Evidence-Based Endocrine Surgery

Rajeev Parameswaran
Amit Agarwal
Editors

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My parents for their love, my wife Vijaya Mohan for her support, my sons Arpit and Vedanta for their understanding and my colleagues, students and well-wishers for their admiration and encouragement

Amit Agarwal

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Part I

Thyroid

Evidence-Based Surgery

1

Rajeev Parameswaran and Amit Agarwal

Surgery has always been learnt via the apprenticeship model with the teachers showing the way to perform based on their experience. This model of learning was not ideal, as it meant that learning was dependent on the mistakes made by oneself or others. The appearance of the concept of evidence-based medicine in the late twentieth century in a document published from McMaster University changed the way clinicians practice effective and efficient clinical care today [1]. Evidence-based surgery incorporates integration of best available evidence from research, clinical circumstances, and patient and clinical experience to treat patients effectively [2].

Evidence-based medicine has four main components [2], known as 1-2-3-4; one goal, two fundamental principles, three components, and four steps. The goal of evidence-based practice is to improve the health-related quality of life through decisions in relation to clinical and healthcare policies. The two fundamental principles include *hierarchy of evidence* and *insufficiency of evidence alone* in decision-making. The three components include *evidence*, *expertise*, and *expectations of patients*. The four steps are *ask*, *acquire*, *access*, and *apply*. In relation to surgery, evidence-based practice can be divided into two categories [3]:

- Evidence-based surgical decision-making
- Evidence-based surgical guidelines

The knowledge to practice evidence-based surgery is obtained from data obtained through research, measuring evidence through statistics and clinical experience and practice.

Hierarchy of Evidence

The results of the research designs are not all equal in terms of the risk, error, and bias, with some research providing better evidence than others. The validity of results obtained from research is therefore based on the type of studies, with randomized controlled trials providing the most reliable evidence [2, 4]. Once the studies have been selected, it is important to identify those studies that carry a higher methodological weight. Hierarchies of evidence allow for research-based recommendations to be graded and reflect the susceptibility of bias observed in the various types of study. The simplest hierarchical tool that is commonly used is Sackett's levels of evidence (Table 1.1).

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Table 1.1 Sackett's level of evidence

Level	Type of evidence
I	Large RCT with clear results
II	Small RCT with not so clear results
II	Cohort and control cases studies
IV	Historical cohorts or control cases studies
V	Series of cases, studies with no controls

RCT randomized clinical trials

Randomized Controlled Trials

The randomized controlled trial (RCT) is one of the simplest, most powerful, and revolutionary tools of research [5, 6] and offers the maximum protection against bias [7] [8]. RCT is a study in which individuals are allocated randomly to receive one of several interventions, with the control group receiving an accepted treatment or no treatment at all (Fig. 1.1). The outcomes from RCT's can be described as continuous or discrete [9]. The problem is that RCTs in surgery are less performed when compared with medical interventions, and this may be due to problems such as standardization of interventions, issues with recruitment, and blinding of subjects and investigators [10, 11]. Similarly, trials may have to be discontinued earlier than planned [12], and this can have a significant scientific, ethical, and economic impact [13, 14].

A meta-analysis is a systematic review of randomized controlled trials where the outcomes of the studies are pooled. The advantage of meta-analyses is that it effectively increases the sample size, with the Cochrane collaborators calling the results of meta-analyses the "pinnacle of scientific knowledge" as it improves the statistical power of the evidence given by a single RCT [2]. However, the problem with pooling of data is that the outcomes are dependent on the quality of the RCT's. Even meta-analyses are not without their pitfalls and commonly include *publication*, *bias*, *heterogeneity*, and *robustness of studies.*

Observational Studies: Case-Control and Cohort Studies

Case-control studies are those where the subjects meet the definition of a "case" and subjects that are not cases. These are typically retrospective studies as they look back in time to identify causable factors and have a longitudinal aspect to the data. An outline of the study design is shown in Fig. 1.2. These studies can be used for study of common diseases and useful for studying etiologies of rare disease as well. However, these studies are not without bias—*incidence bias*, *selection bias*, and *"healthy volunteer" effect.* The biases in case-control studies may be minimized by the following criteria: *appropriate case selection* (representative of all patients with the disease), *appropriate controls* from the healthy population, and *information from cases and controls are collected the same way*. An example of such a study in thyroidology is that of metabolic and cardiovascular risk in patients with a history of thyroid cancer from Italy [15].

Cohort studies unlike case-control studies are truly not retrospective but prospective in the sense that the risk factor is collected first and then the disease outcomes are collected downstream, after a period of follow-up. These studies are useful to make observations or study associations between a risk factor and subsequent development of a disease. A flow chart of such a study is shown in Fig. 1.3. Cohort studies can be of many types:

- Nonconcurrent, historical, or retrospective cohort studies
- Concurrent or prospective cohort studies
- Nested cohort studies

The advantages of cohort studies are that the cases diagnosed are incident, rather than prevalence obtained from case-control studies; provide information about the natural history of the disease and estimates of risk, less risk of bias; and study multiple outcomes. Unlike case-control studies where rare disease can be studied, prospective cohort studies help study a rare exposure. The disadvantages of cohort studies are that the study durations are generally very long, follow-up can be expensive, and large study populations are required. An example of a cohort study in endocrine surgery is that of a Korean study considering the benefits and risks of prophylactic central neck dissection for papillary thyroid cancer [16].

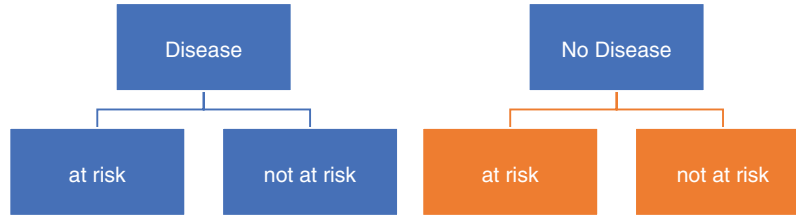

Fig. 1.1 Layout of a case-control study with patients with or without disease identified at the start of the study, and information is collected retrospectively

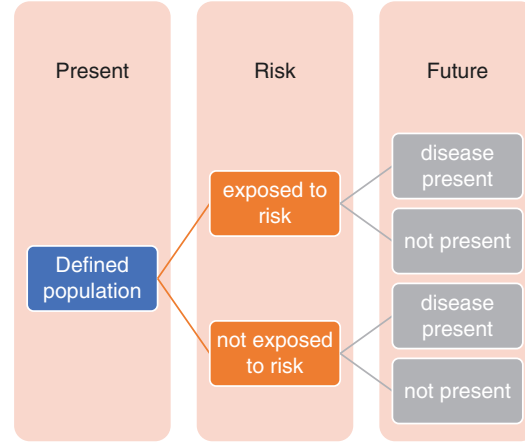

Fig. 1.2 Layout of a prospective cohort study, which may be longitudinal concurrent or nonconcurrent historical [1]

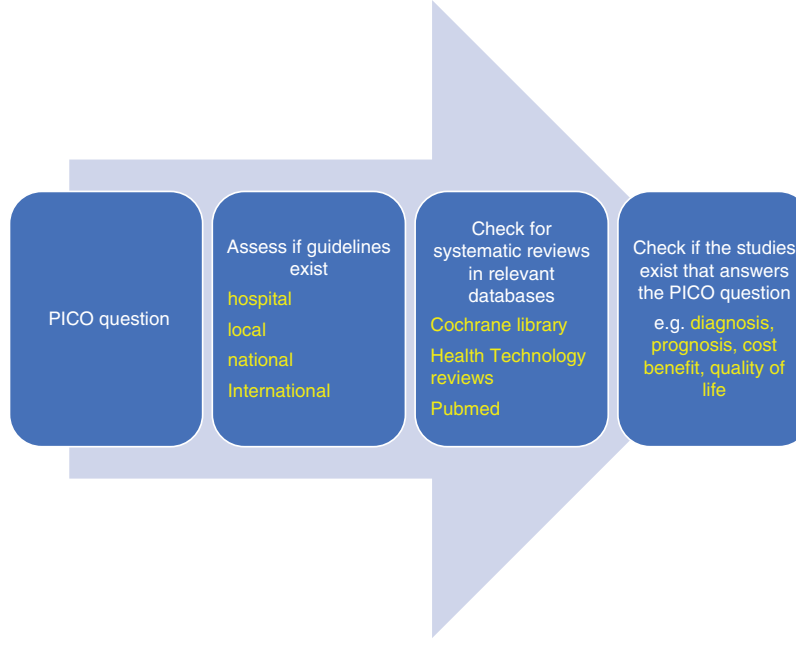

Fig. 1.3 Finding evidence in surgery based on McCulloch and Badenoch

Case Reports and Series

Case report describes a single case and series describes similar cases, with both describing clinical characteristics about individual patients. Case reports represent the lowest evidence of published clinical evidence and are generally uncontrolled descriptive studies of outcomes related to a type of intervention [17]. Retrospective case series are the most common evidence in surgical literature and makes causal inferences about the relationships between outcomes and risk factors [17]. Case series have inherent biases and are usually based on single center or surgeon's experience which cannot be generalized to the population. Despite its drawbacks, case series can be used for hypothesis generation and providing information on rare diseases [18].

Identifying the Evidence

Identifying the best evidence can be challenging but is an essential skill required for surgeons in their day-to-day practice. Various methods have been employed to perform a search on a research topic, but the most widely used is the PICO (Population/problem, Intervention/exposure, Comparison, and Outcome) tool developed by the McMaster University (Table 1.2). PICO enables researchers to frame research questions and search terms, enabling a systematic search strategy [19, 20]. It is the best tool adopted by most researchers and has been adopted by the Cochrane collaboration [21].

Other tools besides PICO that have been proposed for qualitative research include SPICE (setting, population, intervention, comparison, and evaluation) [22], ECLIPSE (expectation, client group, location, impact, professionals, service) [23], and CIMO (context–intervention–mechanism–outcome) [24]. None of the abovementioned tools are suitable for use with qualitative research questions. Once the appropriate tool has been selected, the next step is to work through finding the sequence of evidence (as shown in Fig. 1.3) [25].

Sources of Evidence

There are wide range of sources for collection of data for research, with each of them having advantages and disadvantages (Table 1.3). No matter whatever the source, this should be appraised critically before it is applied to the patient.

The first option of getting an evidence in surgical practice is mainly from senior colleagues or a peer with significant experience. This source of evidence is sought mainly by inexperienced professionals and turn to colleagues for help and advice when faced with clinical uncertainties as shown in a study on dental practitioners [26]. Similarly, one may seek the opinion of an expert, an advanced practitioner in his or her specialty. In terms of evidence, these sources are considered as low level, and other problem is that it is not uncommon to see disagreements between experts. Similarly, books though are a good source of information, the time it takes to research and publish a book is quite long, and the information may be out of date after a few years.

The *Internet* has changed the world, in terms of how people work and obtain information, with

Table 1.2 Outline of PICO

PICO	
P: patient population	Group for which you need evidence
I: intervention	Operation or treatment whose effect you need to study
C: comparison	What is the evidence that the proposed intervention produces better or worse results than no intervention or a different type of intervention?
O: outcomes	What are the effects and end points of the intervention?

Table 1.3 Examples of the various sources of evidence available for the surgeon

Colleagues
Books
The Internet
Journals
Electronic databases
Specialist organizations
Guidelines

an estimated 52% using the Internet globally. One can practically obtain information on any subject from anywhere, with relatively easy access. The information that can be accessed from the Internet include research evidence, clinical guidelines, and patient information and resources [27]. The disadvantage with the Internet is that not all information obtained from the Internet may be accurate and can be time-consuming. A search on Google retrieved a total of 52,200 sites using the search words evidence-based endocrine surgery, but of these many might be factually inaccurate or useless. Criteria to help individuals assess the quality of health-related websites have been published by many organizations [28].

Journal reading is most common method of keeping up to date in surgery, and there are many journals published in surgery and their subspecialties (both with low and high impact factor). Journals unlike books contain more recent information on various topics, which are available in print form or electronic version (e-version). There are over 1000 journals published worldwide, and to read articles of interest in one's specialty is a big task. Ways of keeping pace with research articles in journals are the following: decide which specialist journal is most relevant to your clinical practice and review contents regularly, host journal clubs, and use evidence-based supplements.

Electronic databases are specialized bibliographic databases that are available electronically and focusing on a subspecialty. The most commonly used database for medical-related information is MEDLINE, compiled by the US National Library of Medicine (NLM). It is freely available on the Internet and can be searched by the free search engine PubMed. Currently the database contains over 25 million records from 5633 publications to date. Over 80% of the published articles are in English, and the most common topic published is cancer.

Specialist organizations like Cochrane collaboration (www.cochrane.org) provide high-quality information to make health decisions and maintain a database of systematic reviews, meta-analyses, and randomized controlled trials. Two similar organizations are the NHS Centre for Reviews and Dissemination (CRD) based in UK and the National Library for Health (NeLH).

Clinical Practice Guidelines

Clinical practice guidelines were developed to support clinicians in decision-making along with their knowledge and experience. However, clinical practice guidelines are now being used for broader purposes: as institutional policy, to inform insurance coverage, for deriving quality of care criteria, and for medicolegal liability standards [29]. However clinical guidelines are not without problems in terms of bias and misguidance [30], and despite this many clinicians follow this. Some of the examples of clinical guidelines in endocrine surgery are shown in Table 1.4.

Table 1.4 Examples of guidelines available for clinicians involved in the management of thyroid disease

2017	European Thyroid Association Guidelines regarding thyroid nodule molecular fine-needle aspiration cytology diagnostics [31]
2017	Radioactive iodine therapy, molecular imaging, and serum biomarkers for differentiated thyroid cancer: 2017 guidelines of the French Societies of Nuclear Medicine, Endocrinology, Pathology, Biology, Endocrine Surgery and Head and Neck Surgery [32]
2017	2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum [33]
2016	2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer [34]

Why Evidence-Based Surgery?

Practicing evidence-based surgery is challenging, and applying it to surgical practice is a four-step process: creating evidence, summarizing evidence, disseminating evidence, and implementing evidence into practice [1, 35]. Evidence-based practice is more evident in the field of general medicine than in surgery as high-quality surgical research is very difficult [36, 37]. In 1996 only about 7% of the papers published in surgery was from RCTs [38] compared to 24% of surgery in 2009 [39], much lesser than the 50% of RCTs in general medicine [40]. Clinicians are now recognizing this shortfall [11, 41] and pushing for evidence-based practice in surgery [41, 42].

Currently there is a lot of discrepancy between our knowledge and the way we practice [43], and this gap can be bridged with evidence-based practice. So many our clinical practices are guided by what is taught during the apprenticeship of surgical training, and one example of this is the use of drains in thyroid surgery. Surgical practices are also dependent on policies dictated by the needs of the population in a country, and healthcare policies. A lot of these policies and practices are aimed at reducing the cost of health, rather than actual value to the patient. Value-based surgery focuses on patient outcomes, quality of life, and cost using evidence-based practice [44].

Besides the benefits to the patients and healthcare industry by the practice of evidence-based surgery, the benefits are also to the surgeon in the form of improved teamwork, decision-making, enhanced research, and improvements in training and satisfaction [45]. The benefits of evidence-based surgery are summarized in Fig. 1.4. To promote improved outcomes and benefits, there is a concerted effort by national, regional, and international societies and organizations to use evidence-based surgery [46].

National surgical organizations have increasingly focused on using EBM to enhance the practice and outcome of surgical care. The ACS are exemplary in this process but are not alone. Efforts are occurring in all surgical specialties through national and regional societies and organizations.

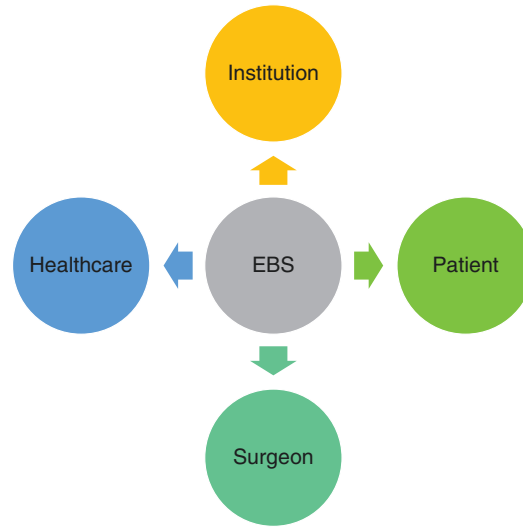

Fig. 1.4 Benefits of Evidence Based Surgery (adapted from Athanasiou T, Debas HT, Darzi A. Key topics in surgical research and methodology)

Conclusion

Evidence-based surgery is not just about doing randomized controlled trials but for the global benefit of patients and healthcare. The principle of evidence-based practice is obtained from best available evidence and requires a change in mentality at all levels of healthcare. As surgeons, one should move away from the old-fashioned approach to surgery and embrace the change of evidence-based practice. To do surgeons must gather, analyze, and collate data to derive best practice and outcomes for the benefit of patients ultimately. For the next generation of surgeons, surgery should not be about intuitions but based on best evidence. As Ubbink and Legemate put in their editorial article in *British Journal of Surgery*, *evidence-based surgery is not a passing creed—it is a lasting need.*

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Graves' Disease

2

Chiaw-Ling Chng

Introduction

Graves' disease (GD) is an autoimmune disease with a myriad of clinical manifestations and exerts a profound effect on the metabolism of the individual affected [1]. It is the most common cause of hyperthyroidism in areas of sufficient iodine intake, with annual incidence of 21 cases per 100,000 per year [2]. The disease shows female predominance, with female-to-male ratio between 5:1 and 10:1 [3]. Although the onset of GD can occur at any age, it is most common between 40 and 60 years of age [4]. In this review, pathogenesis, diagnosis, and treatment, including recent advances in the understanding of this disease, will be discussed.

Etiology

The pathogenesis of this autoimmune disease is thought to be multifactorial, with the primary trigger being loss of immunotolerance and development of autoantibodies that stimulate thyroid follicular cells by binding to TSH receptor. These antibodies result in continuous and unregulated thyroid stimulation, resulting in excess production of thyroid hormones and thyroid gland enlargement. A genetic predisposition, coupled with environmental stressors, underlies the pathogenesis of this disease. A higher concordance rate of the condition is found in monozygotic twins than dizygotic twins [5]. Several disease susceptibility loci have been identified for GD, including specific polymorphisms of HLA [6], CTLA-4 [7, 8], CD40 [9], protein tyrosine phosphatase-22 [10], thyroglobulin [6], and TSH receptor [6, 7]. Among these, HLA is the major genetic factor in the susceptibility to GD [6]. Environmental factors postulated to contribute to this condition include psychosocial stress [11], smoking [12], and childbirth [13]. In particular, a positive family history of thyroid disease, especially in maternal relatives, is associated with an increased incidence of the disease at a younger age of onset [14]. The interaction between these predisposing factors in the pathogenesis of GD is likely to be complex, and further studies are required to elucidate the precise roles of these factors in the cause of this condition.

Presentations, Investigations, and Treatment Options

Clinical Presentation

The clinical presentation of overt hyperthyroidism due to GD is characterized by a variety of signs and symptoms related to the widespread

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Table 2.1 Symptoms and signs of overt hyperthyroidism

System	Symptoms	Signs
Metabolic/ thermoregulatory	Increased appetite Weight loss Heat intolerance Increased perspiration and polydipsia	Warm moist skin
Cardiovascular	Palpitations	Tachycardia Increased systolic blood pressure atrial fibrillation Congestive cardiac failure
Respiratory	Dyspnea	Tachypnea
Gastrointestinal	Increased bowel movement	
Reproductive	Irregular menses oligomenorrhea Reduced libido and reduced fertility	Gynecomastia (in males)
Neuromuscular	Tremor of extremities Muscle weakness	Fine hand tremors Proximal myopathy Hyperreflexia
Dermatological	Hair loss Pruritus	Palmar erythema
Psychiatric	Anxiety and irritability Insomnia Altered mood	Altered mood, e.g., mania or depression

actions of thyroid hormones (Table 2.1). The most common presenting symptoms are weight loss (61%), heat intolerance (55%), and tremulousness (54%), and the most common physical finding is a palpable diffuse goiter (69%) [15].

Older patients are less likely to have tachycardia and tremor, and they more often present with weight loss or depression, a clinical entity referred to as apathetic hyperthyroidism [13, 16]. Atrial fibrillation and congestive cardiac failure are also more common presenting problems in patients over age of 50 years old [16]. It is important to note that these signs and symptoms of overt hyperthyroidism are not specific to GD and can be found in patients with hyperthyroidism from other causes such as toxic nodular goiter or hyperthyroid phase of thyroiditis. However, GD is uniquely characterized by extra-thyroidal manifestations, including Graves' orbitopathy (GO), thyroid dermopathy and thyroid acropachy, and thyrotoxic periodic paralysis.

Graves' Orbitopathy

GO is the main extra-thyroidal manifestation of GD, affecting 25% of patients at diagnosis. Majority of the presentation is mild, with moderate to severe form affecting 5% of cases, which can progress to sight-threatening disease. The disease is autoimmune in etiology and is characterized by inflammation and extensive remodeling of the soft tissues surrounding the eyes [17]. Proliferation of subpopulations of orbital fibroblasts plays a crucial role in the pathogenesis of this condition, leading to expansion of retro-orbital fat and enlargement of extraocular muscles [18]. Disease manifestations include redness and swelling of the conjunctivae and lids, forward protrusion of the globes (proptosis), ocular pain, debilitating double vision, and even sight loss due to compressive optic neuropathy or breakdown of the cornea [19]. There is some evidence to suggest Asian patients with GO may manifest milder phenotypic features, with less proptosis, extraocular muscle involvement, and restriction, although dysthyroid optic neuropathy may occur more readily [20]. Patients with GO are more likely to be women by a 2:1 ratio, while men with GD appear to be at higher risk for the development of more severe disease [21]. Smoking is the most important risk factor for the occurrence and progression of GO. Other risk factors for developing or worsening GO include thyroid dysfunction (both hyperthyroidism and hypothyroidism), radioiodine therapy, and higher level of TSH receptor

antibodies (TRAB) [22]. Apart from smoking cessation, current treatment options for GO include supportive measures, high-dose intravenous steroids, or other immunosuppressive therapy such as cyclosporine, methotrexate, or azathioprine. Radiotherapy or orbital decompression surgery may be recommended depending on the severity and activity of the disease [23].

Thyroid Dermopathy and Acropachy

Both thyroid dermopathy and acropachy are rare extra-thyroidal manifestation of GD. Thyroid dermopathy is characterized by slightly pigmented thickened skin, primarily involving the pretibial area (hence the term "pretibial myxedema"), although involvement of the upper body, particularly sites of repeated trauma and surgical scars, can occur [24]. Thyroid dermopathy is present in about 0.5–4.3% of patients with GD and 13% those with severe GO [25, 26] . One quarter of these patients have acral changes called thyroid acropachy, of which the most common manifestation is clubbing of the fingernails [24, 27]. Almost all patients with dermopathy have significant GO, and both conditions are characterized by an accumulation of glycosaminoglycans (GAGs) in either the dermis and subcutaneous tissues (thyroid dermopathy) or retro-orbital space (GO) [24, 28]. The onset of thyroid dermopathy typically follows GO and on the average occurs 12–24 months after the diagnosis of thyrotoxicosis, although this interval may be longer in some cases [24]. Thyroid acropachy almost always occurs in association with GO and thyroid dermopathy [29]. It is usually asymptomatic but can occasionally be painful due to the associated periostitis [27]. Similar to GO, normalization of thyroid function should be the first goal in the treatment of these extra-thyroidal manifestations. Smoking is associated with severity of thyroid dermopathy and acropachy; hence patients should be strongly advised to stop smoking [30]. Most patients with mild asymptomatic skin changes may not require intervention. The lesions may partially or completely resolve over time, spontaneously, or as a result of systemic corticosteroid therapy given for the associated GO [24, 31]. Specific treatment for the skin lesions include topical steroid therapy, intralesional steroid injection, complete decompress physiotherapy, and surgical excision [30]. No specific treatment is available for thyroid acropachy although pain management with anti-inflammatory agents may be needed in cases with painful periostitis of acropachy [29].

Thyrotoxic Periodic Paralysis

Thyrotoxic periodic paralysis (TPP) is a potentially lethal complication of hyperthyroidism characterized by hypokalemia and muscle paralysis affecting mainly males of Asian descent [32]. The clinical presentation of TPP is characterized by the classic triad of flaccid paralysis, signs of thyrotoxicosis, and hypokalemia due to intracellular potassium shifts during the paralytic episode. The paralytic attack is characterized by recurrent, transient episodes of muscle weakness that range from mild weakness to complete flaccid paralysis, affecting the proximal muscles more than the distal muscles [32]. Electrocardiographic changes resulting from hypokalemia leading to life-threatening ventricular arrhythmias were previously reported [33, 34]. Triggering factors for these attacks include carbohydrate-rich meals, strenuous exercise, trauma, infection, and emotional stress [35, 36]. The exact pathogenesis of this condition remains unknown, although it has been hypothesized that hormonal modulators (such as excessive levels of T_3 and testosterone), carbohydrate-rich meals (with resultant hyperinsulinemia), and rest following exercise could alter ion channel dynamics in the cell membranes of neuromuscular junctions in genetically susceptible individuals harboring ion channel mutations (e.g., Kir2.6 mutations) [36]. Treatment of TPP should include control of the underlying hyperthyroidism, use of β-adrenergic blockers, and judicious replacement of potassium to avoid rebound hyperkalemia during recovery of the paralysis when the potassium is shifted back into the intravascular compartment [32, 37]. In general, definitive therapy, i.e., RAI or thyroidectomy, is recommended for treatment of hyperthyroidism in patients with TPP in view of the potential lethal consequences of this condition.

Investigations

Thyroid function testing in GD typically reveals overt hyperthyroidism, with elevated free T_4 and/or T_3 coupled with suppressed TSH. In mild hyperthyroidism, only serum T_3 may be raised and associated with subnormal TSH, while serum T_4 can be normal. This is known as "T_3-toxicosis" and may reflect early stages of hyperthyroidism [38]. The ratio of total T_3/total T_4 is also helpful in differentiating hyperthyroidism caused by GD or toxic nodular goiter from painless or postpartum thyroiditis [39]. This ratio is typically >20 in hyperthyroidism from GD or toxic nodular goiter due to increased T_3 production compared to T_4 by the hyperactive gland, whereas T_4 is more elevated than T_3 in thyroiditis [40]. The latest American Thyroid Association (ATA) Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of thyrotoxicosis recommend measurement of TSH receptor antibodies (TRAB), determination of the radioactive iodine uptake (RAIU), or measurement of thyroidal blood flow on ultrasound if the diagnosis is not apparent based on initial clinical and biochemical evaluation, depending on the available local expertise and resources [41].

There are two currently available methods of measuring TRAB. The first are competition-based assays that detect TRAB in patient's sera by their ability to compete for binding of TSH receptor (TSHR) with a known TSHR ligand (TSH or monoclonal anti-TSHR antibody). These assays cannot differentiate between stimulating or non-stimulating TRAB (inhibitory or neutral) but are widely available commercially for clinical use. The second are assays that detect cyclic adenosine monophosphate (cAMP) production in cells incubated with patients' sera, also known as bioassays. These assays can measure the ability of TRAB to stimulate or inhibit TSHR activity (thyroid-stimulating or thyroid-blocking antibodies). However, bioassays are seldom utilized in the management of GD since the presence of TRAB in a thyrotoxic patient is usually adequate to diagnose a patient with the condition. Interestingly, it has been found that the more specific thyroid-stimulating antibodies correlated better with GO, whereas TRAB tend to be associated with hyperthyroidism in Asian patients with GD [42]. The utility of TRAB is not limited to diagnosis of GD but also in the prognosis of disease remission with medical treatment [43, 44] and in the assessment of the risk of fetal/neonatal hyperthyroidism in maternal Graves' disease [45].

The two most commonly used agents for imaging the thyroid are technetium pertechnetate (Tc-99m) and iodine-123 (I-123). A radioiodine uptake scintigraphy measures the percentage of administered radioiodine (I-123) that is concentrated into the thyroid gland after a fixed interval, usually 24 h. Unlike I-123, which is both concentrated and organified within the thyroid, technetium pertechnetate is only concentrated in the thyroid. A technetium uptake scintigraphy measures the percentage of administered technetium that is trapped in the thyroid after a fixed interval, usually 20 min. Technetium pertechnetate is readily available and associated with less total body radiation, thus more widely used than I-123 [46]. Diffuse increased uptake of Tc-99m or I-123 is suggestive of GD, whereas a diffuse reduced uptake is seen in subacute, painless, or postpartum thyroiditis [47]. The use of isotope uptake tests in the diagnosis of GD has declined considerably over the past 20 years [48], presumably due to advent of third generation TRAB assays with excellent sensitivity and specificity [49] and the associated high cost and inconvenience of isotope scans [50].

Thyroid ultrasonography with color flow Doppler was first employed in 1988 in the diagnosis of GD, where the term "thyroid inferno," referring to the pulsatile blood flow pattern in GD (Fig. 2.1), was obvious in all 16 patients with GD compared to controls in the study by Ralls et al. The role of ultrasound with color Doppler evaluation was further confirmed by a larger prospective study, with high sensitivity and specificity in the diagnosis of GD [51]. Quantitative Doppler evaluation which measures the peak systolic velocity of the inferior thyroid artery was recently proposed as a potential quantitative tool to supplement the qualitative tool of tissue vascularity in the diagnosis of GD [52].

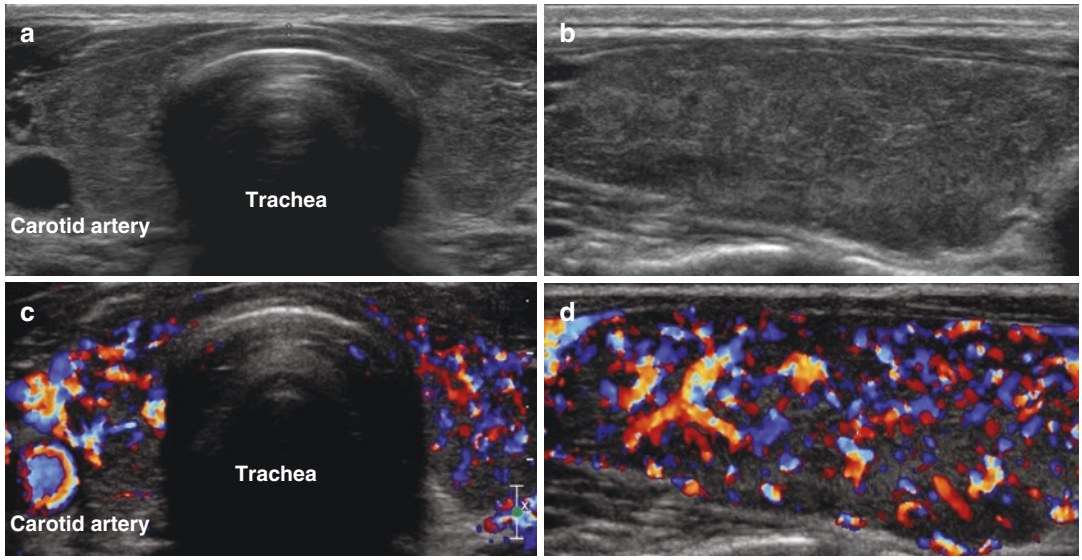

Fig. 2.1 Thyroid ultrasound appearance in Graves' disease. (**a**) Transverse image of the thyroid gland and (**b**) longitudinal image of the right thyroid lobe showing heterogenous thyroid echotexture. (**c**) Transverse image of the thyroid gland and (**d**) longitudinal image of the right thyroid lobe with color flow Doppler demonstrating increased vascularity (thyroid inferno)

Treatment

The three treatment options for GD are antithyroid drugs (ATDs), radioactive iodine ablation (RAI), and thyroidectomy. The choice of therapy depends on patient preference and several clinical factors as outlined in Table 2.2.

Antithyroid Drugs (ATD)

The thioamide compounds, methimazole (MMI), its prodrug derivative, carbimazole (CMZ), and propylthiouracil (PTU), are the mainstay of medical management of GD. The main mode of action of thioamides is to inhibit thyroid hormone synthesis by interfering with thyroid peroxidase-mediated and coupling of tyrosine residues [53]. PTU, at larger doses, also inhibits peripheral conversion of T_4 to T_3 via inhibition of type 1 deiodinase [53]. The choice of ATDs as the first-line treatment is largely driven by practical considerations and regional preferences. ATDs are more favored in Asia and Europe compared to the United States, which tend to prefer RAI as the first-line treatment [54, 55]. Two widely used ATD regimes for GD treatment are the "titration" regime, which involves a titrating dose of ATD over 12–18 months of treatment period and the "block and replace" regime, which entails a fixed high dose of ATD combined with levothyroxine over 6 months. Recent studies have not found superiority of one regime over the other in terms of long-term efficacy or maintaining stable thyroid function [56, 57]. However, the "block and replace" regime is generally less favored in clinical practice due to the higher pill load, more drug-related adverse effects, and potential patient non-compliance issues [53, 58]. This regime is also contraindicated in the management of GD in pregnancy due to the risk of fetal hypothyroidism and goiter. Treatment with ATDs should be considered in patients with clinical characteristics that may predict remission with medical treatment: women, mild hyperthyroidism, small goiter, and low TRAB levels at diagnosis [41, 59]. A typical initial adult dose of ATD will comprise of 30–40 mg of CMZ (equivalent to 20–30 mg MMI or 300-400 mg PTU) followed by gradual titration to maintenance dose (generally 5–10 mg CMZ) depending on the severity of hyperthyroidism at diagnosis and response to the ATD treatment. In addition, β-adrenergic blockers (e.g., propranolol) are typically prescribed in the initial management of these patients for relief of symptoms caused by increased sympathetic action

Table 2.2 Factors favoring, advantages, and disadvantages of the three treatment modalities for Graves' disease

Factors that favor ATDs	*Factors that favor RAI*	*Factors that favor thyroidectomy*
Patient preference	Patient preference	Patient preference
Facilities for surgery or radioiodine are not available	Relapsed GD	Relapsed GD
Patients unable to adhere to radiation safety rules, e.g., parents of young children and nursing home residents	Persistent thyrotoxicosis in patients with previous operated or irradiated necks	Concomitant suspicious nodules or thyroid cancer
Patients with contraindications to RAI, e.g., pregnancy and severe GO	High surgical risk	Concomitant moderate to severe GO
Persistent thyrotoxicosis in patients with previous operated or irradiated necks	Patients with contraindications or serious adverse effects to ATD	Symptomatic and large goiters
High surgical risk	Patients with thyrotoxic periodic paralysis	May be preferred in women considering pregnancy in less than 6 months who wants to avoid potential risk of ATD-related birth defects
Patients with characteristics that favor remission with ATD, e.g., women, small goiter, mild hyperthyroidism, low TRAB levels		Concomitant primary hyperparathyroidism requiring surgery
		Patients with contraindications or serious adverse effects to ATD
		Patients with thyrotoxic periodic paralysis
Advantages of ATDs	*Advantages of RAI*	*Advantages of thyroidectomy*
Outpatient treatment	Outpatient treatment	No radiation exposure
Low risk of hypothyroidism	Achievement of desired end point, i.e., hypothyroidism in the majority of patients treated with a single administration of sufficient radiation dose	Low disease recurrence rate after surgery (especially with total thyroidectomy)
No exposure to radioactive material, anesthetic, or surgical risks	No anesthetic or surgical risks	Rapid normalization of thyroid dysfunction
No adverse effects on GO	Reduces goiter size	Definitive histology results
Disadvantages of ATDs	*Disadvantages of RAI*	*Disadvantages of thyroidectomy*
High relapse rate upon withdrawal	Permanent hypothyroidism	Permanent hypothyroidism (especially with total thyroidectomy)
Regular monitoring of thyroid function required	Risk of de novo development of GO or exacerbation of pre-existing mild GO	Permanent scar
Potential serious adverse effects	Requires compliance to radiation safety rules	Potential anesthetic and surgical risk—e.g., recurrent laryngeal nerve palsy and hypoparathyroidism
Risk of carbimazole or methimazole associated birth defects	Conception needs to be delayed (usually 6 months) in women considering pregnancy	High cost
		Require hospitalization

such as sweating, anxiety, palpitations, and tremors. Biochemical monitoring of thyroid function should be performed every 4 to 6 weeks in the first 3–6 months of therapy, followed by three monthly intervals when biochemical euthyroidism is achieved. The use of thioamides is associated with uncommon adverse effects. Minor side effects include pruritus, urticaria, and rash, which occur in 3–6% of patients on ATDs [60]. These can be generally managed with

concurrent antihistamines in mild cases. Switching to another ATD or consideration for other treatment modalities such as RAI or surgery may be required if the side effect is persistent. Major side effects associated with ATD usage include agranulocytosis, hepatotoxicity, and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis. Agranulocytosis (defined as absolute neutrophil count or ANC <500) occurs in approximately 0.1–0.3% of treated patients and tends to manifest in the first 90 days of drug initiation [53, 61, 62]. CMZ-/MMI-induced hepatotoxicity is often cholestatic, whereas PTU is associated with hepatocellular damage, including fatal fulminant hepatic necrosis [63]. The incidence of ATD-associated hepatotoxicity is between 0.03 and 0.07% and most often occurs in the first 3 months of therapy [64, 65]. PTU is associated with higher reported rates of liver failure compared to CMZ/MMI [64, 66]. The US Food and Drugs Administration, the European Medicines Agency, and the UK Medicines and Healthcare Regulatory agency have all issued warnings on the risk of liver failure with PTU [67]. Hence, the current ATA guidelines recommend that CMZ/MMI should be used in all patients (including children) selected for treatment with ATDs, except during first trimester of pregnancy, in the treatment of thyroid storm, and in patients who have minor adverse effects with CMZ/MMI who refused RAI or surgery [41]. All patients should be counselled on these potential side effects prior to initiation of ATD, and baseline full blood count and liver function should be considered prior to initiating ATDs [41]. Although low white cell count and elevated liver enzymes may be encountered in newly diagnosed GD patients, it is recommended that initiation of ATDs must be seriously reconsidered if the neurotrophil count is <1000/mm^3 or liver transaminase levels are more than fivefold upper limit of normal [41]. ANCA-positive vasculitis is an uncommon adverse effect associated with ATD. It has been more commonly reported in children, patients of Asian ethnicity, and PTU usage and its risk increase with duration of therapy [68, 69]. Other rare adverse effects of CMZ/MMI have also been reported [70, 71], including higher risk of congenital birth defects such as aplasia cutis and choanal atresia when used in the first trimester of pregnancy [72]. The main disadvantage of ATDs is the high relapse rate after discontinuation of therapy, which is estimated to be 50–55% [56]. The risk of relapse is highest in the first 6 months after withdrawal of ATD. In particular, patients who are male, young, smokers, has large goiter, high TRAB levels at diagnosis or persistently positive TRAB levels prior to stopping the drug are more likely to have disease recurrence [73, 74]. Patients who have relapse after ATD discontinuation will typically be advised to consider definitive treatment with RAI or thyroidectomy, although recent growing evidence suggest long-term low-dose ATD may be considered in selected groups [75, 76].

Radioactive Iodine Ablation (RAI)

In the treatment of GD with RAI, the radioactive form of iodine (I-131) is taken up by iodide transporter of the thyroid the same way as natural iodine and is similarly processed. The beta particles released result in ionizing damage to the thyroid follicular cells and gradual destruction of the gland, leading to volume reduction and control of the thyrotoxicosis. Radioiodine is given orally as a single dose of I-131 labelled sodium iodide in liquid or capsule form. The goal of RAI therapy is to render the patient hypothyroid, which can be achieved in 80% of patients after one administration of sufficient radiation dose [77]. The optimal method for determining iodine-131 treatment doses remains controversial. Radioiodine can be administered in fixed amounts or calculated doses based on the estimated thyroid gland size (either clinically or from imaging) and the 24 h radioiodine uptake. The current literature does not support the superiority of one method over the other [77, 78]. Absolute contraindications to radioiodine treatment are pregnancy, lactation, and inability to comply with radiation safety rules. Pretreatment with ATD prior to RAI is generally not required, except in older patients and in patients with coexisting ischemic heart disease due to potential increased risk of complications due to short-term worsening of hyperthyroidism following administration of RAI. Radioiodine

treatment may result in de novo development of GO or exacerbation of pre-existing mild GO, particularly in smokers, in severe hyperthyroidism (high free thyroid hormone levels and/or TSH receptor autoantibodies), and hyperthyroidism of recent onset [79, 80]. The current European Thyroid Association/European Group on Graves' Orbitopathy Guidelines recommend that oral prednisone prophylaxis be given in radioiodine-treated patients at high risk of progression or de novo development of GO [80].

Thyroidectomy

Thyroidectomy is the least often used treatment modality of GD but may be preferred in selected cases, such as presence of large goiter and concomitant suspicious thyroid nodules or thyroid cancer and in patients who prefer rapid and definitive treatment for their disease. Patients treated with surgery or medication showed a gradual fall in serum TRAB levels with disappearance of TRAB in 50–60% of patients after 1 year, whereas increasing TRAB levels was found in those treated with RAI [81]. This surge in TRAB levels during the 1st year after RAI is associated with a risk of developing or worsening of GO [82]. Current literature suggest GO remain stable or even improve in some patients after thyroidectomy [83, 84]. Hence, thyroidectomy instead of RAI is the recommended definitive treatment for patients with moderate to severe GO whose hyperthyroidism cannot be adequately controlled with ATDs. Near-total or total thyroidectomy is the recommended procedure of choice in view of virtually 0% risk of recurrence, whereas subtotal thyroidectomy may have an 8% chance of persistence or recurrence of hyperthyroidism at 5 years [85]. Notably, more recent data support the safety of total thyroidectomy for benign thyroid disease if the surgery is performed at a high-volume center, keeping the risk of permanent morbidity at <2% [86]. In a recent meta-analysis of 23 studies comparing these two surgical approaches, total thyroidectomy was associated with a decrease in recurrent hyperthyroidism but with only a small increase in both temporary and permanent hypoparathyroidism [87]. Progression of GO and incidence of permanent recurrent laryngeal nerve palsy were similar between these two groups [87]. The rates of complications of thyroid surgery are inversely correlated with surgeon's experience and annual volume of thyroidectomies. In a study of 166,954 patients who underwent total thyroidectomy for thyroid disease, it was demonstrated that the likelihood of experiencing a postoperative complication decreased with increasing surgeon work volume in a dose-dependent fashion up to 26 (95% CI 22–32) total thyroidectomies per year [88]. Based on the results of this study, the authors identified a surgeon volume threshold of more than 25 total thyroidectomies per year to define a high-volume thyroid surgeon [88]. The risk of permanent hypoparathyroidism has been determined to be <2%, permanent recurrent laryngeal nerve palsy to be <1%, and frequency of bleeding necessitating reoperation to be between 0.3 and 0.7% following thyroidectomy by high-volume surgeons [89, 90].

Perioperative Management of GD for Thyroid and Non-thyroid Surgery

Patients with GD should be as close as possible to clinical and biochemical euthyroidism using ATDs before going to surgery. Elective surgeries should be postponed until this is achieved. This is rarely an issue in patients undergoing thyroidectomy for treatment of their GD since surgery is considered a second-line treatment. Surgery in patients with poorly controlled thyrotoxicosis can potentially precipitate thyroid storm—a life-threatening condition caused by the exaggeration of clinical manifestations of thyrotoxicosis associated with significant risk of mortality [91]. However, it is common for TSH values to remain suppressed in prolonged hyperthyroidism in patients who otherwise have normalized their T_4 and T_3 on ATDs and should not be considered a contraindication to surgery.

In the unusual circumstances where urgent non-thyroid surgery or urgent thyroidectomy is required in an overtly hyperthyroid patient with GD, rapid preoperative preparation using several drugs is employed. The same multimodality approach targeting at different steps in the production and metabolism of thyroid hormones is