patients were spared from decompressive surgery. The group of Salvi [42] reached the same conclusions. In a retrospective study, IVMP was administered daily for three consecutive days and repeated the following week. At 6 months, 17 of 40 (42.5 %) eyes had complete visual recovery and were spared from surgical decompression.

There is only one randomized study comparing medical treatment with surgery in DON [9]. Six patients were treated with surgical decompression and nine with methylprednisolone i.v. pulses for 2 weeks, followed by oral prednisone for 4 months. In the surgery group, five out of six patients did not respond because of insufficient improvement in vision ($n=3$) or persistent chemosis ($n=2$), and all needed further immunosuppression. In the steroids group, four out of nine patients did not improve in visual acuity, and they needed decompressive surgery. All patients

Table 19.3 Protocol for vision-threatening GO

Indication: vision-threatening GO
Contraindications:
1. Any active inflammation
2. Ulcus ventriculi or duodeni
3. Unexplained liver enzyme abnormalities
4. Relative contraindication: diabetes mellitus, osteoporosis
Check before you start:
– Hb, leukocytes, creatinine, Na, K, glucose, AF, ASAT, ALAT, gammaGT, bilirubin, glucose. Start when levels are normal
– Blood pressure, pulse
– Echography liver
Treatment:
– Methylprednisolone 1,000 mg intravenous, on day 1, 2, 3 and on day 8, 9, 10 administration:
– Methylprednisolone dissolved in 50 ml NaCl 0.9 %, intravenous administration in 60 min
– Next: from day 15 oral prednisone
2 weeks 40 mg 1 dd
4 weeks 30 mg 1 dd
4 weeks 20 mg 1 dd
Then tapering down with 2,5 mg per week
Adverse effects:
– In case of too fast administration: (500 mg in less than 10 min) arrhythmia of the heart, circulatory collapse, and heart arrest
– Nausea, vomiting
– Latent diabetes mellitus becomes manifest
– Hypertension, sodium and fluid retention
– Euphoria, sleeplessness, depression, and psychosis
Check:
– During administration—RR, pulse, glu before infusion and immediately after infusion
– On day 3 and on day 10: AF, ASAT, ALAT, gammaGT, bili, glucose, T4, TSH, T3
Osteoporosis prophylaxis:
– Alendronaat (Fosamax) 70 mg 1× per week, calcium 1,000 mg 1dd1, cholecalciferol (Devaron) 400 IE 1dd1 from week 1–week 12

in whom therapy failed were switched to the other treatment arm and visual acuity improved in almost all patients. It was concluded that, immediate surgery does not result in a better outcome and therefore methylprednisolone pulse therapy appears to be the first-choice therapy.

The Amsterdam protocol (Table 19.3) follows the recommendations of the EUGOGO. Patients with DON are treated with 1 g methylprednisolone daily for 3 days (day 1, 2, 3) and for another cycle of 1 g daily after 1 week (day 10, 11, 12). When there is insufficient improvement of visual functions, decompressive surgery is performed. When vision does improve, but inflammatory signs are still present, patients are treated subsequently with orally administered steroids.

Irradiation for Moderately Severe GO

Efficacy

Orbital radiotherapy (ORT), often termed retrobulbar irradiation, for patients with Graves' orbitopathy has a long history. Reviewing 37 patients who received orbital radiation for ocular changes of Graves' disease, Ravin et al., in 1975 [43], found signs of orbital congestion to be improved in many patients. Proptosis, extraocular muscle involvement, and corneal involvement were not appreciably altered. The best response was found in patients with optic nerve involvement. Side effects were also noted in an early stage. Four patients with severe retinopathy (three legally blind) were described, but these complications could be attributed to errors in dosage calculations and radiotherapy technique [44].

It is not surprising that corneal involvement did not respond to irradiation, but it is remarkable that these first researchers found no improvement in ocular motility. Perhaps because their measuring technique was not sensitive enough. Anyway, later controlled studies showed that especially ocular motility responds to irradiation. The first controlled study, in which ORT as a mono-treatment was compared to oral steroid [22], showed ORT to be equally effective as oral prednisone, although prednisone was slightly more effective on soft tissue changes and ORT more effective on motility impairment. This lack of sensitivity of proptosis for ORT was confirmed by another, retrospective, Dutch study [45].

Donaldson [46], one of the founders of ORT for GO, stated in 2001, based on non-controlled studies, that 20 Gy ORT is safe and effective treatment for progressive GO, with a 96 % overall response rate, 98 % patient satisfaction rate, and no irreparable long-term sequelae, with follow-up extending 29 years. No serious side effects either, but a remarkable improvement of ocular motility (and absence of proptosis reduction) were found in a retrospective series of 104 patients treated In Germany [47].

However, in the next double-blind randomized clinical trial, less encouraging results were found [48]. Thirty patients with active, *moderately severe* GO had radiotherapy (20 Gy in ten fractions), and 30 were assigned sham-irradiation (ten fractions of 0 Gy). Treatment outcome was measured qualitatively by changes in major and minor criteria and quantitatively in several ophthalmic and other variables, such as eyelid aperture, proptosis, eye movements, subjective eye score, and clinical-activity score at 24 weeks. The treatment outcome was successful in 18 of 30 (60 %) irradiated patients versus nine of 29 (31 %) sham-irradiated patients at week 24. This difference was caused by improvements in diplopia grade, but not by reduction of proptosis, or of eyelid swelling. Quantitatively, elevation improved significantly in the radiotherapy group, whereas all other variables remained unchanged. The field of binocular single vision was enlarged in 11 of 17 patients after irradiation compared with 2 of 15 after sham-irradiation. Nevertheless, only 25 % of the irradiated patients were spared from additional strabismus surgery. It was concluded that in these patients with moderately severe GO, radiotherapy should be used only to treat motility impairment. In another sham-irradiation controlled study [13], but

this time in patients with *mild* GO, the primary outcome was successful in 52 % of the irradiated versus in 27 % in the sham-irradiated patients. Radiotherapy was found to be effective in improving eye muscle motility and decreasing the severity of diplopia. However, quality of life improved similarly in both groups.

Even devastating was the conclusion of a prospective, randomized study in the Mayo Clinic [49], in which in 42 patients with active and moderately severe GO, one randomly selected orbit was treated with 20 Gy of external beam therapy and sham therapy was given to the other side. Six months later, the therapies were reversed. No clinically or statistically significant difference between the treated and untreated orbit was observed in any of the main outcome measures at 6 months. At 12 months, muscle volume and proptosis improved slightly more in the orbit that was treated first.

No controlled trials have been specifically performed in patients with dysthyroid optic neuropathy, but several anecdotic reports claim some efficacy.

Radiotherapy Combined with Glucocorticosteroids

For more than 30 years the Pisa Group has employed and advocated a combined treatment of ORT and oral, later intravenous glucocorticosteroids [50–52]. It is hard to evaluate the outcome of these studies because of the different study designs, application techniques, cumulative dosages etc., but the overall conclusion appears to be a slightly better outcome when ORT is combined with steroids. This was also the concluded in a few meta-analyses [53, 54]. The disadvantage, however, of combined treatments is the likelihood of the sum of the expected side effects of the individual therapies, which becomes apparent in these studies as well.

Dose of Orbital Radiotherapy

The aim and supposed target of orbital irradiation is the orbital fibroblast. A total dose of 20 Gy (external beam linear accelerator) delivered as 2 Gy per day over a 10 day's period is the usual treatment for patients with GO. Fibroblasts, however, are extremely sensitive to irradiation and lower doses proved to be equally effective. Kahaly et al. [55] randomly compared the efficacy and tolerability of three ORT protocols. ORT (telecobalt) was administered either in 20 divided fractions of 1 Gray (Gy) weekly over 20 weeks (group A) or in 10 fractions of 1 Gy (B) and 2 Gy (C) daily over 2 weeks. They concluded, that in patients with moderately severe GO, similar response rates were observed for low and high ORT doses, but the 1 Gy/week protocol was more effective and better tolerated than the short arm regimens. Another German study [56] concluded that if the aim of ORT is primarily to reduce soft-tissue signs, cumulative doses as low as 12 Gy are sufficient. If a patient also suffers from dysmotility, doses exceeding 12 Gy may be more effective.

Gerling et al. [57] found no difference of outcome after 2, 4 and after 16 Gy. They concluded, that either ORT is ineffective or the maximal effect is already been reached at 2.4 Gy.

Safety

From the very start of ORT for GO, a number of possible side effects has been warned for. These include cataract formation, retinopathy, optic neuropathy, and carcinogenesis. The risk of developing fatal radiation-induced cancer after ORT regimens applied for GO has been calculated as varying between 0.0067 and 1,2 % [58, 59].

In a prospective study in 42 individuals with GO treated with 20 Gy external beam irradiation [60], de novo or aggravation of microvascular abnormalities were found in three patients. In another follow-up study [61], 245 patients were screened 10–20 years after having received either 20 Gy external beam irradiation or oral prednisone. No difference in mortality rate or cataract formation between the two groups could be assessed. However, definite retinopathy (e.g., more than five lesions) was assessed in five irradiated patients, of whom four had diabetes and one hypertension. These and other studies conclude that ORT might be a risk in patients who might develop retinopathy, such as patient with diabetes mellitus.

Conclusion

As long as ORT is given to nondiabetic patients older than 40–50 years of age, the side effects of ORT are negligible. A modest improvement of inflammatory signs and ocular motility can be expected in patients with active and mild or moderate Graves' orbitopathy. This improvement can possibly be amplified when glucocorticosteroids are added.

> Orbital external beam irradiation, especially in combination with low dose oral prednisone, may improve eye motility in patients with active GO.

Other Medical Treatment Modalities

A number of anti-inflammatory treatments other than corticosteroids and radiotherapy have been proposed for patients with GO. Among these are plasmapheresis, Azathioprine, Cyclosporine, IVIG (intravenous immunoglobulins), somatostatin analogs, and recently added biologicals such as cytokine-antagonists TNF-alpha

inhibitors and anti-CD20 monoclonal antibodies. Most of these treatments have not been extensively studied, and only few have been evaluated in a decent study design.

Case histories show that plasmapheresis may have some importance as an initial intervention, but subsequent immunosuppressive treatment is warranted to preserve the beneficial effects. In the only controlled, but small study on the efficacy of Azathioprine [62], Petros Perros et al. from Newcastle-upon-Tyne, concluded that Azathioprine is not an effective treatment for patients with moderately severe GO. The history of Cyclosporine in the treatment of GO shows how careful we must be in interpreting the outcome of non-controlled studies. After a few very enthusiastic reports, a randomized study showed that Cyclosporine as a mono-treatment has no place in the management of GO [12]. However, the same study showed that Cyclosporine together with oral prednisone might be effective in patients who do not respond to either of the drugs alone, a message that is often forgotten! Intravenously administered immunoglobulins (IVIGs) are applied in a large number of autoimmune disorders and have dramatically changed the outcome of such diseases as Steven Johnson's syndrome. IVIGs exert their effect on autoantibodies, complement, phagocytic cells, etc. IVIGs also inhibit orbital lymphocytes and fibroblasts through inhibition of IL-1 or/and TGF-beta. The efficacy and safety of IVIGs have been tested in two controlled trials [24, 63], showing that this treatment is equally effective as i.v. methylprednisolone and has few side effects. However, the high costs limit this option as a first-choice treatment. About the efficacy of somatostatin analogs we can be short. Somatostatin receptors are located on the surface of orbital fibroblasts and blocking of these receptors has been supposed to interfere with local immune responses. A meta-analysis evaluating a number of controlled studies on the efficacy and safety of several analogs (Octreotide-LAR, Lanreotide) showed no clinical relevant superiority to a placebo, perhaps because of the low receptor-affinity of the tested drugs [64]. Moreover, somatostatin analogs are expensive. Etanercept (Enbrel), a TNF-alpha inhibitor, in a small and non-controlled study reduced the inflammatory signs of GO temporarily [65].

Rituximab (RTX)

Among all new drugs proposed for the treatment of GO, this humanized chimeric anti-CD20 monoclonal antibody is perhaps one of the most promising at this time. Mario Salvi et al. [66] reviewing the literature on RTX concluded: "Targeting of CD20+ cells removes B lymphocytes in all intermediate stages of B-cell maturation, activated memory B, and short-lived plasma cells by depleting their immediate precursors. RTX has been used off-label in various autoimmune disorders but is approved for clinical use only in non-Hodgkin's lymphoma and rheumatoid arthritis. To date, RTX has been used in 43 patients with active GO. The disease has become inactive in as many as 39 (91 %), has not changed in three, and worsened in one patient. In most patients, proptosis and eye motility have been shown to improve. Side effects have been reported in about one-third of patients, usually

infusion-related reactions. Because RTX does not seem to modify circulating TSH receptor antibodies, its effect may result from the blockade of antigen presentation by B cells after anti-CD20-induced lysis. Although evidence from controlled trials is needed before proposing RTX as a novel therapeutic tool in this disease, collected data suggest that RTX does significantly affect the activity and severity of GO. Controlled studies will also help decide whether RTX is to be used in any patients with active GO or only in those with otherwise unresponsive disease of a severe degree. The data reported on RTX therapy in GO suggest that B-cell depletion may be pursued shortly after diagnosis, and not only as a therapeutic option when standard immunosuppression has failed."

The efficacy and safety of new drugs for GO have to be demonstrated in RCTs.

Selenium

The trace element Selenium ameliorates biochemical parameters associated with oxidative stress. In a randomized, double-blind, placebo controlled study in 159 patients with mild GO, the EUGOGO demonstrated, that Selenium in a dose of two times 100 μg a day improved the quality of life, decreased eye involvement and slowed the progression of GO as compared with placebo. The decrease of the clinical activity score was most pronounced in patients receiving Selenium [67].

Flow Chart for Medical Treatment in Graves' Orbitopathy

Once a diagnosis of GO has been established (based on medical history, typical clinical findings and imaging), the severity and activity of the disease are ascertained. Mild and inactive cases are followed up and surgically treated if needed. Mild and active cases are treated with selenium. Moderately severe and inactive cases are followed up and undergo surgery when symptoms have been unchanged for at least 3 months. Moderately and active cases are treated according protocol I. Alternatively and especially when diplopia is the main problem, the can be treated with radiotherapy with or without a low dose oral prednisone. Patients with vision-threatening orbitopathy are treated according to protocol II and if they do not respond sufficiently undergo orbital decompression. When glucocorticosteroids as monotherapy fail, a combination of prednisone and cyclosporine can be tried. Finally, RTX offers a possibility for unresponsive cases (Fig. 19.3).

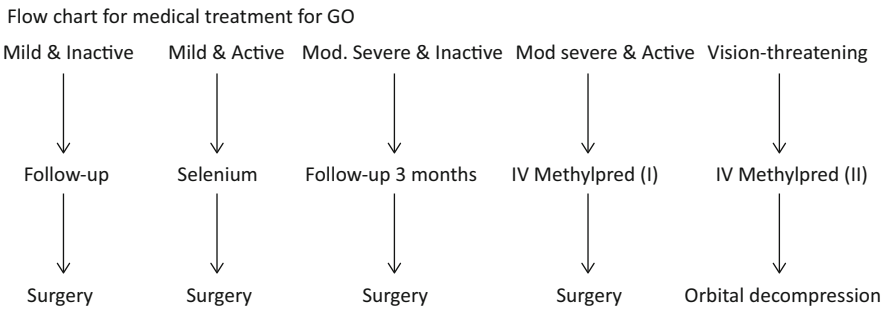

Fig. 19.3 Flowchart for medical treatment of GO

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Chapter 20
Preoperative Assessment and Orbital Decompression Surgery in Patients with Graves' Ophthalmopathy

James A. Garrity

The decision to perform a surgical procedure (of any type) is not taken lightly. In our training program we instruct trainees that one of the most difficult decisions is trying to figure out who should NOT undergo a surgical procedure. Surgeons with a track record of "good results" consider such variables as natural history of the disease, findings on clinical examination, patient expectations, age, comorbid diseases such as diabetes, outcomes of previous therapies such as corticosteroids or orbital radiation therapy, tempo of the disease, smoking history, impact on the patient's quality of life, a firm understanding of what the operative procedure can deliver in terms of outcomes along with its attendant side effects, and whether non-surgical therapy is a better option. This is especially true in Graves' ophthalmopathy (GO) where the clinician is challenged to determine not only if a surgical procedure would be beneficial but also when the procedure should be performed.

It is axiomatic that correct therapy is predicated upon a correct diagnosis. The first decision point is whether or not the diagnosis is correct. GO remains a clinical diagnosis as there is no single clinical finding or laboratory test that is diagnostic of GO [1]. While there is generally little diagnostic confusion in a patient with a history of hyperthyroidism, bilateral proptosis, and pretibial dermopathy, a patient with unilateral (or markedly asymmetric) ophthalmopathy and no history of thyroid dysfunction can present a diagnostic challenge. We have encountered diagnostic difficulties in patients with dural carotid-cavernous sinus fistulas, extraocular muscle lymphomas, sphenoid wing meningioma, an exophytic optic nerve sheath meningioma, orbital myositis, breast metastasis to the extraocular muscles, and IgG4-related disease in the extraocular muscles.

The patient (65 F) with a dural carotid-cavernous sinus fistula had Hashimoto's thyroiditis and unilateral orbital findings which included an audible bruit, vision

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loss over several days (unusual for dysthyroid optic neuropathy (DON)), proptosis, abduction deficit, corkscrew conjunctival vessels that reached the corneal limbus, typical fusiform enlargement of the inferior and medial rectus muscles, but more importantly an ipsilateral dilated superior ophthalmic vein. The visual field examination showed a superior paracentral defect (unusual for DON). A subsequent cerebral angiogram was not only diagnostic for a dural carotid-cavernous sinus fistula but proved to be therapeutic in that the fistula closed immediately after the procedure with rapid resolution of all symptoms and signs.

Two types of meningioma have created diagnostic confusion. One patient (42 F) with Hashimoto's thyroiditis presented with unilateral proptosis, enlargement of the posterior portion of the medial rectus muscle, a contrast-enhancing optic nerve in the orbital apex, and amaurosis with lateral gaze (very uncommon with DON). Subsequent evaluation confirmed an exophytic optic nerve sheath meningioma. The other patient was a euthyroid 65-year-old male who presented with proptosis and lower lid retraction. Imaging, in retrospect, showed minimal but definite hyperostosis of the greater wing of the sphenoid and enlargement/infiltration of the lateral and inferior rectus muscles. The adjacent orbital fat was also subtly infiltrated with meningioma.

We have seen two patients with MALT lymphomas of the extraocular muscles and another with IgG4 related disease of the orbit. A 70-year-old male with no history of thyroid dysfunction became "steroid dependent" for his orbital congestion. He was also exotropic (unusual with GO and as a general rule should prompt the clinician to think of concomitant myasthenia gravis) and his imaging showed enlargement of all the extraocular muscles and an apparent nodule on his lateral rectus muscle which was biopsied showing a MALT lymphoma. A 68 F with a history of Hashimoto's thyroiditis had previously undergone orbital decompression elsewhere and we evaluated her for recurrent proptosis. Biopsy of the extraocular muscle and adjacent orbital soft tissue revealed MALT lymphoma. The last patient was a 38 M with no history of thyroid dysfunction who had also undergone orbital decompression for excess proptosis. When we evaluated him for recurrent proptosis, we noted disproportionate enlargement of the lateral rectus muscles and enlarged infraorbital nerves. Biopsy of the lateral rectus muscle revealed IgG4 disease [2].

The ophthalmic portion of the examination includes measuring visual acuity, color vision, pupillary function; inspecting the eyelids for edema/erythema; measuring eyelid fissures and lagophthalmos; noting lid lag; examining the globe for chemosis, caruncle edema, and conjunctival injection; exophthalmometry; measuring ocular deviation in primary and reading position and in various fields of gaze; recording ocular ductions in six cardinal positions; slit lamp evaluation for exposure keratitis and superior limbic keratoconjunctivitis; and finally examining the ocular fundus for disk edema or choroidal folds. Formal examination of the visual fields are not routinely performed but are done if there is unexplained visual loss, an afferent pupillary defect, acquired dyschromatopsia, or a swollen optic disk. Orbital imaging is not a routine portion of our examination either unless there is asymmetric orbitopathy, the diagnosis is otherwise in question, or if orbital decompression surgery is planned. We do not see a role for imaging with an MRI. In addition to being quicker and cheaper, computed tomography has the added advantage of

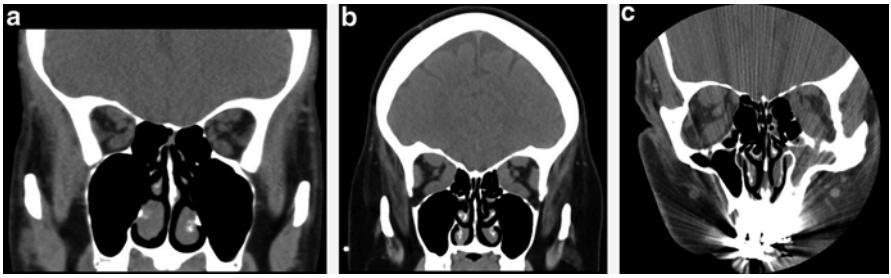

Fig. 20.1 (**a**) Coronal CT of orbits demonstrates a thin ethmoid sinus roof, especially on the *left*. This patient is at risk of a cerebrospinal fluid leak during the ethmoidectomy portion of the orbital decompression. (**b**) Coronal CT of orbits demonstrates a very thick ethmoid sinus roof. This patient has a very low risk of cerebrospinal fluid leakage during the ethmoidectomy. (**c**) Coronal CT of orbits demonstrates hypoplastic maxillary sinuses (*left* more so than *right*), a chronic left maxillary sinusitis, and thin ethmoid sinus roof

showing bone. Because of the inherent contrast between orbital fat and other orbital structures, we do not routinely use contrast material. The iodinated contrast material will interfere with therapy directed at the thyroid after administration of contrast. Pre-decompression CT scanning serves to confirm the diagnosis of GO, provide anatomic details of the paranasal sinuses, and most importantly to demonstrate the bony competence of the fovea ethmoidalis as cerebrospinal fluid (CSF) leaks can arise from this area during the ethmoidectomy (Fig. 20.1a, b). Figure 20.1c also shows a chronic sinusitis which many years ago was initially thought to be a contraindication to a decompressive procedure that opened into that sinus. As time has shown however, decompression into the diseased sinus does not result in an orbital cellulitis and in fact is curative of the underlying sinusitis.

Many of the signs and symptoms of GO can be attributed to a discrepancy between the fixed volume of the bony orbit and the increased swelling of the retrobulbar tissues. In some patients, mostly younger patients (generally <40 years old) there can be expansion of mainly the fat compartment whereas older patients and those with more severe disease can have an almost selective expansion of the extraocular muscle compartment. In reality, most patients have elements of both but patients with more severe disease tend to have greater enlargement of the extraocular muscle component. Of the patients who develop GO, previous natural history studies suggest that 65 % will have a course associated with spontaneous improvement while 22 % did not change and 13 % experienced progressive deterioration [3]. Indeed, in a population-based epidemiologic study of 120 incident cases, we found that only 20 % of patients required surgery whereas 6 % had therapy with either oral steroids or orbital radiation therapy. The vast majority, 74 %, had supportive measures only consisting of lubricating eye drops, sunglasses, cool compresses, and head elevation when sleeping [4]. For the patients in whom some form of treatment is required, one can consider the eyelids, the eye muscles, or the orbit. In broad general terms, one can treat issues related to orbital disease by either attempting to “shrink” the swollen retrobulbar tissues (theoretically with

corticosteroids or orbital radiation therapy) or expanding the bony orbital volume (with surgical orbital decompression). This chapter will be devoted to the orbit only and specifically with orbital decompression. In addition, this chapter will also briefly address orbital fat decompressions.

In the surgical treatment of GO, it is generally accepted that operations should be staged. Since the former can affect the latter, orbital decompression, if required, should be done initially followed by strabismus surgery, if required, and lastly followed by any eyelid surgery. Many types of orbital bony decompression have been described and they can be categorized based on the surgical approach to the orbit (transantral, lateral, transfrontal/coronal, transconjunctival, caruncular, endoscopic transnasal, balanced medial and lateral wall) or on the number of bony walls removed (one, two, three, or four wall). An experimental study has shown that pressure reduction occurs with removal of the bony wall and proptosis reduction occurs with incision of the periorbita [5]. Both experimental and clinical studies demonstrate that the amount of proptosis reduction increases with the number of orbital walls decompressed [6]. (Table 20.1). Favored approaches vary by surgeon or institution and currently most orbital decompressions are two-wall procedures, either antral-ethmoidal (transantral, transnasal endoscopic, caruncular) or medial (transnasal endoscopic) plus lateral decompression. For patients with an extreme amount of chemosis or lid edema, a caruncular approach or through the inferior fornix via a swinging lower eyelid flap can be challenging and this is another reason why working through the sinuses (e.g., transantral approach) can be technically easier.

Each approach should offer an acceptable balance between resolution of symptoms and incidence of side effects. We favor the transantral approach in most patients for bilateral disease because of its lack of surgical scar, short operating room time, overnight hospitalization, and excellent posterior orbital access to treat optic neuropathy, with an acceptable complication rate. Anecdotally it has been our preference to use a transnasal endoscopic approach for unilateral decompressions (approximately 15 % of our decompressions) because of less infraorbital nerve hypesthesia, diplopia, and hypoglobus. Operating times with this approach can be longer if conditions such as septal deviation are present and must also be addressed. We have also used a transfrontal approach as a "salvage" operation for the few patients that need additional decompression [7].

Table 20.1 Proptosis reduction as a function of number of walls decompressed [6]

Walls decompressed	Globe recession
1 (medial wall)	0–4 mm
2 (lateral wall + floor or floor + medial wall or medial + lateral walls)	3–6 mm
3 (medial + lateral wall + floor)	6–10 mm
4 (all 4 walls)	10–17 mm
Fat decompression (no bone)	5.9 mm average [16]
Lateral wall + fat decompression	1.8 mm average [21]
	3.4 mm average [19]

Indications for orbital decompression vary. In our series of 428 consecutive patients with severe Graves' ophthalmopathy who underwent transantral decompression [8], the most common indication for decompression was optic neuropathy, which occurred in 217 (51 %) of patients. Other indications included severe orbital inflammation/congestion (27 %), excessive proptosis (13 %), disfiguring proptosis (8 %), and corticosteroid side effects (1 %). Excessive proptosis does not have an absolute exophthalmometry number. For example, a patient with premorbid exophthalmometry readings of 10 mm and now has readings of 18 mm may be more severely affected than a patient with premorbid readings of 25 mm who now has readings of 28 mm. Symptoms in combination with the exophthalmometer readings are the best measure of "exposure keratitis." In our current practice, these indications and relative percentages have remained remarkably stable over time.

In terms of timing for surgery, we believe that corneal ulceration resulting from excessive proptosis is the only emergent reason for orbital decompression. Evaluation of the patient with corneal ulceration first determines the relative contributions of eyelid retraction and proptosis to the corneal disease. Patients with eyelid retraction and minimal proptosis can be treated with eyelid surgery. Those with excessive proptosis require orbital decompression.

Optic neuropathy and globe subluxation are indications for urgent (not emergent) decompression. Optic neuropathy is heralded by symptoms of decreased visual acuity at both distance and near, visual field loss (typically involving the inferior field and only rarely involving the superior field), and loss of color vision (in the 10 % of normal males with congenital color blindness one loses this parameter of optic nerve function). Visual blurring is very common and exposure keratitis is a frequent cause especially in patients with GO. Symptoms typically get worse toward the end of the day or prolonged visual exertion, reflective of the cumulative effects of tear film evaporation. The blurring usually improves with blinking and supplemental artificial tears. Blurring due to an optic neuropathy, on the other hand, does not improve with blinking and/or artificial tears. The most important sign of unilateral or asymmetric optic neuropathy is an afferent pupillary defect. The optic disk may appear congested/swollen (in 20 % of our cases), or normal in acute cases, and may become pale with long-standing optic neuropathy. While corticosteroids and orbital radiation are treatment options for optic neuropathy, orbital decompression offers the most prompt and reliable therapy [8, 9]. We were formerly of the opinion that optic neuropathy due to Graves' ophthalmopathy required emergent treatment. However, based on our experience with 215 cases [10], we now believe that urgent treatment, begun within several weeks, is acceptable for optic neuropathy. Many patients in our series had evidence of optic neuropathy for many months and following transantral orbital decompression their outcomes were equally favorable.

Globe subluxation occurs when the proptotic globe prolapses anterior to the eyelids and is usually related to excess proptosis combined with excessive eyelid retraction. This is frightening and painful for the patient but is treatable through orbital decompression and/or eyelid surgery. Orbital decompression more fundamentally addresses the excess proptosis by expanding the orbital volume whereby eyelid surgery (typically a lateral tarsorrhaphy) just reduces the eyelid aperture making it less

likely that the globe will sublux. Subluxation can lead to visual loss through its effect on the optic nerve or its vasculature. Less urgent indications for orbital decompression include severe orbital congestion, disfiguring proptosis, either to reduce excessive proptosis prior to extraocular muscle surgery or to reduce proptosis-related exposure keratitis, steroid intolerance, and pain. We have seen the orbital congestion clear literally within hours of orbital decompression which most likely speaks to venous congestion as a major contributing cause. For some patients an inflammatory cause is likely and many of these patients are also steroid dependent. While it may be difficult to distinguish true orbital inflammation from congestion, it is noteworthy that 12/116 (10 %) of our patients required additional therapy for their "congestion" following orbital decompression [8].

In our opinion, it is not necessary that the orbital disease is "inactive" prior to orbital decompression. In fact, virtually all measures of clinical activity [11] (eyelid edema/erythema, chemosis, globe injection, caruncle edema, and pain (at rest and with eye movement)) improve or even resolve after orbital decompression. This probably speaks to the role of orbital pressure and impedance of venous outflow in the pathogenesis of many of the parameters of disease activity. We do strongly suggest waiting for inactive disease before considering a "fat" decompression or a bone decompression for disfiguring proptosis, however (our preference in this setting would be lateral wall decompression with debulking of inferior temporal orbital fat).

In our practice we utilize a one-wall decompression (lateral wall + fat debulking), various two-wall decompressions (transantral (antral-ethmoidal), endoscopic antral-ethmoidal, balanced medial (endoscopic ethmoidal) + lateral, transfrontal (roof + lateral wall), and a three-wall procedure (endoscopic antral-ethmoidal plus lateral wall). The choice of procedure reflects what might best serve the patient given the findings on examination and surgeon choice. The majority of procedures at our institution are bilateral transantral decompressions. Most of our patients have fairly symmetric disease, operating time is roughly 90 min for both sides, there is no visible external scar, and patients spend one night in the hospital. In our review of 428 transantral decompressions, the procedure had better than 90 % effectiveness in maintaining/restoring 20/20 vision and the average proptosis reduction was 4.7 mm. In terms of side effects, we noted new-onset diplopia in 74/116 patients (64 %) with no pre-decompression diplopia. After all surgical therapy 268/300 patients (92 %) who underwent strabismus surgery had no diplopia in primary gaze or could be corrected with prisms. Infraorbital nerve hypesthesia was temporary in all patients but permanent in 23/428 (5 %). Medial lid entropion was noted in 38 patients (9 %) and this can be readily addressed with recession of the lower lid retractors. Leakage of the cerebrospinal fluid was noted in 15/428 (3.5 %), but preoperative recognition of patients at risk for this complication (Fig. 20.1) has reduced the incidence to two instances in the last 20 years (approximately 700 decompressions). Oral corticosteroid use beyond 6 months was noted in 15 patients and there were 13 patients who underwent additional decompression, most commonly for persistent optic neuropathy. Postoperative sinusitis is an infrequent complication but when it occurs it is typically related to obstruction of the naso-antral window. Reopening of the naso-antral window is curative.

In the setting of a "failed" bony decompression (i.e., persistent or worsening symptoms/signs for which the original decompression was performed), there are at least four therapeutic options: observe, steroids (oral or IV), orbital radiation therapy, or additional decompression. When decompression has been selected, we have typically relied on transfrontal decompression for persistent optic neuropathy or severe congestion. Historically the Naffziger procedure decompressed only the orbital roof [12]; our transfrontal procedure is also an extradural procedure but also decompresses the lateral orbital wall [13]. For a bilateral decompression we currently allow about 4–5 h of operating time, one night in the ICU, and 1–2 days on the general floor prior to discharge. In a series of 10 transfrontal decompressions done for persistent optic neuropathy, visual acuity improved in 70 % and visual field scotomas decreased in 80 %. There were no complications in this group [7]. This operation has been useful as a "salvage" procedure in other patients with persistent excess proptosis and chemosis in association with a failed previous decompression.

For patients with disfiguring proptosis, inactive disease, no other symptoms/signs, and a strong desire to avoid any potential side effects notably diplopia or infraorbital hypesthesia, we have relied on two procedures: an orbital fat decompression or a lateral wall decompression plus debulking of the fat in the inferior temporal orbit.

Orbital fat decompression should be most effective in those patients with an expanded fat compartment as visualized on preoperative imaging and least effective in patients with primarily an enlargement of the extraocular muscle compartment. Liao and Huang [14] have described a proportionate response in proptosis reduction as a function of the amount of fat removed but can too much fat be moved? Or can disruption of too many intermuscular septae cause problems [15], especially in the superior temporal quadrant with adhesions to the globe or to the periosteum? Or when should a fat decompression include some bone decompression? Avoidance of diplopia is a major focus of a fat decompression procedure but yet Richter and associates [16], in their review of 1,635 patients who underwent fat decompression, noted temporary (lasting up to 6 months) new-onset diplopia in 127/440 (29 %) and 89/440 (20 %) beyond 6 months who underwent strabismus surgery. They were able to achieve a mean proptosis reduction of 5.9 mm with an average fat resection of 6.3 cc. Kazim et al. have also reported their favorable experience with fat decompression in the management of five selected patients with DON and an expanded fat compartment who had failed steroids or orbital radiation therapy [17]. One of the issues surrounding fat decompression is whether or not fat decompression should be done more frequently. An editorial suggests that this procedure is not for everyone and there are side effects from this operation [18]. Sometimes one asks too much of a procedure and this might be the case for fat decompressions. An alternative procedure might be decompression of the lateral wall and debulking of the inferior temporal fat compartment. The entire lateral wall is thinned from the orbital roof to the floor and from the apex up to the orbital rim. The rim is not removed as some lateral decompressions do. Orbital fat from the inferior temporal quadrant is then debulked in amounts typically ranging from 1.5 to 3 cc. Our technique is similar to that reported by Ben Simon and associates [19]. In their series, 116 patients (201 orbits)

had a mean proptosis reduction of 3.4 mm and there were no complications. The rate of new-onset diplopia in primary gaze was 2.6 %.

Graves' ophthalmopathy has a profound impact on quality of life affecting both appearance and function [20]. At first mention, orbital decompression for GO might seem an overly aggressive therapy [21]. For the selected patient, orbital decompression can be rewarding for the patient, their family, and health care provider.

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Chapter 21
Surgical Management of Extraocular Muscle Dysfunction in Patients with GO

Anja Eckstein and Joachim Esser

Pathogenesis of Extraocular Muscle Dysfunction in GO

Impairment of motility in GO is caused by fibrotic eye muscle changes [1]. This results in a reduced elasticity with preserved or even forced contractility. Smokers and elder patients are significantly more often affected [2]. The extraocular muscles are not affected in the same frequency: The inferior rectus muscle is most often involved followed by the medial rectus muscle. Usually both eyes are asymmetrically involved; therefore single muscle involvement can occur.

Restriction of the inferior rectus muscle causes an elevation deficit. Fortunately, deficits of both eyes equate each other. Diplopia only occurs in patients with asymmetric elevation deficit. However, patients with marked elevation deficit will develop a compensatory head tilt (chin up). Small vertical angles can also be compensated by a chin up head tilt. Misalignment due to inferior rectus muscle restriction results in vertical squint angles with excyclotorsion (with largest angles in upgaze).

Restriction of the medial rectus muscles causes an abduction deficit. Unfortunately, deficits of both eyes add up and cause a convergent squint angle. Slight unilateral abduction deficits can be compensated by a horizontal turn of the head. Convergent squint angles can occur in addition after medial wall decompression due to the prolapse of extraocular muscles into the ethmoidal cells. There is a direct correlation between displacement of the medial rectus muscle and the abduction deficit [3].

Troublesome cyclotorsional squint angles occur mainly after decompression [4] or after large inferior recessions (Incyclotorsion) [5, 6]. Incyclotorsion with A-shaped incommitance can occur after medial–inferior decompression as a consequence of increased superior oblique tension by downward movement of the bulb [7–10].

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Indications for Eye Muscle Surgery

Diplopia and compensatory head tilt are the most common indications for eye muscle surgery. Marked upper lid retraction due to co-innervation in patients with bilateral elevation deficit rarely occurs without compensatory head tilt, but is certainly an indication for bilateral inferior recession and not for lid lengthening. Since marked constriction is associated with gaze-dependent increase of IOP, advanced glaucoma damage can also be a rare indication for muscle recession since recessions can lead to a reduction of IOP [11].

Evaluation of Motility Prior to and After Surgery

All patients should be seen several times before surgery to ensure consistent motility and squint angles for at least 6 months prior to surgery. Surgery should only be performed in stable and inactive disease. In complex situations MR imaging should be performed to recognize the affected muscles. A forced duction test should be done as first step intraoperatively, to prove the fibrotic origin of the motility defect.

Orthoptic assessment before surgery should include the following measurements:

- Visual acuity
- Monocular bulbar excursions
- Squint angle—in more complex situations in nine directions of gaze and including cyclotorsion
- Field of binocular single vision with and without prisms
- Head tilt

Practical advises for the examination: The measurement of the squint angle should be performed while fixating with the eye showing better excursions. The alternating prism cover test can be used in primary position. Maddox screen or Harms tangent screen has to be applied in complex situations for measuring the angles in nine directions of gaze including cyclotorsion. Cyclotorsion should always be measured if the squint angle cannot be compensated with vertical and horizontal prism alone, in case of head tilt, or if oblique muscle surgery is planned.

After surgery it is important not only to measure the squint angle in primary and reading position but also to evaluate the field of binocular single vision. The BSV field allows assessing patients' ability to work, drive a car, etc. and assessing the grade of disability.

Basic Concepts of Surgery

The main aim is to restore symmetrical eye movements which will result in alignment. The basic concept of muscle surgery in Grave's orbitopathy is to recess the constricted muscle(s). Therefore, the first intraoperative step is a forced duction test

to prove the fibrotic nature of the squint. Two surgical concepts are available to improve the constricted motility: the so-called duction correction and deviation correction techniques. In the duction correction technique, the amount of recession is determined intraoperatively by examination of passive or active motility [12]. In the deviation correction technique, the amount of recession is preoperatively determined according to the measured squint angle in primary position by means of dose-effect calculations. The latter technique is more suitable for inexperienced surgeons. Superiority of one method over the other has not been shown (summary in [13, 14]. Experienced surgeons report more success with duction correction [15] in comparison to deviation correction. However, the best predictor of preoperative deviation is the difference between restriction of the contralateral opposing recti [16], so the preoperative squint angle seems to be a suitable base for surgery to achieve symmetric eye movements. Consequently, many groups have reported high success rates with the deviation correction procedure, too [13, 17].

The duction correction technique has to be performed under topical anesthesia, enabling the patient to collaborate. This technique is not suitable for anxious patients. The patient has to look in primary position after the restricted muscle has been desinserted from the eye bulb. The muscle is then reinserted to the sclera at the place where the muscle can be positioned free of tension [12, 18].

The amount of recession is limited by the length of the arc of contact for each muscle. Fortunately, the most often involved inferior rectus muscle has the largest arc of contact (9 mm) in comparison to the other muscles (e.g., medial rectus muscle 6.3 mm) [19]. Recessions outside the arc of contact would induce a duction deficit (which is only sometimes useful—e.g., Inferior rectus fibrosis one side and Superior rectus fibrosis other side). Large squint angles, which would require recession distances exceeding the arc of contact, require extra considerations (implants, surgery on the ipsi- or contralateral antagonist, or recession on the ipsilateral antagonist).

Adjustable sutures are difficult to perform in GO patients, since the effect of recessions increases within 1–2 months after surgery due to strengthening of the antagonist muscle when released after recession [20, 21].

In restrictive strabismus, muscle resection should be avoided if possible. Any restrictive situation is likely to be aggravated if a muscle is shortened, inducing gaze limitation and possibly a smaller field of binocular single vision.

Extraocular muscle surgery after decompression requires special considerations and will be described in an extra section.

Typical Situations and Surgical Approach

The Most Common Situation: Unilateral Elevation Deficit Resulting in Hypotropia

Unilateral or rather asymmetric elevation deficits result in a vertical deviation with diplopia. Patient with smaller deviation can usually still read but experience diplopia in primary position (PP) and upgaze. To prevent diplopia in PP in patients with

head tilt (chin up), the eye with the more impaired elevation should be patched prior to surgery, to find out if head tilt is given up. If not, head tilt is a result of both bilateral elevation deficit and diplopia prevention. In case the head tilt persists, bilateral inferior recession should be considered (with asymmetric recession distances).

If deviation correction is performed, a dose effect of about 2.0° squint reduction per mm inferior recession can be applied (summary in: [13]). The dose effect is higher in comparison to squint surgery for concomitant squint due to increased muscle tension and low elasticity in Grave's orbitopathy patients [22] (see Tables 21.1 and 21.2). Respecting the arc of contact, squint angles up to 15–17.5° (30–35 pdpt) can be corrected with a single inferior recession. Seven millimeters of recession distance should not be exceeded, in order not to risk diplopia in downgaze. Usually, 1 day after surgery patients present with a significant under effect. This will resolve for two reasons: The superior rectus muscle has not been maximally contracted for a while and needs to be trained. In addition, most of the patients have normal fusion and even increased vertical fusional capacities. Final results will be reached after 2–3 months.

The primary aim of the surgery is binocular single vision in downgaze and primary position. In patients with larger squint angles diplopia persists in upgaze, which is not bothering most of the patients, as only downgaze and primary position are important for everyday life.

Table 21.1 Dose-effect coefficients for extraocular muscle recessions in Graves' orbitopathy: squint angle reduction in primary position per mm recession distance (without prior decompression)

Recession	Dose effect (squint angle [in primary position] reduction per mm recession distance)	Literature
Inferior rectus	1.9–2.1	[21, 23–25]
Unilateral medial rectus	1.6–1.7	[13, 21, 26]
Bilateral medial rectus	1.5–1.6	[13, 21, 26, 27]
Superior rectus	1.5 (primary)	[28]
	1.4 (second step after inferior recession contralateral)	
Inferior oblique	0.5	[29]
Combined Inferior rectus Medial rectus	2.1 or more 1.8	[26]

Table 21.2 Dose effects (squint angle reduction in primary position per mm recession) for inferior and medial recessions after decompression

Surgical procedure	Dose effect (squint angle [in primary position] reduction per mm recession distance)	Literature
Inferior rectus	2.0	[30]
Unilateral medial rectus	1.2–1.3	[30, 31]
Bilateral medial rectus	1.1–1.3	[30]
Tendon elongation Inferior rectus Medial rectus	2.0 0.9–1.0	[30, 32]

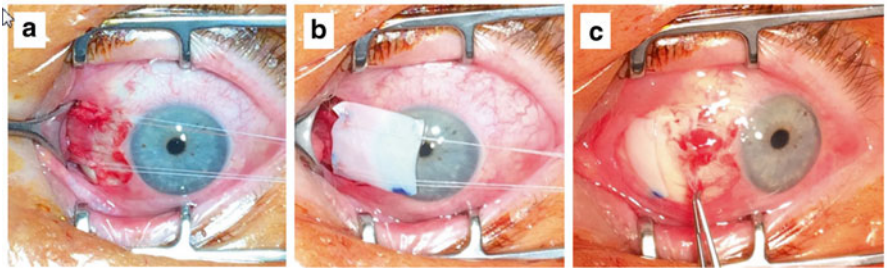

Fig. 21.1 Medial rectus tendon elongation with a Tutopatch® interponate in a patient with marked abduction deficit and a large convergent squint angle (27.5°/55pdpt) after balanced decompression to treat dysthyroid optic neuropathy. She was treated with a medial recession of 6 mm in the eye with the better abduction and with a combined tendon elongation (Tutopatch 9×12 mm), and with a medial recession of 4 mm at the eye with the more markedly reduced abduction. The interponate is sutured to the sclera with nonresorbable sutures 4 mm behind the original insertion in order not to shine through the conjunctiva. (**a**) nonresorbable sutures at the insertion—the muscle is still attached and the bulb can only be abducted 5°–10° over the midline. (**b**) The interponate is sutured to the muscle. (**c**) The muscle is detached from the insertion—now the eye bulb can be fully abducted and the free end of the interponate is almost positioned at the place where it will be sutured to the sclera

Because downgaze is so important, in patients with very small vertical squint angles with the risk of creating an over effect, surgery at the contralateral antagonist (inferior oblique muscle other eye) should be taken into consideration [29]. While a surgical over effect at the inferior rectus muscle causes diplopia in downgaze, an over effect at the inferior oblique muscle would result in diplopia in upgaze, which is much less troublesome in the daily routine.

Another, more difficult situation is a very large squint angle in patients with highly asymmetrical monocular excursions. Three options can be considered: the usage of an interponate (sclera, bovine pericard [Tutopatch®]), the contralateral superior rectus recession, or a combined recession/resection procedure. Since the main aim is the restoration of symmetric eye movements, recessions/implants should be preferred. Implants serve to preserve the arc of contact (see Fig. 21.1) [32].

Resection may lead to a reduction of motility and therefore may result in a rather small central field of binocular single vision, and especially in diplopia in downgaze. Therefore resection should be prevented.

Binocular Elevation Deficit

If elevation is markedly reduced in both eyes, patients will develop a head tilt (chin up) not only to compensate diplopia. The head tilt will persist when the more impaired eye is patched. This situation is an indication for bilateral inferior recession. In bilateral inferior recession, recession distances of more than 6 mm should be avoided. With increasingly large recession the eye's other depressor, the superior oblique muscle, is called upon to contribute. Whereas the inferior rectus is an

adductor, the superior oblique is an abductor so the eye abducts and turns inwards during downgaze, resulting in an A-pattern misalignment [8, 9]. This effect can be possibly reduced by transposing the inferior rectus temporally to the insertion at the time of recession surgery. The risk of incyclotorsion and A-pattern misalignment increases with recession distance and is rare in unilateral recessions and more common in bilateral procedures especially after decompression [5]. It can be corrected successfully by superior oblique weakening procedures [6, 7, 10, 33].

Vertical and Cyclotorsional Squint After Decompression

The dose effect of inferior rectus recession does not change after decompression, since there is less downward displacement of the eye bulb after inferior nasal compression [3]. However, the displacement may have significant impact on the superior oblique muscle function and the risk of incyclotorsion and A-pattern misalignment after inferior recession increases with decompression [8, 9]. Recessions of the rotatory antagonist (inferior rectus muscle) exacerbate this effect and have to be done in these patients with caution [7–9]—(see above).

Abduction Deficit and Convergent Squint

Comparable to inferior rectus recessions there is also a good linear correlation between the amount of recession of the medial rectus muscle and squint angle reduction. The dose effect is lower; about 1.7° squint angle reduction per mm recession distance for unilateral medial rectus recession and about 1.5°/mm for bilateral medial rectus recession (see Table 21.1). The arc of contact is about 6 mm for the medial rectus muscle. Squint angles up to 10° (=20 pdpt) can be corrected with a unilateral medial rectus recession. Squint angles up to 20° (=40 pdpt) can be corrected with a bilateral medial rectus recession. Comparable to the inferior rectus recession, the goal for medial rectus recession is to increase abduction and to induce symmetric eye movement. Therefore, in bilateral procedures recession distances for both eyes should be determined according to the monocular excursion of the bulb. A calculation with respect to monocular excursion levels is possible (see [21]). Asymmetric impairment of abduction should result in asymmetric recession distances. Without prior decompression squint angles rarely exceed 40 pdpt. As described for the inferior rectus muscle, implants and resection of the external rectus muscle have to be considered in very large squint angles.

Convergent Squint Angles After Decompression

Bony orbital decompression serves to enlarge bony orbital volume to reduce exophthalmos and to decompress the orbital content including the optical nerve. The enlargement of the orbital contents leads to a change in extraocular muscle

pathways, especially medial, because highest volume increase is gained through medial wall decompression into the ethmoidal sinus. An MRI study after three-wall decompression revealed a centrifugal displacement (outward from the orbital axis) of the medial rectus muscles [3]. The amount of displacement was shown to inversely correlate with the range of reduction of abduction and to directly correlate with horizontal diplopia postoperatively. Since volume increase is the aim of decompression, patients have to be informed prior to surgery about the risk of postoperative diplopia. The diplopia risk depends on the surgical approach and the motility status preoperatively. The risk of developing new diplopia in primary position is low after lateral decompression (about 0–7 %) [34–36], whereas medial wall decompression increases the risk significantly. In balanced decompression (lateral/medial) the risk varies between 4 and 12 % if the patient has no prior impairment of motility, and it varies between 25 and 41 % in patients with prior impairment (diplopia in external directions of gaze preoperatively) [37, 38]. The risk is high after performance of inferior medial decompression techniques (50–70 %) [39, 40]. Preoperative dysthyroid optic neuropathy (DON) has the highest risk of developing new diplopia after surgery.

Displacement of the muscles after decompression changes their lever action and reduces dose effects for medial rectus recessions [30]. The correlation coefficient between the amount of recession and squint angle reduction is lower in comparison to surgery done in patients without decompression [30, 41], which means that there is a higher variability of postoperative results. Therefore, surgical correction of diplopia is more difficult in patients after decompression [42].

Due to the lower dose-effect coefficients (see Table 21.2) in these patients the maximal convergent squint angle, which can be corrected while respecting the arc of contact of 6.0 mm, is about 14°–17° (28–35 pdpt). Mocan et al. [31] reported undercorrection for recessions with adjustable sutures in patients with prior decompression, too [31]. Patients with larger convergent squint angles are difficult to manage. Lateral rectus resections can be performed if no equilateral inferior rectus surgery is necessary. In the latter patients interponates and hang back sutures are the procedures of choice. Over- and undercorrection occur due to the higher variability of the effect of the recessions. In this setting it is a great advantage that interponates with Tutopatch® can be easily revised [30] (Fig. 21.1). Because of the higher variability of the effect of recession after decompression, step-by-step procedures are advisable. On the other side highest dose-effect coefficients can be reached with simultaneous inferior/medial recessions—so eye by eye may also be an advice.

Combined Elevation and Abduction Deficit

As stated in the chapter about decompression, combined inferior and medial rectus recessions influence each other. The dose effect increases especially for inferior rectus recession (see Table 21.1) [26]) and dose effects are more variable. In addition, small vertical squint angles often disappear or turn to be latent after medial recession(s). Consequently, convergent squints—if the angle exceeds the vertical squint angle—should be corrected first and the effect on the vertical situation should

be awaited. If vertical squint exceeds the convergent squint, inferior recession can be performed together with medial recession to reach higher dose effects, however, more variable dose effects have to be kept in mind. Therefore, a step-by-step procedure will be more precise especially for smaller squint angles, with the correction of the higher squint angle first (either horizontally or vertically). It is more difficult for large angles. Comparable with the situation in patients after decompression—in rare constellations of large combined angles, the highest dose effects after combined surgery can be successfully used (Fig. 21.2 a–e). However the patients have to be informed prior to surgery about the variable unpredictable dose effects and the necessity of a second surgical step at the better contralateral eye.

The Influence of Extraocular Muscle Dysfunction on Lid Configuration

Since vertical extraocular muscle surgery influences lid configuration, it should precede eyelid correction. Horizontal squint corrections can be performed simultaneously with lid corrections.

The levator palpebrae muscle and the superior rectus muscle are innervated by the same branch of the oculomotor nerve. When upgaze is restricted due to fibrosis of the inferior rectus, upper lid retraction may be induced on attempted upgaze. This upper lid retraction in intended upgaze resolves after inferior rectus recession.

Another comparable situation can be found at the lower lid. The Tenon capsule of the inferior rectus muscle is connected with the lower lid retractors at approximately 15 mm distance from the limbus. This is called the capsulopalpebral head. Recession of the inferior rectus results in posterior displacement of the capsulopalpebral head and can cause disfiguring lower lid retraction. Therefore, the capsulopalpebral head has to be detached from the muscle in the same session before inferior rectus recession [43] or should be even reattached anterior to prevent lower lid retraction [8, 9]. Meyer et al. [44] have described a primary infratarsal lower eyelid retractor lysis to prevent eyelid retraction after inferior rectus muscle recession. If disfiguring lower lid retraction appears, lower lid lengthening is necessary [45].

The Influence of Extraocular Muscle Surgery on Intraocular Pressure

In patients with marked eye muscle fibrosis, the intraocular pressure (IOP) rises and highest values are reached in the direction of restriction. After recession of the restricted eye muscle, intraocular pressure decreases early in the postoperative period [11]. Since IOP values are usually normal in downgaze—which is the preferred viewing direction in daily routine—higher IOP values are rarely harmful in GO patients. However, patients with the comorbidity of glaucoma should be treated with caution. If marked bilateral elevation deficit occurs in these patients, bilateral inferior recession should be considered to reduce IOP.

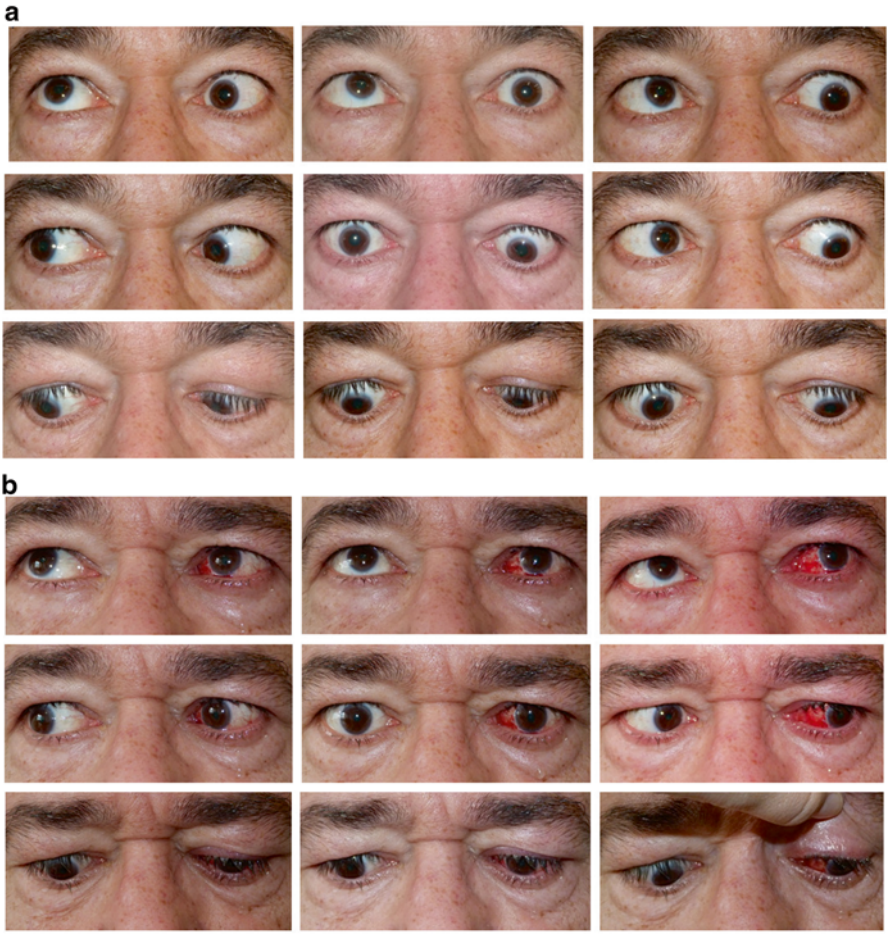

Fig. 21.2 Patient example for a combined Medial and Inferior rectus recession pre- (**a**) and post-operatively (**b**): In the simultaneous prism cover test in primary position the measured angles [+9°, +VD15°/18 PD convergent squint and 30PD of vertical squint—hypotropia left eye] were slightly lower in comparison to the measurement using the Harms Wall—[see **c** preoperatively; +12°, +VD22° and Excyclotorsion 10°]. The patient was not decompressed. Because of the large squint angles, maximal effect was intended and simultaneous correction of convergent and vertical squint angle was performed. The medial rectus muscle was recessed 5 mm [underlying dose effect 1.8°/mm] and the inferior rectus was recessed 6.5 mm [underlying dose effect 2.1°/mm]. The capsulo-palpebral head has been detached. Postoperatively at day 1 after surgery, the patient presented with a residual + VD of 3° (6 PD). The mild under effect was an optimal result since it is known that the effect will increase in the first 6 weeks after the surgical procedure. The postoperative 6 weeks Harms Wall measurement is displayed in **d**. The patient had only residual diplopia in extreme upgaze [see **e**—field of binocular single vision]

c

-	+VD24°	+12°	+VD12°	+10°	+VD11°
Ex 12°		Ex 16°		Ex 16°	
+7°	+VD 23°	+12°	+VD 22°	+11°	+VD18°
Ex 5°		Ex 10°		Ex 18°	
12°	+VD20°	+11°	+VD 20°	+12°	+VD 12°
Ex 3°		Ex 9°		Ex 18°	

Right gaze — Left gaze

d

-1,5	+VD2,5°	+0,5°	+VD2,5°	-1°	+VD2°
Ex 5°		Ex 5°		Ex 6°	
-	+VD1°	-0,5°	+VD1°	+0,5°	+VD1°
-		Ex 1°		Ex 2°	
-	-	-1°	-	-	-
-		Ex 1°		Ex 1°	

Right gaze — Left gaze

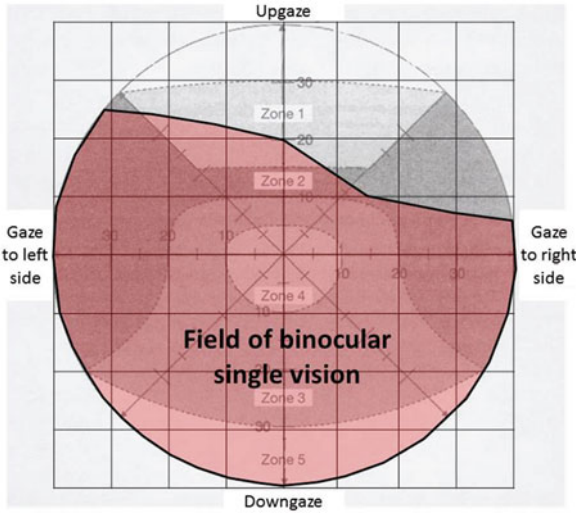

Fig. 21.2 (continued)

Success Rates

In most cases it is possible to improve the field of binocular single vision substantially. Final results are only reached after 4–8 weeks. Postoperative muscle tone increase occurs in structures that were previously relaxed, e.g., the antagonist and the "passive orbital tissue." They return to their original tension, which leads to a further globe rotation against the direction of the recession. Therefore, the effect of squint angle reduction increases significantly within the first postoperative month.

Without prior decompression about 90 % of the patients reach binocular single vision in primary position with one or two procedures. However, diplopia in external directions of gaze especially in upgaze (in cases of inferior rectus fibrosis) and in side gaze (in cases of medial rectus fibrosis) will persist. There is a direct correlation between the size of the field of binocular single vision and the preoperative asymmetry. Most of the patients will be able to drive a car again. It may not be possible for patients with special professions like pilots, taxi drivers, etc. to be employable in these professions again.

For correction of vertical misalignments due to inferior constriction, surgeons should rather aim to undercorrect a deviation since binocular single vision in downgaze is much more valuable than in upgaze. Contradictory is the situation in rare cases of superior rectus fibrosis, where overcorrections should be intended to achieve a sufficient field of BSV in downgaze. The prognosis is generally worse in these patients.

Complications

Slippage especially of the inferior rectus can occur. Unfortunately, revisions with reinsertion have a limited prognosis. Inferior recessions at the contralateral side should be considered. Other causes of overcorrection may include consecutive fibrosis of the contralateral inferior rectus. Overcorrections may also occur when the muscle is not directly fixed to the sclera but is adjusted on the following day. This probably occurs due to adaptation of the muscles to changed tension during the operation.

In patients with large recessions bare sclera technique may end up with dry eye symptoms. In patients with difficult ocular surface situations, amnion transplantation can be applied to improve the surface problems.

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Chapter 22
Quality of Life in Graves' Ophthalmopathy

Elizabeth A. Bradley and Molly L. Fuller

Clinical Impact of Graves' Ophthalmopathy

Clinicians involved in the diagnosis and treatment of thyroid eye disease have the responsibility of addressing both the physical and psychological sequelae of this disease. Graves' disease is rarely life threatening and Graves' ophthalmopathy (GO) is rarely sight threatening, so the primary focus of care is on minimizing the negative effects of the disease on ocular health. The success with which patients' signs and symptoms are ameliorated and visual and social functioning are improved by treatment has a direct and significant impact on the quality of their lives. Thus, it behooves care providers to assess each patient's health-related quality of life (HRQL) at each stage along the course of the disease, allowing for changes in HRQL to help guide the next phase of treatment.

GO is the most common cause of proptosis and eyelid retraction in adults and is a frequent cause of adult-onset strabismus. In addition, patients with GO report a variety of symptoms including altered appearance, ocular pain, diplopia, and vision loss. These changes lead to significant alteration in psychosocial functioning, mood, and ability to work, with both personal and economic ramifications. Some symptoms tend to be transient, so conservative measures are able to provide relief while the disease follows its natural course to spontaneous resolution, while other symptoms are potentially permanent, requiring a patient to invoke a variety of coping mechanisms and life adaptations to find a "new normal." The degree to which a patient's life is altered by the disease course is deeply personal and, by definition, subjective. HRQL is a multifactorial concept incorporating physical, psychological, and social issues and is influenced by an individual's perceptions, interactions, and adaptability [1]. Thus, the only way to assess the effect of GO on HRQL is to ask the patient.

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Throughout the course of the disease, both medical and surgical therapies are available to aid in the management of GO, but unfortunately, some of the side effects or risks of these therapies have the potential to negatively affect HRQL while others are simply incompletely effective at improving HRQL. Steroids are able to limit the inflammatory congestive symptoms of GO, but the side effects of steroids, including weight gain, osteoporosis, blood sugar elevation, hypertension, mood alteration, glaucoma, and cataracts, often counter their beneficial effects. Additionally, steroids are ineffective against the fibrotic changes of GO such as extraocular motility restriction and eyelid retraction [2]. Surgical treatment of GO includes decompression of the orbit, strabismus surgery, and eyelid retraction repair. The most common potential sequela of orbital decompression is the development of diplopia, occurring in up to 64 % of patients who do not have preoperative diplopia [3]. Although most of these patients ultimately achieve single vision through spontaneous improvement, strabismus surgery or prism glasses, the high rate of postoperative diplopia tempers enthusiasm for the procedure. Additionally, while decompression decreases the degree of proptosis, and eyelid lengthening surgery diminishes the palpebral aperture in an attempt to lessen ocular exposure and altered appearance, surgery cannot necessarily restore patients to their original appearance. Bartley et al. surveyed 120 patients up to 17 years after the diagnosis of thyroid-associated eye disease and found that 60 % of respondents felt their appearance was dissimilar to before thyroid disease, 52 % felt that appearance was abnormal, and 38 % were unhappy about their eyes' appearance. Furthermore, almost a third of those surveyed reported eye discomfort, most often related to dry eyes [4]. Clearly, GO is a chronic disease with the potential to affect HRQL for the rest of a patient's life.

Because GO manifests as a complex constellation of symptoms and signs and is treated with therapies that carry significant potential side effects, no single measure can be used to assess disease severity and treatment outcome. Although objective measures exist for some GO manifestations, these measures fail to provide a comprehensive assessment of the impact of the disease and its treatment on HRQL. Moreover, assessments of quality of life have been found to be predictive of treatment costs and outcomes, independent of clinical indices and laboratory results [5]. Therefore, the ability to measure change in HRQL provides an important endpoint for evaluating medical and surgical treatment of GO. This allows the clinician and patient to have common treatment goals and expectations in order to achieve an acceptable outcome.

Indices of Disease Severity

Historically, clinicians have favored instruments of disease assessment which offer an objection measurement. Given the complexity of presentations of thyroid eye disease, the use of composite measures has been integrated into clinical practice. Numerous quantitative scales of severity have been used to assess GO, including the Clinical Assessment Score (CAS) [6], "NOSPECS" [7], and Gorman diplopia scale [8]. Although NOSPECS is a useful mnemonic for the clinical characteristics of GO,

it is a composite index that includes both subjective and objective measures of disease severity and is subject to imprecision from interobserver variation. Additionally, a patient who worsens in an important aspect of the disease such as optic neuropathy but improves in a less important feature, such as eyelid swelling, could be reported as being unchanged. Similarly, CAS allows for the presence or absence of a clinical feature without grading of its severity, and with equal weight contributed by each of the included symptoms. The limitations of these scales prompted the committees of the World Thyroid Associations to recommend that these classifications be abandoned in favor of separate objective measures of the various manifestations of GO [9].

A significant obstacle to adequate clinical appraisal of GO is the fact that several of the most bothersome characteristics are difficult to assess objectively, including external appearance, diplopia, and pain symptoms. Additionally, objective measures do not necessarily correlate well with HRQL [10]. For example, evidence of improved extraocular muscle alignment may not correlate with a lessening of diplopia symptoms. In patients with GO, diplopia is a bimodal symptom which is either present or absent in a particular gaze. A small degree of ocular deviation may produce symptoms that are just as bothersome as those produced by a large degree of ocular deviation. Similarly, eyelid retraction in GO leads to widened palpebral fissures and lagophthalmos, which in turn cause symptoms of dry eye, foreign body sensation, tearing, and decreased vision. Eyelid position can be improved with lid lengthening surgery, but any residual lagophthalmos or ocular exposure may continue to cause symptoms that the patient perceives as equally severe. Thus, demonstrating that an intervention lessens, but does not completely eliminate, symptoms may not be a clinically relevant finding. Finally, because vision loss from optic neuropathy is relatively rare in GO, assessments of optic nerve function such as visual acuity, color vision, and visual field tests have a narrow window of applicability in studies of GO. Recognizing the need to include patient-reported outcomes in monitoring thyroid eye disease and response to treatments, the World Thyroid Association consensus statement suggested that "investigators, in addition to the objective measurements… should include self-assessment of the eye condition by the patient. Such assessments…should include commentary on appearance, visual acuity, eye discomfort, and diplopia" [9].

Overview of HRQL Instruments

As the importance of evaluating the impact of diseases and their treatments on health-related quality of life has been recognized, instruments that measure HRQL have been developed. Recently designed and implemented measures of HRQL include generic, disease-specific, and vision-specific instruments. General health instruments include the Medical Outcomes Short Form (SF-36) [11] and the Sickness Impact Profile (SIP) [12]. Although generic measures allow the comparison of HRQL across different diseases, they have been shown in several randomized trials to be less powerful than disease-specific instruments in detecting treatment effects [13, 14].

Disease-specific instruments are therefore more appropriate for clinical trials evaluating therapeutic interventions [15]. The National Eye Institute has recognized that "a patient's quality of life is an important facet to consider in assessing visual health" [16] and has supported the development of the National Eye Institute-Visual Function Questionnaire (NEI-VFQ). The NEI-VFQ was developed to measure the symptomatic effect of common ophthalmic conditions, including cataract, age-related macular degeneration, primary open angle glaucoma, diabetic retinopathy, CMV retinitis, and low vision [17]. The VFQ has been used by several groups to assess HRQL in GO. Ultimately all available instruments have strengths and weaknesses, and their use in clinical practice needs to be tailored to the needs of the patients and goals of the care providers.

General Health

The Medical Outcomes Study Short Form Health Status Survey (MOS-36 or SF-36) is a commonly used instrument to assess HRQL in thyroid disease and its ophthalmic manifestations. The survey probes eight subtopics: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions [11]. The general questionnaire can be scored to create a Mental Component Summary and a Physical Component Summary. To improve the convenience of the survey for clinical use, it has also been used in shorter formats as the SF-24 or SF-12.

To determine if the type of treatment used to make a patient with Graves' disease euthyroid affects the long-term HRQL, 172 Swedish patients were surveyed with the SF-36. Patients in all treatment groups (thyroidectomy, antithyroid medications, or radioactive iodine (RAI)) had a decreased quality of life compared to the control population without thyroid disease. There was no difference in quality of life associated with the type of treatment for thyroid disease. Younger patients were more likely than older patients to report eye symptoms with only 13–15 % of young patients bothered compared to 20–38 % of older patients [18]. The authors were unable to determine if the patients with chronic eye symptoms had a lower quality of life; therefore they later undertook a study to determine if treatment modality for Graves' disease led to a change in incidence of GO and altered HRQL. A total of 308 patients were recruited into treatment with RAI or antithyroid medications, and then followed for 4 years. The RAI group contained 53 de novo cases of GO while the antithyroid medication group had 23 new cases of GO, a statistically significant difference. While there was no difference in the SF-36 QOL score between treatment groups, when divided into GO versus non-GO patients, those with GO have a significantly worse QOL. Finally, GO patients' physical recovery preceded their mental recovery [19]. The patients' objective clinic eye exam did not correlate with the SF-36 scores, again reinforcing the idea that HRQL assessments need to be performed separately and in addition to objective clinical measures.

In Amsterdam, Gerding published a study of 70 euthyroid patients with GO of various degrees of severity and compared the SF-24 with 3 subscales of the Sickness Impact Profile (SIP) which assesses 136 items in 12 categories [12, 20]. GO patients had lower SF-24 scores on 6 subscales, including a physical functioning score that was 28 points less than the control population. SIP scores were also lower in GO patients than in the control group. In comparison to patients with other diseases, those with GO scored lower than diabetes mellitus, emphysema, and heart failure. The QOL scores did not correlate with the clinical severity or duration of GO symptoms.

A similar study was completed in Germany using the SF-36, assessing 102 patients with varying severity of thyroid-associated ophthalmopathy. Patients scored much lower than the control group, particularly on energy/fatigue, social functioning, mental health, general health perceptions, and bodily pain. The presence of a high degree of anxiety or depression as quantified by The Hospital Anxiety and Depression Scale correlated with lower SF-36 results. Again, the SF-36 scores did not correlate with duration or clinical severity of ophthalmopathy [21]. To examine the role of steroids in medical treatment of GO, the same group employed the SF-36 to follow 70 euthyroid patients with untreated, active, and severe disease. Scores improved to a much greater degree in the patients receiving IV steroids compared to those taking oral steroids. Whereas before treatment 9 % and 11 % of patients in the IV and oral steroid groups, respectively, reported good or excellent QOL, after treatment positive responses increased to 80 % and 54 % [22].

Conversely, a Polish study of 29 euthyroid patients sought to determine if a combination of IV steroids and orbital radiation therapy could improve QOL in GO. Patients underwent 6 cycles of 1 g of methylprednisolone and between cycle 2 and 4 they received orbital radiation. Similar to previous studies, pretreatment scores were lower than a control population in all 8 subscales. While treatment led to improvement in the clinical features of the disease by objective measures, QOL scores increased for only 3 subscales of the SF-36: physical role functioning, bodily pain, and vitality (energy/fatigue) [23].

Several authors have specifically looked at the emotional component of dealing with GO by incorporating a mood assessment into their studies. Lee et al. used the Beck Depression Inventory in addition to the SF-36 to analyze 49 Korean patients with various severities of GO, including 4 with sight-threatening disease. Those patients with lower depression scores had lower SF-36 scores and this correlated with higher clinical activity scores. Additionally, patients with higher Gorman diplopia scores or with sight-threatening GO had lower Physical Component Summary scores on the SF-36 [24]. Farid et al. recruited 48 euthyroid GO patients who were using no mood altering medications and submitted them to the Profile of Mood States survey, a 65-item survey with a 5-point Likert scale. Patients were divided into high or low clinical severity and categorized as predominantly proptotic or restrictive. Those with higher disease severity were found to have higher levels of emotional distress, and the disfiguring signs of disease correlated more strongly than functional deficits with emotional distress, in other words proptosis was more distressing that diplopia [25].

Vision-Specific Instruments

Given that GO is a disease affecting the visual system, it is possible that a HRQL instrument designed to assess visual health would be more sensitive and highly correlated with clinical features of GO than a general health instrument. A wide variety of diseases which alter visual functioning have been analyzed for their influence on HRQL with the NEI-VFQ. The diseases differ from GO in that they are not disfiguring and typically are not associated with ocular discomfort and binocular diplopia. Conversely, vision loss, which is a major feature of all of the diseases for which the NEI-VFQ was developed, is rare in GO. The original VFQ was a 51-item questionnaire with 12 vision-related subscales scored 0–100 [17]. It has since been shorted to a 25-question version with confirmation of validity and reliability in numerous ocular diseases. Bradley et al. tested whether the VFQ-25 could adequately assess the HRQL of GO patients, with the knowledge that several important issues relating to binocular function and body image are not assessed by the NEI-VFQ. Thirty consecutive patients with GO were administered the VFQ-25 after which they were invited to offer feedback in an interview. Respondents demonstrated moderately impaired HRQL, most impaired for the subscales of Mental Health (50) and Role Difficulties (50) and least impaired for Color Vision (100) and Social Function (88). The overall median composite score was 69 but was lower in patients with diplopia (61) than those without diplopia (90). Interestingly, there was no difference in Role Difficulties based on the presence or absence of diplopia, but Driving and Peripheral Vision both scored significantly lower in patients with diplopia. The high scores observed in the Social Functioning subscale suggest that this subscale fails to capture the concerns with appearance and self-consciousness in social settings that are important to many GO patients. Indeed, in the feedback interview, 10 patients reported that the instrument did not adequately address altered physical appearance. Other issues the patients recommended addressing included additional pain-related items, tearing, ocular irritation, and psychosocial issues such as frustration, fear, and self-consciousness [26]. More recently, the Chinese translation of the VFQ-25 was used to assess HRQL in dysthyroid optic neuropathy (DON). Patient with moderate to severe thyroid-associated ophthalmopathy were divided into a group of 23 with DON and 13 without DON. DON patients had significantly lower VFQ-25 scores with comparative composite scores of 54 versus 77. Similar to the previous study, Role limitations and Mental Health were the most affected subscales. While diplopia and exophthalmos were not correlated with any subscale, most subscales did show moderate correlation with activity and severity of ophthalmopathy quantified by NOSPECS or CAS [27].

Disease-Specific Instruments

The most specific and potentially most sensitive method for determining changes in HRQL in GO is in applying a disease-specific instrument. Simple measures of patients' perceptions of ocular health have been included in several studies evaluating GO therapy. In a clinical trial of oral prednisone versus orbital radiotherapy,

investigators asked patients to rate their ocular condition on a 1–10 scale, and termed this measure the "subjective eye score." While the primary outcome, improvement in the NOSPECS score, suggested that approximately half of patients responded to either treatment, improvements in the subjective eye score were modest [7]. A subsequent placebo-controlled trial of orbital radiotherapy indicated that orbital radiation resulted in improved ocular motility, but no difference was detected in the subjective eye score [28].

Several studies from the Mayo Clinic have attempted to quantify subjective patient concerns relating to GO and its treatment by using simple three- or five-point scales. In a case series of 428 patients who underwent orbital decompression surgery for functional indications, a follow-up questionnaire revealed significant cosmetic concerns: only 21 % of patients were very satisfied with their appearance, 32.5 % were satisfied, 35.6 % considered their appearance to be acceptable, and 10.9 % were dissatisfied or very dissatisfied with their appearance [3]. In a later study of 34 patients who underwent orbital decompression primarily for physical disfigurement, 37.9 % of the 29 patients who completed the follow-up questionnaire were very satisfied with their appearance, 31.0 % were satisfied, and 31.0 % reported that their appearance was acceptable [29]. While this type of evaluation may enlighten the clinician about a patient's emotional concerns, it addresses a single clinical issue and only indirectly addresses quality of life, leaving the field still wanting for a comprehensive HRQL instrument.

In an attempt to create a questionnaire that could assess patients during the longitudinal course of Graves' disease, a Swedish group surveyed 149 patients with hyperthyroidism using a three-part instrument. The first section comprised 8 questions about life from disease onset to initiation of treatment for hyperthyroidism. Another set of 25 questions pertained to their experience once treatment was started. The final section included 5 questions about ophthalmopathy. Patients were treated with thyroidectomy, RAI, or antithyroid medications and followed for 4 years. Of the 93 % of patients employed at the onset of their disease, 63 % reported that treatment affected their ability to work very little or not at all, but 19 % were not able to work for at least 1 month. There was no significant difference in economic impact or HRQL between the three treatment groups [30].

Watt et al. gathered 13 physicians and two nurses who treat patients with thyroid disease and 80 patients with thyroid disease, including 17 with ophthalmopathy, to rate survey questions for their relevance to quality of life. Of the 15 domains deemed most relevant to thyroid-related QOL, less than half overlapped between the patient and clinician groups. Care providers rated questions about disease-associated symptoms like eye complaints in patients with ophthalmopathy as most relevant, whereas patients rated psychological issues like nervousness and emotional concerns as most important [31]. This highlights the need for patient input into HRQL instrument development and confirms the finding that objective measures may not necessarily be correlated with QOL scores.

Previous research on the importance of input by both the patient and clinician was highlighted by the Food and Drug Administration. In the early 2000s, a task force consisting of members from the International Society for Quality of Life Research, the International Society for Pharmacoeconomics and Outcomes Research, the

Pharmaceutical Manufacturer's Association Health Outcomes Committee, and the European Regulatory Issues on Quality of Life Assessment was assembled to unify and standardize criteria for patient-reported outcome measures, a subset of which are HRQL measures. In their formal report, they state, "There are several potential sources of data…, i.e., patients, clinicians, and caregivers. Each source… may provide a unique and valuable perspective on the disease and the efficacy of a therapy. For example, patients may focus on the changes in their own health; families may react not only to the impact on the patients, but also to the impact on family life; and clinicians and researchers view disease and its treatment from a clinical perspective." [32] To that end, more formal HRQL instruments have been created with an attempt to broadly assess both clinical and psychosocial patient issues.

The Graves' Ophthalmopathy Quality of Life (GO-QOL) instrument is a Dutch language instrument consisting of a total of 16 questions, with 8 questions assessing each of 2 subscales: Visual Functioning and Appearance [33]. It was developed from a combination of previously employed HRQL instruments and free-form responses from a group of 24 GO patients to address the need for a disease-specific HRQL measure. The scores range from 0 to 100 and in their pilot study of 70 euthyroid GO patients, the mean score for Visual Functioning was 54.7 and for Appearance was 60.1. It has been shown to be a reliable instrument in a Dutch population based on both test-retest reliability and internal consistency studies [34]. The Visual Functioning subscale correlated with SF-24 and SIP, and lower scores were associated with increased age and more severe motility dysfunction. The Appearance subscale correlated well with mental health and was found to be more troublesome to women. Surprisingly, proptosis did not correlate with the Appearance score. Several years later, the same group looked at long-term follow-up of a median of 11.7 years for 163 euthyroid patients who had been treated with steroids or orbital radiation. More than half of patients had diplopia and proptosis greater than 20 mm, and those with diplopia had lower scores. Radiotherapy-treated patients scored an average of 3–15 points lower than prednisone-treated patients. Overall scores for the entire group were worse than healthy controls, but better than newly diagnosed patients by 23.5 points for Visual Functioning and 17.1 points for Appearance [35].

The GO-QOL has been translated into six languages and used around the world in countries such as Germany, Australia, Taiwan, and Korea [36–39] (English language version available free to the public at http://www.eugogo.eu/_downloads/clincial_evaluation/GO_QOL_EN.pdf). Several issues should be acknowledged when considering the use of this HRQL instrument internationally. The GO-QOL instrument asks about cycling and outdoor walking, which might be less applicable to GO patients in societies where those activities are less prevalent. The Australian version of the GO-QOL, for example, replaced the questions about cycling with inquiries about effects on work and performing domestic activities. Next, the instrument has only been validated in its native language; third, it does not include a subscale that assesses ocular pain; and finally, the visual functioning and appearance subscales do not correlate strongly with disease severity [33]. Taking these caveats into consideration, there have been numerous studies using the GO-QOL which have evaluated the HRQL of GO patients and the success of treatments for GO. When the GO-QOL

was administered in Korea, the composite scores were 67.8 for total QOL with Visual Functioning subscore of 73.7 and Appearance subscore of 61.9. Unlike in the original study, the Korean study found that GO-QOL scores correlated with the clinical assessment scores of NOSPECS and CAS. Additionally, lower Visual Functioning scores were correlated with higher extraocular muscle involvement, and lower Appearance scores were correlated with higher severity of proptosis and soft tissue involvement [39]. In Germany, 310 patients with thyroid eye disease were assessed and stratified by clinical severity. GO-QOL scores were lower in moderate-severe cases compared to mild cases, in active versus inactive cases, and in patients with sight-threatening orbitopathy or diplopia [36]. Appearance scores were lower in patients undergoing psychotherapy. A significant limitation to this tool is the ceiling effect, which the authors set at >15 % of respondents choosing the highest score, being reached in 27 % of patients on Visual Functioning and 19 % of patients on Appearance with respective composite scores of 72.5 and 71.3. These scores are higher than in other countries and may limit the sensitivity of GO-QOL in German patients with more mild disease or mild changes in HRQL. The Australian GO-QOL, utilized after several adjustments, resulted in a Visual Functioning score of 59.0 and Appearance score of 54.5. Additionally, when asked about the usefulness of counseling and education, only a quarter of patients felt it was beneficial or adequate, highlighting an area in need of improved quality of care [37]. In Taiwan, the GO-QOL was administered to 271 GO patients and, similar to the results in Australia, the composite scores were 58 for Visual Functioning and 54 for Appearance. Both scales correlated with clinical disease severity, with lower Visual Functioning scores in active disease and lower Appearance scores in patients with diplopia [38]. This is in contrast to the Korean study where Appearance was correlated with proptosis rather than diplopia [39].

With the ability to monitor a patient's HRQL comes the ability to measure the impact of treatment on the disease process. Implementation of a standardized survey and interpretation of the results requires clinicians to understand what change in the score represents clinically significant improvements in HRQL. Terwee et al. enrolled 164 patients at various stages of treatment for GO from radiotherapy to eyelid surgery. Patients who experienced a moderate to large subjective improvement in QOL had an average increase in GO-QOL of 5 points in Visual Functioning and 8 points in Appearance. Correlation between the objective score and subjective report of change in HRQL was only moderate [40].

Bartalena et al. used the GO-QOL in a randomized, double-blind clinical trial to determine how several doses of intravenous methylprednisolone affected clinical signs and patient experiences. Three different doses were given as 12 weekly infusions to 159 patients with active, moderate to severe GO. CAS scores were improved in the high and medium dose groups, and extraocular muscle motility improved in the high dose group, but the benefit was transient. When GO-QOL scores were gathered 24 weeks after the initiation of treatment, there was no difference between dosage groups [41]. The role of selenium replacement for treatment of mild GO has also been assessed with GO-QOL. GO patients were given oral selenium, pentoxifylline, or placebo twice daily for 6 months. Of the 53 patients treated with selenium,

62 % had an increased Visual Functioning score and 75 % had an increased Appearance score, while there was no significant difference in QOL in the placebo or pentoxifylline groups [42].

Surgical outcomes have also been investigated for influence on HRQL, especially given that surgical treatments tend to be more expensive, warranting evidence that patients experience improved quality of life in exchange for the increased costs. In 2008, the European Group on Graves' Orbitopathy published a multicenter report on outcomes of decompression. Eleven countries included 139 euthyroid patients with stable GO who underwent decompression for disfiguring proptosis. A total of 18 different surgical approaches were used, including 132 two-wall decompression and 112 three-wall decompression, with an average reduction in proptosis of 5 mm. The range of preoperative Appearance scores was 17.7–55.1 and decompression led to an average increase of 20.5 points. There was no difference in the Appearance scores between groups, except that trans-lid and endoscopic approaches led to only an average of 1.8 point change. Visual Functioning scores decreased after decompression, particularly in the patients who underwent coronal approach which led to the largest incidence of new onset diplopia [43]. In contrast, Fichter et al. analyzed the outcomes of the single surgical technique of en bloc resection of the lateral orbital wall with fat excision and found an increased GO-QOL score for both subscales. Thirty orbits of 18 patients were included and the GO-QOL composite scores improved from 34.1 to 26.1 for Visual Functioning and Appearance, respectively, to 69.0 and 50.1 at 6 months postoperatively. The improvement in Visual Functioning score correlated with decreased proptosis and vertical palpebral fissures. Finally, two patients with dysthyroid optic neuropathy had their Visual Functioning scores increase from 14.3 and 18.8 to 64.3 and 93.8 [44].

Given the lack of validation of the GO-QOL in the United States and the previously mentioned limitations of this instrument, the field of quality of life in thyroid eye disease was still lacking. To fill this void, Dr. Yeatts undertook a comprehensive plan to formulate an American English questionnaire designed to examine the multitude of factors that contribute to QOL in GO [45]. He created a survey of 105 questions adapted from other pertinent and validated instruments: SF-12 for general and mental health, Dermatology-Specific QOL Questionnaire for self-perception and social function, VFQ-51 for general visual function, and Graves' ophthalmopathy assessments for disease-specific visual function. After administering the questionnaire to 203 GO patients, he reported good validity, with the scores from GO patients being lower than those for the control group for physical and mental health, self-image, sleep, social and work function. The individual items engineered to evaluate symptoms, such as diplopia, dry eye, and blurred vision, were correlated with clinical disease severity. Additionally, several of the vision function questions which correlated well with visual quality of life asked about visual discrimination, as in finding an item on a crowded shelf or recognizing a face from across the room. This is in contrast to GO-QOL questions that ask about reading or driving, activities which did not strongly correlate with overall visual QOL. Clearly a 105-item instrument may be difficult to integrate into regular clinical practice, so Yeatts also created a 9-item questionnaire with face validity and good clinical correlation for use

in a more practical setting, titled Graves Ophthalmopathy Quality-of-Life-Scale (GO-QLS).

In the interest of clinical efficiency, a group in British Columbia created a three-question instrument, TED-QOL. The three questions inquired about overall quality of life, appearance, and visual functioning, asking the patient to assign a 0–10 score for each. The survey showed good correlation with the GO-QOL and GO-QLS and good test-retest reliability. Patients reported good clarity and ease of survey completion. The main benefits of this instrument are the low burden on the patient, leading to high completion rate, and time efficient administration requiring only 1.6 min to complete. Again, there was only moderate correlation between the TED-QOL results and the clinically apparent disease severity [46].

Qualitative Studies

The final means of determining the personal impact of GO on patients is to step away from the desire to quantify individual components of life. The qualitative approach is reasonably intuitive to physicians since it is the method by which most patient symptoms are identified during daily patient encounters. While it may be harder to standardize and schedule into a finite window of time, qualitative assessments can offer powerful data about the issues GO patients are facing.

Estcourt et al. conducted interviews of 25 British patients with thyroid eye disease and distilled commonly mentioned topics into three major themes. The first is an altered identity which developed due to change in appearance, adjustments in role functioning, and limited abilities from the consequences of eye disease. The second was the development of new coping mechanisms, including emotional stoicism, social avoidance, and denial. Third, patients highlighted anger, frustration, and disenchantment with the medical establishment due to uncertainty with their diagnosis, treatment, or disease course, which in turn led to more difficult interactions with healthcare providers [47]. This evidence bolsters the idea that the medical system needs to improve the quality of communication and be aware of the issues at the forefront of the patient's mind, since it may not be the same issue that is at the forefront of the practitioner's mind.

A separate study of 250 German patients looked at levels of work disability and participation in psychotherapy to further elucidate the emotional and economic stressors that were contributing to decreased HRQL. Nearly half of patients complained of significant restrictions on daily activities because of their symptoms, 36 % were on sick leave from work, 28 % were on disability, and 5 % had chosen to take early retirement. The severity of disease and ocular dysmotility were correlated with longer time on sick leave and likelihood of being on disability. In addition, 21 % of patients were undergoing psychotherapy and they were more likely to be on sick leave or disability. Interestingly, proptosis was not correlated with limited ability to work, though both patients with severe proptosis and patients with ocular dysmotility were more likely to be receiving psychotherapy [48]. The same authors

followed up the first study with another report looking specifically at the economic burden of GO. Of the 215 GO patients they analyzed, 22 % were temporarily disabled and 5.6 % were permanently disabled. The average amount of sick leave taken was twice the national average: 22.3 days per year compared to 11.6 days per year for the general population, with the disease severity correlating with length of sick leave. A multivariate analysis found diplopia to be the primary predictor for work disability [49].

Conclusions

Graves' ophthalmopathy is a complicated disease with a multitude of effects on patients suffering its sequelae. While the medical world works to gain further insight into disease mechanisms and improved treatment modalities, patients are left struggling to cope with seemingly innumerable physical and psychosocial issues. As healthcare providers, it is our responsibility to identify those issues and offer assistance by whatever means are available. The HRQL questionnaires reviewed here all have a potential place in clinical practice. While there is no clearly ideal instrument for measuring the effect of GO on HRQL, the only way we will be able to improve patients' lives is by asking how we can help, and asking about quality of life is as important as asking about eye pain or diplopia. Implementing an assessment of HRQL into standard practice will go a long way towards giving patients the voice they need to best participate in their own care.

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Chapter 23
Future Therapy for Graves' Disease and Ophthalmopathy

Mario Salvi and Guia Vannucchi

Introduction

The therapy of Graves' disease (GD), when associated with orbitopathy (GO), aims at achieving restoration of euthyroidism as rapidly as possible. Available treatments for Graves' hyperthyroidism include antithyroid drugs as the initial approach and subsequent definitive ablation of thyroid tissue by surgery or radioiodine therapy, as a causative treatment in GD is not available, due to the unknown pathogenic mechanisms at the basis of disease. The choice among the different therapeutic approaches for GD is based on several considerations such as the patient's age, the thyroid volume, the presence of GO, and its degree of activity and severity. Restoration of permanent euthyroidism is frequently obtained only after definitive treatment with radioiodine or surgery. Based on the recent evidence, low-dose steroid prophylaxis should be encouraged when treating radioiodine patients with GD, with or without pre-existing GO, as long as risk factors for developing GO are identified [1–3]. On the other hand, no conclusive data are available so far in the literature on the possible risk of newly occurring GO or reactivation of previous GO after thyroidectomy.

Stable euthyroidism may induce spontaneous amelioration of milder degrees of GO [4, 5] and may contribute to the optimization of the potential responsiveness to immunosuppressive treatments in moderate-severe disease, when indicated. Euthyroidism also represents the essential condition in which patients may undergo rehabilitative surgical procedures in the burnt-out phase of GO.

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Glucocorticoids

The treatment of moderate-severe GO is based on immunosuppressive therapy during the active phase of the disease. To date, glucocorticoids represent the mainstay of immunosuppression. However, treatment effectiveness much relies on great interindividual variability that may lead to either treatment failure or drug-induced toxicity. Significant response to therapy has been reported in as many as 60 % of patients with oral glucocorticoids (prednisone) [6, 7]. However, oral administration is more often associated with long-term side effects, including hepatotoxicity, Cushing' syndrome, osteoporosis, glaucoma, and diabetes mellitus. More recent studies have shown that pulsed intravenous methylprednisolone (ivMP) is more effective (70–80 % of patients) [8] and has a better safety profile compared with oral prednisone. Nevertheless, this modality of treatment is also burdened by the occurrence of serious cardiovascular and hepatic morbidity that has led to reduction of methylprednisolone pulse doses in more recent years, down to a cumulative dose not larger than 8 g [9]. This dose is considered safe, but strict monitoring of liver function tests, hepatitis virus markers, serum glycemia, and blood pressure is warranted. A recent multicenter clinical trial of EUGOGO [10] has shown that an effective treatment schedule and dose of ivMP is 830 mg methylprednisolone administered weekly for 6 weeks followed by 415 mg for another 6 weeks, up to a cumulative dose of 7.47 g. This treatment schedule results in a short-term and transient advantage over lower doses, although it is associated with a slightly greater toxicity. Therefore it has been suggested that this dose regimen may be used in more severe cases of GO while an intermediate dose regimen may be used in most cases with moderate disease. The limitation of such treatment is that 20–30 % of patients are poorly responsive or unresponsive at all to ivMP and approximately 10–20 % of patients present with disease reactivation after drug withdrawal [9].

Targeted Therapy

Over the past decade, innovative treatments have been sought based on better understanding of the mechanisms involved in GO pathogenesis. Some authors have recently proposed to directly target orbital tissue remodeling that results in tissue expansion in GO, without interfering with the immune reactions occurring in the orbit. Immunosuppression, on the other hand, would target the main players involved in the active, inflammatory phase of GO. These may be the antigens expressed on the target organ of inflammation, namely the TSH receptor (TSH-R) and the IGF-1 receptor (IGF-1R) on the fibroblasts, the cytokines and other humoral factors involved in the various stages of disease progression, and the immune effector cells, B and T cells (Figs. 23.1, 23.2, and 23.3).

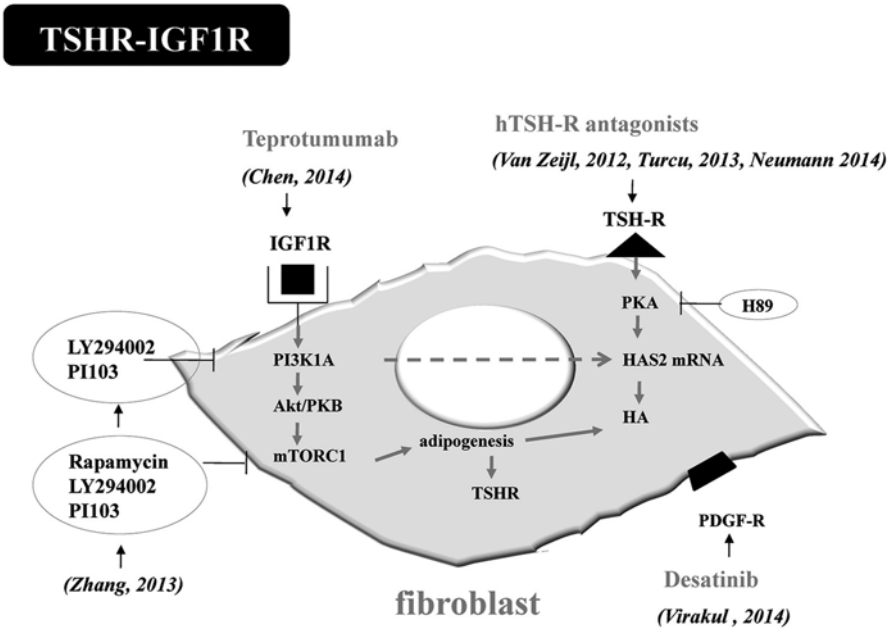

Fig. 23.1 Potential targets of nonimmunosuppressive and immunosuppressive therapy on orbital fibroblasts. TSH-R: Thyroid stimulating hormone receptor; IGF-1-R: Insulin growth factor-1 receptor; PDGF-R: platelet-derived growth factor receptor

Targets for Nonimmunosuppressive Therapy

It is well known that in GO adipogenesis and hyaluronic acid overproduction are the two central mechanisms leading to orbital tissue expansion that are driven by signal transduction through the TSH-R and IGF1-R [11, 12] (Fig. 23.1). Recently, Zhang and coworkers employed in vitro orbital fibroblasts and orbital fat tissue models to mimic GO pathology and were successful in inhibiting both adipogenesis and hyaluronic acid overproduction by blocking PIK3/mTORC1 signaling cascades [13]. In particular, by using inhibitors of PIK31A, PIK31B, and mTORC1, these authors demonstrated that mTORC1 is a critical player of adipogenesis, while PIK31A is more responsible for HA production. The PI3K/mTOR signaling pathway regulates many basic biological processes such as cell proliferation, survival, migration, glucose metabolism, and nutriment sensors [14, 15]. Targeting of this pathway to improve cancer control has been an intense and promising research field in the last decade. However, first-generation inhibitors, such as wortmannin, LY294002, or rapamycin, and its derivatives have shown undesirable side effects and low specificity in some experiments [16–18]. For these reasons, second-generation inhibitors with improved specificity and pharmacological properties have been developed and are currently used in clinical trials in patients with refractory cancers [19–21].

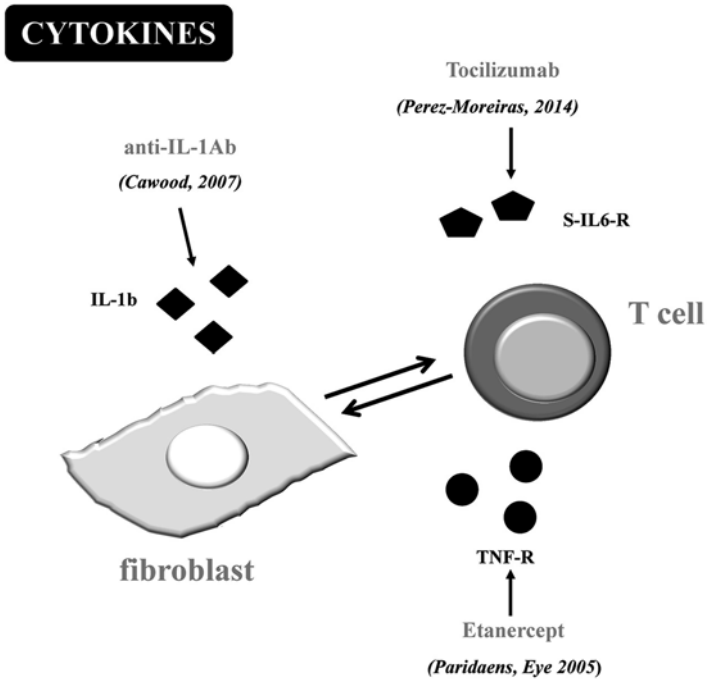

Fig. 23.2 Monoclonal antibodies interacting with cytokines involved in the inflammatory phase of Graves' ophthalmopathy. IL-1: Interleukin-1; TNF-R: Tumor necrosis factor receptor; sIL-6-R: soluble interleukin-6 receptor

Another possible novel target for therapy might be the platelet-derived growth factor (PDGF) receptor, particularly the PDGF-BB isoform which has recently been found expressed and increased in GO orbital tissue [22]. PDGF-BB has been shown to markedly activate proliferation and production of pro-inflammatory cytokines such as CCL2, IL-6, IL-8, as well as hyaluronic acid by orbital fibroblasts [22], thus representing an attractive therapeutic target in GO treatment. Two small molecule-tyrosine kinase inhibitors, imatinib mesylate and nilotinib, have recently been demonstrated to prevent PDGF-induced PDGF-R autophosphorylation and signaling on orbital fibroblast of patients with GO [22] leading to block the PDGF-BB and PDGF-AB induced proliferation, hyaluronic and cytokine production by orbital fibroblasts [22–24]. Since the use of these two compounds has been associated with serious side effects [25], a structurally different tyrosine kinase inhibitor, dasatinib, has been developed and currently approved as a second-line therapy for treatment of chronic myeloid leukemia. Dasatinib has been shown to reduce the production of the extracellular matrix components fibronectin and collagen by skin fibroblasts in a systemic sclerosis patient [26], and very recently it has been found to suppress hyaluronic synthetase 2 (HAS-2), CCL2, IL-6, and IL-8 mRNA levels in orbital tissue from active GO, thus confirming that this or similar compounds may represent a promising therapeutic approach [27].

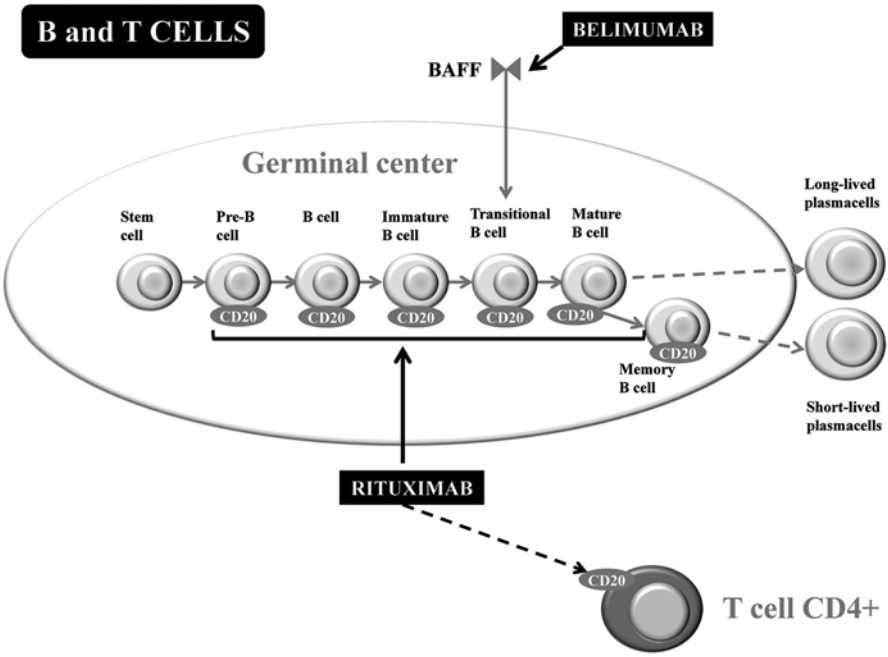

Fig. 23.3 Expression of CD-20 in the different stages of B cell maturation and on T cells. BAFF: B cell stimulating factor

Targeting the TSH Receptor and the IGF-1 Receptor

Over the past few years some TSH analogs, called small TSH molecules, have been chemically synthesized. These low molecular weight compounds can be produced in large quantities and can be administered orally, since they are absorbed by the gastrointestinal tract. These molecules can be used as probes of TSH-R biology or for the treatment of both GD and GO, as they have been tested for their effects on both thyrocytes and orbital fibroblasts (Fig. 23.1). Three classes of small molecules have been developed: (1) TSH-R agonists (ligands that activate receptors), (2) neutral antagonists (ligands that inhibit receptor activation by agonists), and (3) inverse agonists (ligands that inhibit receptor activation by agonists and also basal or constitutive activity) [28].

In primary cultures of human thyrocytes, TSH-R agonists increase mRNA levels of thyroglobulin (Tg), thyroperoxidase (TPO), sodium-iodide symporter (NIS), and deiodinase type 2; more importantly, they increase serum thyroxine and radioiodine uptake by the mouse thyroid gland, after absorption from the gastrointestinal tract following administration by esophageal gavage [29]. The antagonists of TSH-R bind to the transmembrane region of the receptor and act in an allosteric manner by preventing the conformational changes necessary for receptor activation, without

interfering with TSH or TSAb binding [30]. The inverse TSH-R agonists decrease the expression of the mRNAs of TPO, TSH-R, Tg, and NIS in the absence of any agonist in primary cultures of human thyrocytes [31], supporting the hypothesis that they could be used to suppress TSH-independent signaling in humans. TSH-R analogs, antagonists, and TSH-R inverse agonists represent an emerging novel class of therapeutic agents for both GD and GO.

By modifying the chemical structure of the TSH-R agonist NCGC00161870 [32], a series of TSH-R antagonists was developed. Among those, NCGC00242595 is a neutral antagonist while NCGC00161856 and the NCGC00229600 are inverse agonists. This latter compound was shown to inhibit the activation of TSH-R signaling stimulated by TSAb from GD patients' sera in a model cell system and in primary human thyrocytes [33]. More recently, a new compound NCGC00242364 (ANTAG3) has been described that appears effective in inhibiting thyroid gland stimulation by inhibition of TSH-R activation in mice in vitro [34]. It is possible to speculate on the potential use of these molecules in GD patients who are most likely to achieve remission or in patients with thyroid storm, or in those in whom a rapid control of thyrotoxicosis is required [35].

TSH-R antagonists may also represent a novel approach for the therapy of GO, as they can inhibit the activation of TSH-R on Graves' orbital fibroblasts. Recently, it has been demonstrated that the TSH-R autoantibody M22 is able to stimulate cAMP production by GO orbital fibroblasts and that this stimulation can be inhibited by TSH-R small molecule antagonists [36]. NCGC00229600 and Org-274179-0 have been tested on both undifferentiated orbital fibroblasts and orbital fibroblasts differentiated into adipocytes. NCGC00229600 has been found to inhibit both constitutive and GD-IgG or TSH-stimulated cAMP production in model cells overexpressing human TSH-R (HEK-EM293) and in human thyroid cell cultures [33], and to also inhibit the production and accumulation of HA in the orbit [37]. Org-274179-0 dose dependently inhibited cAMP production induced by rhTSH in a hTSH-R-expressing CHO cell line [38] and inhibited cAMP production in differentiated human orbital fibroblasts. More recently, a novel compound ANTAG3 was proposed as a possible useful small TSH molecule because of its ability to inhibit TSH-R signaling in other tissues expressing TSH-R, including orbital fibroblasts/preadipocytes and adipocytes [34].

The IGF-1R has been shown to be co-expressed in orbital fibroblasts with the TSH-R in GO [39]; blocking IGF-1R appears to attenuate TSH-dependent signaling [40]. Teprotumumab (RV 001, R1507) is a specific fully human monoclonal antibody that binds to the extracellular-subunit domain of IGF-1R and has been developed as a therapeutic strategy for several types of solid tumors and lymphomas [41]. Very recently, Chen and coworkers have demonstrated that teprotumumab is able either to decrease the expression of TSH-R and IGF-1R on fibrocytes or to attenuate TSH-dependent IL-6 and IL-8 expression and Akt phosphorylation [42]. Teprotumumab is currently under investigation in patients with moderate-severe GO in a phase 2 multicenter placebo-controlled randomized clinical trial conducted in the USA and in Europe.

Cytokines

The immune reactions in orbital tissues appear to depend on resident immune cells or cells recruited from the bone marrow through the expression and release of cytokines. It has been shown that in the active phase of GO, there is a predominant production of pro-inflammatory and Th1-derived cytokines such as IL-6 and IL-1, and IFN-gamma-induced chemokines, such as CXCL10. Th2-derived cytokines, including IL-4, IL-5, and IL-10, are more likely associated with the inactive phase of GO (Fig. 23.2).

Tumor necrosis factor-α (TNF-α) is a naturally occurring cytokine that plays a pivotal role in inflammatory and immune responses. The progressive understanding of the pathogenic processes involved in autoimmune conditions has driven the development of biological compounds that target specific inflammatory mediators, with the first available class represented by TNF inhibitors (etanercept, infliximab, adalimumab, certolizumab). Subsequently, other molecules targeting different immune pathways have been approved, including the IL-6 receptor antagonist tocilizumab and the IL-1 inhibitor anakinra.

Etanercept is a recombinant dimeric fusion protein consisting of two molecules of the soluble, extracellular ligand-binding portion of the human 75 kDa TNF receptor linked to the Fc portion of human immunoglobulin G1. It binds TNF and lymphotoxin-alfa and blocks the interaction of TNF with receptors on the cell surface, thereby preventing TNF-mediated inflammatory cellular responses and modulating the effect of other TNF-induced or regulated molecules [43]. Based on the evidence for a role of TNF in the pathogenesis of GO [44], in 2005 Paridaens et al. [45] have treated in a pilot study ten patients with active moderate-severe GO and noted clinical improvement of the soft tissue signs in six of ten. The authors could not rule out that the improvement was due to the natural course of the disease and could not show an advantage over therapy with ivMP, in terms of efficacy and side effects.

Another important pathway in active GO is represented by the IL-6/sIL-6 receptor system. Elevated serum sIL-6R concentrations were in fact measured in patients with active GO [46]. Tocilizumab is a recombinant, humanized monoclonal antibody that acts as an interleukin (IL)-6 receptor antagonist and binds selectively and competitively to soluble and membrane-expressed IL-6 receptors, thereby blocking IL-6 signal transduction. Several studies demonstrated the efficacy of intravenous tocilizumab in improving disease activity, structural joint damage, and/or HR-QOL in patients with early or long-standing rheumatoid arthritis, including those with refractory to standard therapy. Promising results have been recently obtained in a study in patients with GO refractory to ivMP treatment [47]. After therapy with tocilizumab, CAS improved in 18/18 patients, proptosis decreased in 13/18, and ocular motility improved in 15/18. One patient with compressive optic neuropathy also improved and did not undergo orbital decompression. These positive preliminary results warrant further clinical trials.

In a study by Cawood et al. [48], a synergic effect on adipogenesis of cigarette smoke extract and IL-1 has been observed in an in vitro model of GO. This synergic effect may explain why smoking in the presence of local orbital inflammatory response driven by cytokines may result in the increased frequency and severity of GO in smokers. In this study, the authors used an IL-1 antagonist, employed in the treatment of rheumatoid arthritis, to block the IL-1 stimulatory effect on adipogenesis and prevent the synergic effect of the smoke extract. This observation may have important therapeutic implications for the treatment of GO, although this hypothesis has not been challenged further in a therapeutic trial.

B Cell Depletion

Rituximab

Rituximab (RTX) has been used off-label in various autoimmune disorders but is approved for clinical use only in rheumatoid arthritis (RA) and antineutrophil cytoplasmic antibody-associated (ANCA) vasculitis. While the success of B cell-depleting therapy has reinforced the value of this approach in several autoimmune disease, many questions on the disparate effect of RTX in specific disease states remain unanswered. In general, RTX depletes more than 95 % of mature B cells in blood and primary lymphoid organs after 2 days by a single treatment, but it is not clear if treatment efficacy is dependent upon full or only partial B cell depletion or on targeting of specific B cell subsets [49]. The entire wide spectrum of B cell functions can be affected by RTX depletion.

Effects on Antibody Production

Germinal centers are functional sites where classical reactions leading to high-affinity antibodies production occur, although T cell-dependent reactions may even occur in extrafollicular sites [50]. Following antigen-specific proliferation, B cells enter into the germinal center microenvironment, where they diversify their antigen receptors and generate pools of long-lived memory B cells [51] which give rise to long-lived plasma cells within the bone marrow that are responsible for producing and maintaining serum antibody levels [52] (Fig. 23.3). Recent work has shown that germinal centers are constituted of a distinct dark zone in which proliferation of B cells results from interaction of the autoantigen(s) and MHC class II molecules presented to follicular helper T cells (classical germinal center autommunity) and of a light zone in which B cell autoreactive clones after clonal expansion are activated by irrelevant selecting antigens bound to follicular dendritic cells (bystander germinal center autoimmunity) [53]. Therefore, B cells trafficking to germinal centers are continuously involved in cycles of proliferation and selection and, when in the light

zone, B cells are in close contact with dendritic cells and present antigen to helper T cells [54]. Interactions of B and T cells in germinal centers depend on the availability of the antigen stimulating proliferation and selection of B cells, with potentially important implications for B cell-depleting therapies. RTX may not sufficiently deplete B cells in germinal centers or may affect only specific clones arising from the different pathways described within the germinal centers or even extrafollicular lymphoid structures and, therefore, may not impact on B and T cell interaction, with resulting little therapeutic impact on pathogenic specific autoantibodies [55]. Autoantibodies may be pathogenic through direct binding to specific receptors (e.g., the TSH receptor on the thyrocyte membrane in Graves' disease) or through the formation of immune complexes in tissues that locally activate complement reactions and induce inflammation [56]. Although in experimental models there is no direct evidence that autoantibodies alone initiate autoimmune disease, it is well known that they are associated with the disease and change in relation to the disease course, suggesting their involvement in the mechanisms of disease pathogenesis.

Antigen Presentation and Cytokines Production

B cells are also important antigen-presenting cells in the initiation of immune responses [57, 58] and in the production of cytokines and chemokines, including GM-CSF, IL-10, IL-4, IL-6, lymphotoxin-α, TGF-β, and IFN-γ [59, 60]. Decrease of cytokines levels after RTX treatment might be an indirect effect of B cell depletion on CD4+ T cell differentiation into Th1 and Th2 cytokine subsets and may contribute to improvement of disease progression, as has been observed in primary Sjogren syndrome [61].

Effects on T Cells

Unexpected depletion of T cells, mainly CD4+ cells, has been recently observed in patients with RA treated with RTX [62] (Fig. 23.3). Peripheral depletion of T cell was delayed, as compared to that of B cell, but likewise persisted as long as 6 months. Interestingly, T cell depletion was shown to correlate with the patients' clinical response better than B cell depletion and therefore it has been suggested that T cell count may help monitoring response to RTX therapy. The implications of this data are that RTX may be indirectly responsible also for the depletion of autoreactive T cells, as a consequence of the decrease of T cell promoting cytokines and chemokines released by B cells, depleted by RTX. In addition, RTX may target T cells expressing low level CD20, which have been reported to account for as many as 5 % peripheral blood CD3+ T cells in patients with RA [63]. These very recent findings disclose a new scenario in the mechanism(s) by which RTX may impact on the direct pathogenetic reactions of autoimmune disease.

Regulatory B Cells

The IL-10-producing subset of B cells, known as regulatory B cells (B regs) or B10 cells [64], plays an important role in the suppression of autoimmune and inflammatory disease. IL-10 induces suppression of both Th1 and Th2 cytokine polarization and inhibits antigen presentation and pro-inflammatory cytokine production by monocytes and macrophages [65]. As a consequence of B cell depletion, there might be disease exacerbation in some autoimmune conditions because IL-10-producing cells, that inhibit regulation on T cell-mediated inflammatory responses, are also eliminated. RTX has in fact been reported to exacerbate ulcerative colitis [66, 67] and trigger psoriasis [68], both conditions representing Th1-mediated autoimmune conditions.

Pharmacokinetics and Dosing

Pharmacokinetics and pharmacodynamics studies performed in patients with B cell lymphomas have shown that serum concentration of RTX usually correlates directly with response and inversely with tumor mass [69]. Reports of variable half lives (11–105 h) may be the result of the different tumor burden and of the changes of CD20 expression on B cells, consequent to repeated RTX administration [70]. In RA, RTX half life has been reported to be as long as 20 days after two doses of 1,000 mg, the dose being used in most autoimmune diseases [71]. Studies that have directly addressed the most appropriate dose/response relationship of RTX are lacking. A recent meta-analysis of randomized trials in RA has shown no significant differences in the primary clinical outcomes when 1,000 mg twice was compared to 500 mg twice, 2 weeks apart [72]. The incidence of first infusion reactions was also decreased with the low-dose RTX treatment. The use of lower RTX doses may ultimately lead to significant reduction of treatment costs for a chronic disease, making it affordable by more clinical centers [70].

Side Effects

Infusion-related reactions are the most frequently reported side effects of RTX [73]. These reactions may be present in about 10–30 % of patients at first infusion and can be severe, but reversible. Release of pro-inflammatory cytokines from macrophages, monocytes, lymphocytes, and NK cells is the underlying mechanism. Activation of complement cascade may be responsible for fever, chill, and skin rashes [74]. Interestingly, during complement activation small fragments (C3a and C5a), which function as anaphylatoxins, help recruit effector cells to the site of inflammation and bind on locally infiltrating macrophages and enhance ADCC activity [75].

Among major side effects, infections have been attributed to the decrease of immunoglobulin levels after RTX repeated doses. Recently, a large retrospective study on 191 patients affected with multisystem autoimmune disease has looked at the incidence, severity, and complications of hypogammaglobulinemia as a consequence of combined immunosuppression with steroids, cyclophosphamide, and RTX [76]. The study has shown that although RTX therapy induced relative low immunoglobulin G levels, severe infections observed in the patients were associated with higher exposure to steroids but not to hypogammaglobulinemia. Another recent review of over 3,000 patients with rheumatoid arthritis showed comparable serious infection rates in those treated with RTX versus placebo plus methotrexate [77]. Data from these large studies are consistent with RTX being considered a safe therapy at least in the population affected with RA, but probably in many autoimmune disease in which lower therapeutic doses may be adopted.

Progressive multifocal leukoencephalopathy (PML) has rarely been reported in patients receiving RTX, especially those with systemic lupus erythematosus (SLE). It is again important to point out that all these patients had previously been treated with other immunosuppressive therapies including cyclophosphamide, azathioprine and even steroids, oral prednisone, or intravenous steroids [78]. Of note, more than 40 % of cases of PML have been reported in patients with SLE who were only minimally immunosuppressed, as if SLE itself may predispose for PML [79].

Other Monoclonal Antibodies Indirectly Targeting B Cells

Atacicept is a fusion protein of the human IgG Fc protein and the BAFF/APRIL receptor TACI. Targeting BAFF or APRIL leads to depletion of B cell progenitors (Fig. 23.3), but not memory B cells; therefore humoral immunity and memory responses to pathogens remain intact. *Belimumab*, an mAb against BAFF, has also been tried in patients with RA and SLE and has shown clear biologic effects on B cells and Ig levels with moderate clinical benefits [80, 81] in SLE, but only modest clinical benefits compared with placebo [82] in RA. Increased serum BAFF concentrations have been detected in patients with Hashimoto' thyroiditis [83] and more recently in those with Graves' disease with and without GO [84], suggesting that anti-BAFF therapy may be an option in the management of Graves' disease.

B Cell Depletion Therapy in Graves' Disease and Orbitopathy

Effects of RTX in Graves' Disease

One controlled [85] and two non-controlled clinical trials have studied the effect of RTX on the hyperthyroidism of GD [86, 87], but included a rather limited number of patients with inconsistence of the clinical parameters considered. In addition,

these preliminary studies have been conducted employing variable schedule and dosing of RTX, from 375 mg/m^2 for four cycles to 1,000 mg twice, 2 weeks apart. El Fassi et al. [85] treated ten patients with newly diagnosed hyperthyroidism with methimazole (MMI) and RTX and ten with only MMI until they became euthyroid. Within 1 year of follow-up all patients treated with MMI alone, but only six of ten treated with MMI and RTX had relapse of hyperthyroidism. Those who did not relapse had persistently low values of serum TRAb levels, considered predictive of sustained remission after RTX. Peripheral B cells were not measured and therefore changes in serum TRAb could not be related to either B cell depletion after RTX or B cell return in the peripheral blood [84]. In a follow-up study, El Fassi et al. [88] proposed that RTX treatment in GD patients may favorably affect disease remission by distinctively acting on the TSAb subpopulation with TRAb, as a result of the effect of RTX on autoreactive short-lived TSAb-producing plasma cells [89].

Heemstra et al. [87] treated 13 patients with relapsing GD, of whom three with mild GO (23 %). Ten patients were also treated with MMI, when hyperthyroid. In four of 13 patients hyperthyroidism relapsed 26 weeks after RTX treatment, while in nine stable euthyroidism was observed for a median of 18 months. Similarly to what reported by El Fassi et al. [85], GD patients who remained euthyroid had relatively low serum TRAb level before RTX therapy. It is unclear why RTX treatment would have no effect on GD patients who were more hyperthyroid and had higher serum TRAb levels, who eventually needed radioiodine therapy. In the study of Salvi et al. [86] none of nine patients treated had improvement of thyroid function after RTX and required MMI to maintain euthyroidism. Of note, one patient, upon MMI withdrawal (for 7–8 days), had a very rapid relapse of hyperthyroidism associated with a surge of serum TRAb, while still being totally B cell-depleted in the peripheral blood after RTX [85]. More recently, Vannucchi et al. [90] were not able to observe a specific effect of RTX on serum TSAb autoantibodies, which did not change after therapy but fluctuated with an identical pattern to serum TRAb in both hyperthyroid and euthyroid GD patients. More studies are needed to address the effect of RTX on TSH receptor autoantibodies and a more conclusive interpretation on the potential role of RTX on the remission of GD hyperthyroidism can only be obtained from larger prospective, controlled studies.

RTX in GO: Dosing and Efficacy

Since the first report on successful treatment of one patient with moderate-severe GO [91], several non-controlled studies on the effects of RTX in GO have appeared in the literature, reporting data on as many as 43 patients. In addition, one randomized controlled trial comparing RTX to placebo [92] and one comparing RTX to steroids [93] in moderate-severe GO have just been completed. Only the preliminary results of these studies have so far been presented and definitive results are awaited.

Dosing schedules of RTX employed in the treatment of GO have been quite different and the lack of randomized trials and dose finding studies leaves us with the question of the appropriate dose for therapy of active GO unanswered. Some investigators have underscored that RTX may be effective in patients with GO even at lower doses than currently suggested in autoimmune rheumatic disease, although the dose of the drug has never been addressed as a study outcome. The infusion of 1,000 mg twice, with a 2-week interval, standardized for the treatment of RA and other autoimmune diseases has been reported to be effective in most open studies [84, 94, 95] and in case reports [91, 96]. The standard RTX dose used in lymphomas and neoplasia of 375 mg/sq meter has also been used successfully in a randomized controlled trial in GD patients [85], described above. Total peripheral B cell depletion following very low-dose RTX was shown in a study by Salvi et al. [97] in two patients in whom RTX was discontinued because of the development of a transient cytokine release reaction, after receiving only 100 mg of the drug. Interestingly, after spontaneous resolution of the side effect, clinical improvement with GO inactivation occurred within a few weeks, despite the administration of a dose about 20 times less than the standard dose used in systemic autoimmune disease. More recently, Mitchell et al. [95] have treated nine patients with steroid-refractory GO, of whom five (55 %) had signs suggestive of DON. While two patients received RTX at the full dose of 1,000 mg twice, six received only 500 mg twice and one patient three times, based on the attainment of peripheral B cell depletion. Monitoring of peripheral B cell depletion in order to titrate the RTX dose has in fact been suggested by some authors in autoimmune renal disease [98]. GO improved in all active patients, with four of nine patients (44.4 %) experiencing minor side effects at the first infusion. Patients with signs of DON also improved their NOSPECS score.

In earlier reports [85, 91] RTX was mainly used in patients with active GO who were unresponsive to standard ivMP therapy. They had a significant decrease of the CAS (<3) and improvement of ocular motility, as early as 4–6 weeks after RTX, that persisted without any additional therapy. Subsequently, RTX therapy has been used as a first-line treatment in patients not treated previously with steroids. In the open study of Salvi et al. [86], the mean CAS values of nine patients with active GO significantly decreased from 4.7 to 1.8 at the end of follow-up and also proptosis, eye muscle motility, and signs of soft tissue inflammation improved significantly in response to RTX. Reactivation of GO was never observed after RTX, but it is known to occur in 10–20 % of patients treated with steroids [10]. In the study of Khanna et al. [94] six patients with active and severe GO, unresponsive to glucocorticoid therapy, were treated concomitantly with steroid therapy. RTX (1,000 mg, twice) had a rapid and sustained therapeutic effect on both activity and severity. While the CAS decreased significantly at 8 weeks and remained low at 6 months, no patients improved in extraocular motility or proptosis. Four of these patients, who had optic neuropathy, showed improvement of visual acuity within 4 weeks, with return to premorbid values at 8 weeks from treatment. When glucocorticoids were tapered off, there was no disease reactivation. Silkiss et al. [99] treated with RTX 12 patients with active GO administered at the dose of 1 g, 2 weeks apart. Disease inactivation was shown by a decrease of the mean CAS at 16 weeks as well as by a decrease of

the mean Thyroid Associated Ophthalmopathy Scale (TAOS), as modified by Dolman and Rootman (VISA Classification) [100]. Patients were studied up to 52 weeks of follow-up, with no evidence of disease reactivation and side effects.

In contrast to all these reports, failure of RTX has been reported in one patient whose GO did not respond to therapy and subsequently progressed to acute DON [101]. Two similar cases have been observed among the series of patients treated by Stan et al. [92], in the preliminary results of their randomized controlled study. It is possible that in these patients subclinical DON was already present at the time of therapy and that the orbital edema caused by cytokine release after the administration of RTX may have increased intraorbital tissue congestion and optic nerve compression. On the other hand, RTX has also been employed successfully in another ten patients with DON [94, 95, 100], resulting in improvement of visual sight.

This data need to be confirmed in larger studies and until then we suggest caution in administering RTX in severe disease, particularly when patients have GO of long duration or subclinical DON.

The preliminary results of two randomized clinical trials employing RTX in GO have just been completed and preliminary results recently presented. Salvi et al. [93] have compared RTX with ivMP in patients with active moderate-severe GO and studied the decrease of the CAS as a primary end point. The CAS decreased more significantly after RTX, whether patients had received 1,000 mg twice or a single dose of 500 mg and, at 24 weeks, 100 % of patients after RTX improved compared to 69 % after ivMP ($P<0.001$). Disease reactivation was never observed in patients treated with RTX, but in five after ivMP. Data on secondary end points (total eye score, motility and quality of life) will allow to assess whether RTX acts as a disease modifying therapy, compared to steroids. Stan and colleagues [92] did not find RTX effective in treating active GO, when compared to placebo. The study was conducted on 21 patients, of whom two, after RTX, had disease progression and developed optic neuropathy. The publication of their final data will probably allow comparing the differences in the criteria of recruitment of the patients, i.e., disease duration, degree of activity, and others that might account for these discrepant results. We envisage that further and larger randomized controlled trials will be needed for definitive data on the potential disease modifying role of RTX in GO and its superiority over standard treatment with steroids.

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ERRATUM TO

Chapter 6
Antithyroid Drug Therapy in Patients with Graves' Disease

Peter Laurberg and David S. Cooper

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The image in Fig. 6.2 of chapter 6 has been captured incorrectly in page 73. The correct image for Fig. 6.2 is as follows:

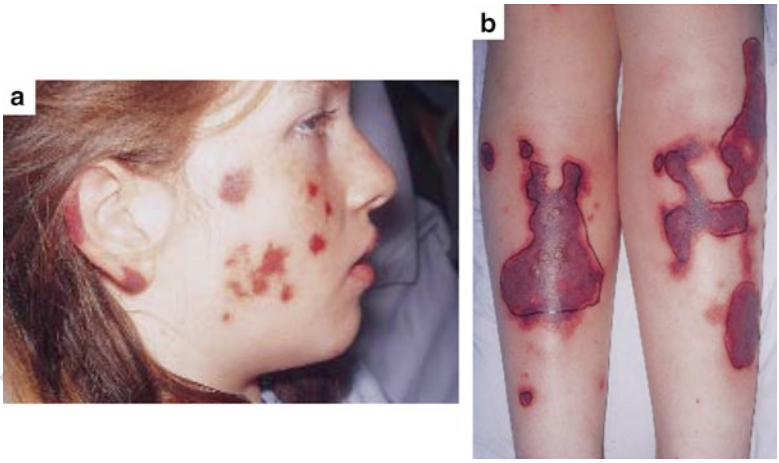

Fig. 6.2 (**a**) Multiple purpuric lesions on the face and ear. (**b**) Bilateral irregular purpuric areas on the lower legs. Lack of progression of the lesions beyond the demarcated borders illustrates their nonmigratory behavior. With permission: Chastain MA, Russo GG, Boh EE, Chastain JB, Falabella A, Millikan LE. Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. J Am Acad Dermatol. 1999;41:757–64 [68]

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