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Surgical considerations for adult Graves' disease: a narrative review of indications, perioperative challenges and postoperative outcomes

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ABSTRACT

Introduction: Graves' disease (GD) is a systemic autoimmune disorder, ultimately caused by autoantibodies stimulating the TSH receptor (TSHR-Ab) on thyroid follicular cells. Novel targeted therapies are under investigation, but treatment of GD still relies on antithyroid drugs (ATDs), radioactive iodine, or thyroidectomy.

Areas covered: Narrative review of original articles, randomized clinical trials, systematic reviews and meta-analyses, guidelines on PubMed from inception to March 2026, using the following terms: GD, management of GD, thyroidectomy, hypoparathyroidism, hypocalcemia, recurrent laryngeal nerve injury, hematoma, near-infrared autofluorescence, indocyanine green angiography, Graves' orbitopathy, thyroid eye disease.

Expert opinion: Thyroidectomy is the least common treatment for GD. However, it effectively eradicates hyperthyroidism, if all thyroid tissue is removed. Preoperative preparation includes ATD treatment to restore euthyroidism whenever possible, iodine solution (controversial in patients rendered euthyroid prior to surgery), and vitamin D (with or without calcium), if deficient. In patients with risk factors for cardiovascular (CV) complications, thyroidectomy may prevent the CV risk associated with unstable/severe hyperthyroidism. Thyroidectomy is safe in the hands of skilled, high-volume surgeons, with a low incidence of the main complications, i.e. hypoparathyroidism, recurrent laryngeal nerve injury, and hematoma.

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recurrent laryngeal nerve
injury; thyroidectomy;
thyroid storm

1. Introduction

Graves' disease (GD) is a systemic autoimmune disorder representing the most frequent cause of hyperthyroidism in iodine-replete areas (1). Autoantibodies binding to and unrelentlessly stimulating the TSH receptor on thyroid follicular cells (TSHR-Ab) are the ultimate effector responsible for thyroid growth and uncontrolled production of excess thyroid hormones (thyroxine, T₄, and triiodothyronine, T₃) [1]. GD is complicated in about one third of patients by an autoimmune orbital disease, named Graves' orbitopathy (GO) or thyroid eye disease [2], far less frequently by skin (thyroid dermopathy) or finger/nails (thyroid acropachy) involvement [3].

Although total thyroidectomy is associated with almost 100% resolution and rapid eradication of hyperthyroidism, surgery is the least popular therapeutic approach compared to the other available therapies for GD (antithyroid drugs [ATDs] and radioactive iodine [RAI] treatment). Several surveys have shown that surgery is the first-line treatment in only 1–2% of newly diagnosed GD patients, although this proportion increases to 15–23% if GO is present at baseline [4–6]. ATDs have gained increasing popularity and are currently viewed worldwide as the first-line treatment under most circumstances [5]. Their major limitation is the very high recurrence rate (about 50%) after drug discontinuation at the end of a typical 18–24-month course [7], but this might to some extent be overcome by prolonging treatment for many years (≥5 years), may be indefinitely in some cases [8]. However, this approach is not universally accepted, because most studies come from the same institution and, after many years of

treatment, at least 20% of patients relapse [9]. RAI treatment has lost much of its popularity for several reasons, including fears of radiation, pregnancy intention, and possible negative effects on GO [7]. Nevertheless, RAI is an effective way of eradicating hyperthyroidism early in the course of the disease or in the case of relapsing hyperthyroidism, thereby reducing the risk of long-term systemic complications of exposure to thyroid hormone excess [7]. In any case and of paramount importance, the choice of treatment should result from a thorough shared decision-making process, in which the role and the expectations of the well-informed patient are essential [10].

Aim of the present narrative review is to discuss the current role of thyroidectomy in the management of adult GD, with particular emphasis on perioperative challenges and postoperative outcomes. To this purpose we searched original articles, randomized clinical trials, systematic reviews and meta-analyses, guidelines on PubMed from inception to March 2026, using the following terms: Graves' disease, management of Graves' disease, thyroidectomy, hypoparathyroidism, hypocalcemia, recurrent laryngeal nerve injury, hematoma, near-infrared autofluorescence, indocyanine green angiography, Graves' orbitopathy, thyroid eye disease, hypothyroidism, levothyroxine.

1.1. Selection of thyroidectomy as the treatment for Graves' disease

In addition to patient preference, there are situations in which thyroidectomy represents a valid and/or necessary treatment

Article highlights

- Thyroidectomy does not represent the cure of Graves' disease (GD). This holds true for the other available treatments, ATDs and RAI, because none of them targets the pathophysiological basis of this autoimmune disease;
- Thyroidectomy is the least used first-line treatment for GD, but it is a very effective way to eradicating hyperthyroidism and to preventing its possible deleterious effects, particularly on the cardiovascular system. Therefore, it should be considered in at-risk patients, for whom a definitive treatment is warranted and surgery represents a valid alternative option to RAI;
- The best surgical approach is total thyroidectomy, because it is not associated with relapsing hyperthyroidism and is not bound to a substantial increase in the rate of complications compared to more conservative procedures;
- Thyroidectomy should be performed by high-volume, skilled surgeons (≥ 25 –50 thyroidectomies/year);
- Preparation of patients to surgery requires restoration of euthyroidism with ATDs, whenever possible. The conventional preoperative use of KI is controversial in euthyroid patients, but is useful in patients with partially controlled hyperthyroidism. VitD deficiency should be corrected prior to surgery, to reduce the risk of postoperative hypocalcemia;
- Fluorescence-based techniques for visualizing parathyroids and their vessels have been associated with a reduced risk of postoperative hypocalcemia;
- Intraoperative neuromonitoring helps reduce the risk of RLN injury;
- GD *per se* is a risk factor for the occurrence of the main complications, hypocalcemia, RLN injury and postoperative neck hematoma;;
- Hypothyroidism is the desired goal of thyroidectomy in GD. The current standard of care is represented by LT4 monotherapy.

for Graves' hyperthyroidism, if an alternative to RAI is warranted or requested by the patient [11,12] (Figure 1). These conditions include:

1.1.1. Relapsing hyperthyroidism following ATD withdrawal

Thyroidectomy can be selected if the patient is unwilling to continue long-term ATD treatment and/or is reluctant to receive RAI treatment because afraid of radiation, has small children, or is planning pregnancy within 6 months. For example, the decline of RAI treatment for GD in Japan may be related not only to the Fukushima nuclear power plant accident in 2011, but also to the longlasting negative impact and mental trauma following the 1945 atomic bombings of Hiroshima and Nagasaki [13].

1.1.2. Unstable hyperthyroidism

Unstable hyperthyroidism with fluctuations in thyroid status and persistently suppressed TSH values after 12 months from initiation of ATD treatment is associated with an increased risk of all-cause mortality, major adverse cardiovascular events (MACE) and atrial fibrillation (AF) [14]. Cumulative periods (>6 months) of low TSH in untreated or pharmacologically-treated patients have been related to a 10% increase in both mortality and cardiovascular (CV) morbidity [15,16]. Furthermore, fluctuations in thyroid status causing suboptimal

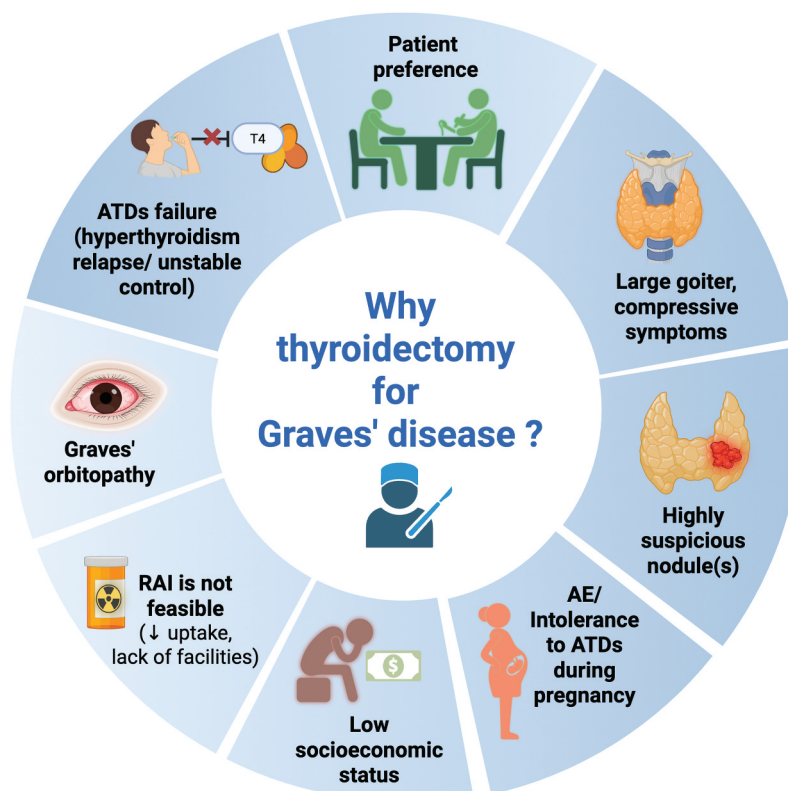


Figure 1. Main indications for selecting thyroidectomy in patients with Graves' disease. AE: adverse events; ATD: antithyroid drugs; RAI: radioactive iodine; ↓ = low. Created in BioRender, Gallo, D. (2026) <https://BioRender.com/5sxa8zf>.

restoration/maintenance increase the risk of GO progression [9]. Under these circumstances, a definitive treatment for GD by either RAI or thyroidectomy seems advisable.

1.1.3. Large goiter with/without compressive symptoms

These cases are less likely to go into remission even with long-term ATD treatment, or may require multiple doses of RAI, thereby exposing the patient to risks of uncontrolled hyperthyroidism. Thyroidectomy is also indicated when GD is associated with primary hyperparathyroidism requiring surgery [17].

1.1.4. Ultrasonographically and/or cytologically highly suspicious nodules

If there is a concrete risk of cancer, surgery is preferable to RAI, because it represents the cure for both hyperthyroidism and associated thyroid cancer.

1.1.5. Intolerance to or severe adverse events of ATDs during pregnancy

This is an exceptional situation, requiring surgery during the second trimester of pregnancy, avoiding the first trimester for the teratogenic effects of anesthesia and the increased risk of abortion, and the third trimester for the risk of premature delivery and lower birthweight [11,18].

1.1.6. Low thyroidal radioactive iodine uptake

This may be due to iodine contamination related to the use of iodine-rich drugs or substances (amiodarone, iodinated contrast media, iodine-rich seaweeds) making RAI treatment unfeasible [19].

1.1.7. Lack of facilities for RAI treatment

In a study from Sub-Saharan Africa the number of thyroidectomies tripled over a 10-year period, because of the paucity of specialized endocrinology and nuclear medicine centers [20].

1.1.8. Presence of GO

If GO is mild and/or inactive, any treatment for GD can be used. If GO is moderate-to-severe and active, current guidelines recommend the use of ATDs while aggressively treating GO [21,22]. However, thyroidectomy is a suitable treatment (with or without RAI ablation) also in these forms of GO, provided that treatment for GO is then promptly instituted [9].

1.1.9. Socioeconomic factors

In a large ($n = 634$) retrospective study patients undergoing thyroidectomy had a lower income and were more frequently uninsured than patients treated with ATDs [23]. Socioeconomic factors may contribute to selecting surgery, since hypothyroidism, inevitably following thyroidectomy, may require a lower degree of surveillance in terms of hospital visits and hormone assays (one TSH measurement per year) compared to long-term ATD treatment [23]. Likewise, a retrospective study of 236 GD patients from Boston showed that patients with limited English proficiency had a shorter time period from endocrinological consultation to surgery compared to English proficient patients, possibly reflecting

communication barriers limiting a robust shared decision-making process [24].

Summary: Although thyroidectomy is the least used treatment for newly diagnosed GD, there are several situations that, in addition to patient choice, make surgery an excellent tool to get rid of hyperthyroidism permanently.

2. Extent of surgery, surgical approaches, and the role of surgical volume

2.1. Extent of surgery

Several surgical procedures have been used for GD, including subtotal bilateral thyroidectomy, lobectomy plus contralateral subtotal lobectomy (Dunhill procedure), near-total thyroidectomy (preservation of a very small posterior remnant, <1 g), and total thyroidectomy (removal of all visible thyroid tissue) (Figure 2). Total thyroidectomy should be the procedure of choice for GD to remove virtually all the intrathyroidal immune cells involved in the pathogenesis of the disease and the TSHR, the antigen ultimately responsible for triggering TSHR-Ab production. Surgery is followed by a relatively fast decrease in serum TSHR-Ab levels [25]. Four systematic reviews and meta-analyses and one randomized clinical trial (RCT) [26–30] investigated the relation between the extent of surgery (subtotal thyroidectomy, near-total thyroidectomy, total thyroidectomy) and the rate of relapsing hyperthyroidism or major complications in GD patients (Table 1). Total thyroidectomy and near-total thyroidectomy were associated with eradication of hyperthyroidism in 99.6–100% of cases, while subtotal thyroidectomy was followed by a relapse of hyperthyroidism in 7.9–9.7% of patients. Total thyroidectomy was associated with a slightly higher incidence of transient, but not permanent hypoparathyroidism or recurrent laryngeal nerve (RLN) injury compared to subtotal thyroidectomy [28] (Table 1). One systematic review of 4 RCTs and 19 non-RCTs showed that total thyroidectomy was associated with a slightly higher incidence of transient and chronic hypoparathyroidism than subtotal thyroidectomy, but differences were insignificant when the analysis was limited to RCTs [29]. In a systematic review and meta-analysis of 2 RCTs and 3 non-RCTs, total thyroidectomy had a slightly higher incidence of transient and permanent hypoparathyroidism than near-total thyroidectomy, but the included studies were not of very high quality [30] (Table 1).

2.2. Surgical approaches

Thyroidectomy is conventionally performed via a central neck incision (transcervical thyroidectomy), using the mini-invasive video-assisted approach, when feasible [31]. Several remote-access endoscopic and robotic approaches have been proposed for both benign and malignant thyroid disorders, aimed at preventing the problem of a visible scar in the neck [32]. These techniques include transaxillary approach, bilateral axillo-breast approach, retroauricular approach, and transoral approach (via vestibular, sublingual, or combined incisions). While the first three techniques primarily use the robotic procedure, the transoral technique primarily employs

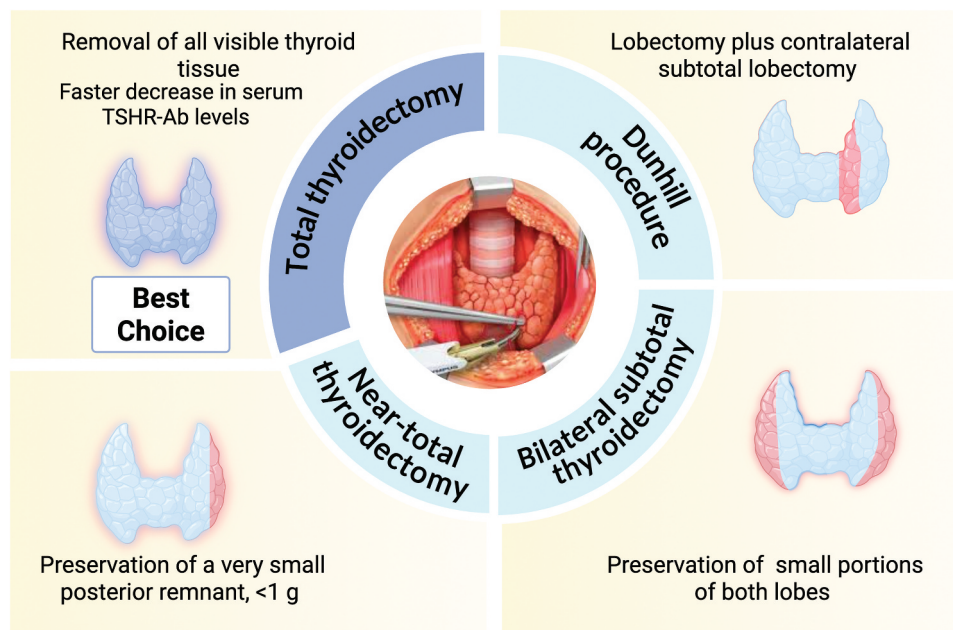


Figure 2. Surgical procedures for Graves' disease. Compared with antithyroid drugs, radioactive iodine treatment, and other surgical procedures, total thyroidectomy is associated with a faster decrease in TSHR-Ab levels. TSHR-Ab: TSH-receptor autoantibody. Created in BioRender, Gallo, D. (2026) <https://BioRender.com/x5ffrvy>.

Table 1. Extent of surgery for Graves' disease and the risk of postoperative relapsing hyperthyroidism and major complications.

Author (yr)	Study design	Surgical procedure (n. of pts.)	Relapsing hyperthyroidism	Major complications	Ref.
Palit (2000)	Systematic review and meta-analysis of 35 studies, 5859 pts. (1965–1988)	TTx: 538 STx: 7203	TTx: 0% STx: 7.9%	No differences in the incidence of chronic hypoparathyroidism or RLN injury	[26]
Genovese (2010)	Review of 19 studies, 4546 pts. (2001–2011)	TTx: 1388 STx: 3158	TTx: 0.3% STx: 10.4%	No differences in the incidence of chronic hypoparathyroidism or RLN injury	[27]
Barczynski (2012)	RCT of 200 pts.	TTx: 96* STx: 95*	TTx: 0% STx: 9.5%	Slight increase in transient (but not permanent) hypoparathyroidism after TTx No difference in RLN injury	[28]
Feroci (2014)	Systematic review and meta-analysis of 23 studies, 3242 pts. (4 RCTs, 19 non-RCTs) (1970–2012)	TTx: 1665 STx: 1557	TTx: 0.4% STx: 8.2%	Slight increase in transient and permanent hypoparathyroidism after TTx** No difference in RLN injury	[29]
Mu (2020)	Systematic review and meta-analysis of 5 studies, 528 pts (2 RCT, 3 non-RCTs)	TTx: 321 NTx: 207	TTx: 0.3% NTx: 0%	Slightly higher incidence of hypoparathyroidism in the TTx group	[30]

*Patients who complete a 5-yr follow-up; **Differences were insignificant in analysis limited to RCTs.

Abbreviations: TTx: Total thyroidectomy; STx: Subtotal thyroidectomy; NTx: Near-total thyroidectomy; RLN: Recurrent laryngeal nerve; RCTs: Randomized clinical trials.

the endoscopic procedure [32]. Detailed description of results using these approaches is beyond the scope of this review. However, a recent consensus statement from major scientific societies concluded that surgical outcomes and the rate of complications of remote-access thyroidectomy are superimposable to, while cosmesis and health-related quality of life (HR-QoL) outcomes due to scar are better than those of

transcervical thyroidectomy [33]. According to the consensus statement, In the case of benign conditions, including GD, remote access approaches can be considered if the goiter is not too large, but are contraindicated if the patient has a history of previous neck surgery, trauma or radiation around the remote incision and path, or is morbid obese [33]. These techniques are not minimally invasive, require specialized

technologies, skilled surgeons, have higher costs than transcervical thyroidectomy, and usually require a longer hospital stay.

2.3. Surgical volume

Guidelines and consensus statement strongly underscore that thyroid surgery should be carried out by high-volume, skilled surgeons [11,18,34]. Definition of high-volume surgeon is a matter of debate. In an analysis of 5860 thyroidectomies (for both benign and malignant diseases) performed in Maryland during a 6-year period (1991–1996), surgeons were categorized in four groups according to the total number of thyroidectomies performed over the study period: A: 1–9; B: 10–29; C: 30–100; D: >100 [35]. The highest-volume surgeons (group D) had the shortest hospital stay (1.4 days vs. 1.7 in groups B and C, and 1.9 in group A) and the lowest rate of overall complications (5.1% vs. 6.1% in groups B and C, and 8.9% in group A) [35]. In a Maryland Health Service database, including 21,270 patients, high-volume surgeons (>24 thyroidectomies/year) had a lower incidence of RLN injury and hypoparathyroidism than low-volume surgeons [36]. In a retrospective, cross-sectional analysis of the Nationwide Inpatient Sample database from 2006 to 2011, including 215,068 patients (11,205 with GD), improved outcomes were reported in centers performing >47 thyroidectomies/year [37]. Data from the UK administrative dataset of 72,594 patients (2004–2012) showed that the rate of complications, as well as the length of hospital stay, greatly decreased if surgeons operated on >50 thyroidectomies/year compared to occasional thyroid surgeons (<5 thyroidectomies/year) [38]. Analysis of another database of 16,954 patients revealed that the odds of having a complication progressively decreased with the increasing number of thyroidectomies/year ([39] (Figure 3). Interestingly, the rate of post-thyroidectomy hypocalcemia was lower in teaching hospitals (with residency programs) than in non-teaching hospitals [40]. A position statement from the European Society of Endocrine Surgeons concluded that >50 thyroidectomies/year is an appropriate threshold to identify a high-volume surgeon, whereas <25 procedures/year is an appropriate threshold to identify a low-volume surgeon [41]. A more recent transcontinental

consensus statement from several scientific societies stated that surgeons offering remote-access thyroidectomy should perform at least 25 thyroidectomies/year [33].

Summary: Total thyroidectomy is the surgical procedure of choice for GD, because hyperthyroidism does not relapse thereafter and the rate of complications is substantially superimposable to that of less radical approaches. The transcervical approach is most used, but remote-access approaches are now also widely used in specialized centers. The risk of complications is reduced in the hands of a high-volume (at least >25, better ≥ 50 thyroidectomies/year) surgeon.

3. Preoperative treatment

3.1. Antithyroid drug treatment

As recommended by current guidelines [11,18,34] GD patients should be rendered euthyroid, whenever possible, with ATDs prior to surgery. In patients with uncontrolled hyperthyroidism, anesthesia, manipulation during surgery, stress, infections may precipitate thyroid storm, a potentially lethal endocrine emergency [42]. However, hyperthyroidism may be poorly/partially controlled prior to surgery for several reasons, including poor compliance, intolerance/allergy to ATDs, severe ATD adverse events (agranulocytosis, hepatotoxicity, vasculitis, pancreatitis), refractoriness to ATDs. A retrospective single-center study of 67 patients showed that no thyroid storm occurred in patients with overt (21%) or subclinical (33%) hyperthyroidism at surgery [43]. In a systematic review and meta-analysis of 8 retrospective studies (low-to-moderate quality) including 1336 patients (96% with GD), patients who were preoperatively euthyroid had lower risks of hypocalcemia, voice impairment, and hematoma than hyperthyroid patients, although differences did not reach statistical significance [44]. However, one patient, whose hyperthyroidism was poorly controlled, had a non-lethal thyroid storm [44]. In a retrospective study of 81 GD patients, 24 were submitted to surgery, mostly because of ATDs adverse events, while still being thyrotoxic under several treatments (Lugol's solution, lithium, steroids); surgical outcomes, including hypocalcemia, hematoma, intraoperative blood loss, operating time, hospital stay did not significantly differ from those of euthyroid 54 GD patients [45]. At variance, in a study of 275 patients (134

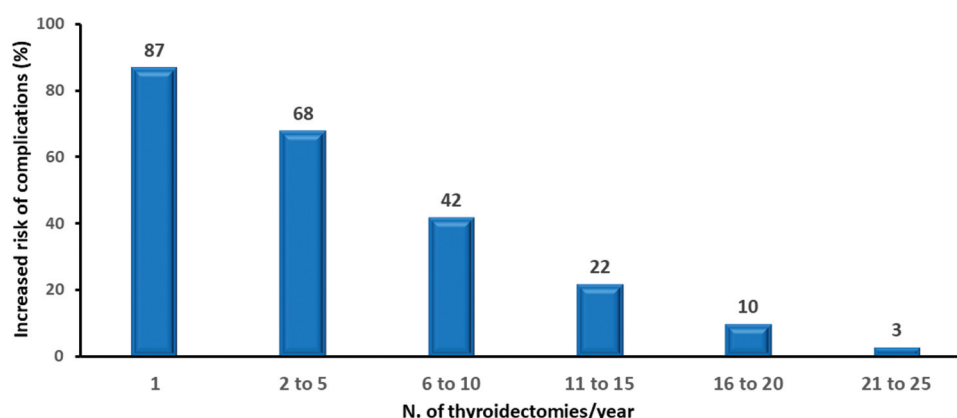


Figure 3. There is a negative relationship between the number of thyroidectomies/year and the risk of postoperative complications. Derived from Adam et al. [39].

euthyroid, 141 hyperthyroid at surgery), uncontrolled hyperthyroidism was associated with a longer operating time (>1 h in 19.8% of hyperthyroids vs. 7.3% of euthyroids), more blood loss (20 ml vs. 15 ml), more frequent postoperative transient hypocalcemia (13.4% vs. 4.7%), although no cases of thyroid storm occurred in hyperthyroid patients [46]. In a retrospective study 56 of 242 patients, hyperthyroid when submitted to thyroidectomy, had a higher heart rate and more frequently needed anti-hypertensive drugs, but no case of thyroid storm was reported nor there were differences in blood loss and arrhythmias compared to patients with well controlled hyperthyroidism [47]. In addition, in a recent study from Japan thyroidectomy in patients with poorly controlled hyperthyroidism was followed by a rapid decline in serum thyroid hormone levels, with no increased stress response (assessed by serum cortisol levels) compared to preoperatively euthyroid patients [48]. Thus, as a rule and in agreement with current guidelines [11,18,34], restoration of euthyroidism should be achieved prior to surgery, but in selected cases thyroidectomy, if urgently needed, can be performed before achieving optimal control of hyperthyroidism, provided that the surgeon and the anesthesiologist are highly expert in this clinical setting.

3.2. Potassium iodide

Current guidelines recommend the preoperative addition of potassium iodide (KI) for a short period of time (10–14 days) prior to surgery [11,18,34]. KI can be given as saturated solution (SSKI, 50 mg iodide per drop, 1–2 drops three times daily) or as Lugol's solution (8 mg iodide per drop, 5–7 drops three times daily). The rationale for using KI resides with the notion that, in addition to blocking peripheral conversion of the prohormone T4 to the active hormone T3, it decreases thyroid gland blood flow, microvessel density, and gland friability, thereby reducing intraoperative blood loss [49,50]. The

potential benefit of preoperative KI was supported by color flow Doppler sonography showing that Lugol's solution normalized the decreased intrathyroidal artery resistance observed in GD patients [51]. The latter finding has been challenged by a recent RCT showing no differences in thyroid vascularization at ultrasonography in GD patients either untreated or pretreated with Lugol's solution [52]. In a European survey of clinical practice, only about 40% of respondents used KI in addition to ATDs in the preparation of GD patients for surgery (4). Results of the literature are not unequivocal, as illustrated in Table 2. A small single-center RCT of 33 GD patients (15 treated, 18 not treated with SSKI) [53] and a systematic review and meta-analysis of 9 studies (with high degree of heterogeneity), including 510 GD patients either treated ($n=223$) or untreated ($n=287$) with SSKI [54], showed that the use of SSKI in the immediate preoperative period significantly reduced intraoperative blood loss and a operating time, with no differences between the two groups in terms of postoperative complications (Table 2). In a retrospective study of 442 GD patients, pretreatment with KI was associated with a significantly longer operating time, but no differences in postoperative complications compared to the untreated control group [55]. Similar results were obtained in a RCT of 90 GD patients from two centers in Spain [56]. It has been argued that pretreatment with Lugol's solution increases thyroid firmness, making it more complicated to remove the thyroid without harming the parathyroids [57]. In a Swedish retrospective register-based study of 813 GD patients, the group pretreated with Lugol's solution more frequently needed postoperative calcium and vitamin D (VitD) supplementation, as surrogate marker of postoperative hypocalcemia [58] (Table 2). In a single-center, single-blind RCT from Italy, 56 GD patients were randomly assigned to receive or not to receive Lugol's solution for 7 days prior to surgery [52]. While the Lugol's solution-treated group showed a significant reduction in serum free T4 (FT4) and free T3 (FT3)

Table 2. Effects of preoperative iodine solution on perioperative and postoperative outcomes of thyroidectomy for Graves' disease.

Author (yr)	Study design	Study groups (pts.)	Operative time	Intraoperative blood loss	Postoperative complications*	Hospital stay	Ref
Whalen (2017)	RCT, single center	SSKI+: 15 SSKI-: 18	Decreased	Decreased	Not reported	Decreased	[53]
Tsai(2019)	Systematic review and meta-analysis of 9 studies (5 RCTs)**	SSKI+: 283 SSKI-: 287	Unchanged	Decreased	Unchanged	Unchanged	[54]
Lindner (2020)	Retrospective, single center	SSKI+: 125 SSKI-: 317	Increased	Unchanged	Unchanged	Unchanged	[55]
Barranquero (2021)	Retrospective multicenter	SSKI+: 44 SSKI-: 56	Unchanged	Unchanged	Unchanged	Unchanged	[56]
Hedberg (2024)	Retrospective registry-based	LS+: 33 LS-: 780	Unchanged	Unchanged	Increased hypocalcemia***	Unchanged	[58]
Schiavone (2024)****	RCT, single center	LS+: 29 LS-: 27	Unchanged	Unchanged	Unchanged	Not reported	[52]
Ciriotto*****	Retrospective, single center	LS+: 57 LS-: 43	Unchanged	Unchanged	Unchanged	Unchanged	[59]
Haroon (2026)	Systematic review and meta-analysis of 11 studies (only 3 RCTs)	IS+: 760 IS-: 1497	Unchanged	Unchanged	Unchanged	Unchanged	[60]

*Transient/permanent hypoparathyroidism, transient/permanent laryngeal nerve injury, postoperative hematoma; **Mostly Graves' disease; ***Indirectly estimated by the increased need of postoperative need for vitamin D and calcium supplementation; ****Lower serum free thyroxine and free triiodothyronine levels at operation; *****Graves' disease: 67%, Toxic nodular goiter: 33%.

Abbreviations: RCT: randomized clinical trial; SSKI: saturated solution of potassium iodide; LS: Lugol's solution; IS: iodine solution (either SSKI or LS).

levels on the day of surgery, there were no differences between the two groups concerning intraoperative/postoperative blood loss, operating time, and postoperative complications [52] (Table 2). Likewise, a retrospective study of 100 patients (67 GD, 33 toxic multinodular goiters) failed to show any significant difference in operating time, blood loss, immediate postoperative complications [59]. Furthermore, a recent meta-analysis of 11 studies including 2257 GD patients showed that the group pretreated with iodine solution and the untreated control group had similar outcomes in terms of intraoperative blood loss, operating time, postoperative hypocalcemia, RLN injury and hematoma [60] (Table 2). These results need to be confirmed by well-designed, larger, multicenter RCTs. However, if SSKI or Lugol's solution is not immediately available or the euthyroid GD patient is not compliant because of the unpleasant taste of the drops, thyroidectomy can be performed safely without iodine solution pretreatment. This recent evidence might be considered in future revisions of guidelines. The situation is different if the patient has uncontrolled hyperthyroidism and needs to be operated on urgently. Under these circumstances, Lugol's solution or SSKI can rapidly decrease serum free thyroid

hormone levels, making surgery safe and uneventful [52,61]. Cases of refractory hyperthyroidism requiring urgent thyroidectomy may also benefit from the use of glucocorticoids, beta-blockers (to achieve a target rate <90 beats per min), iopanoic acid [62], cholestyramine [63], plasmapheresis [64].

3.3. Calcium and/or vitamin D supplementation

GD *per se* represents a risk factor for postoperative hypocalcemia, likely due to the accelerated bone turnover associated with hyperthyroidism ('hungry bone syndrome') [65]. Hungry bone syndrome results from an abrupt increase in the bone formation-to-resorption ratio after surgical treatment of hyperthyroidism, leading to increased calcium demand. Predisposing factors include vertebral osteoporosis, thyrotoxicosis-related-osteodystrophy, rapid antithyroid preparation before surgery, and parathyroid removal [66]. For this reason, studies investigated the preventive role of calcium and/or VitD supplementation prior to surgery (Table 3). A placebo-controlled RCT of 90 patients showed that preoperative combined treatment (oral calcium carbonate + alfacalcidol) reduced the incidence of postoperative hypocalcemia,

Table 3. Impact of vitamin D and calcium supplementation on risk and symptoms of postoperative hypocalcemia.

Author (yr)	Study design	Treatment arms	Results	Ref
Genser (2014)	RCT, 219 pts (GD 14.3%)	111 pts (7 GD): alfacalcidol 2 mcg/d from the day before surgery to POD8 108 pts (10 GD): NS	Hypocalcemia incidence (POD1-2) no differences between the two groups Symptoms alfacalcidol group: 11% NS group: 22%, $p = 0.02$ Hypoparathyroidism after 6 m alfacalcidol group: 0% NS group: 4%, $p = 0.04$ Ca levels 4 h after TTx GD OC group: 8.3 mg/dl NS groups: 8.6 mg/dl, $p = 0.05$. Symptoms GD OC group and non-GD: 10% NS GD: 26%, $p < 0.05$	[68]
Oltmann (2015)	Prospective case-control study	45 GD pts: OC 3 g/d for 2 w 38 GD pts: NS 40 non-GD pts: NS	Ca levels 4 h after TTx GD OC group: 8.3 mg/dl NS groups: 8.6 mg/dl, $p = 0.05$. Symptoms GD OC group and non-GD: 10% NS GD: 26%, $p < 0.05$	[69]
Sessa (2022)	Prospective comparative study, 300 pts (43.3% with AITD)	100 pts: calcitriol 1 mcg the day before surgery and 4 h after surgery followed by calcitriol 1 mcg/d and OC 3 g/d from POD1 (high dose S) 100 pts: calcitriol 0.5 mcg/d the day before surgery followed by calcitriol 1 mcg/d and OC 3 g/d from POD1 (low dose S) 100 pts: NS unless evidence of PTH decrease > 50% at 4 h (PTH based S)	Hypocalcemia incidence (during hospitalization) no differences between groups Symptomatic hypocalcemia high dose S: 1/100 low dose S: 1/100 PTH based: 6/100, $p = 0.042$ Mean hospitalization length high dose S: 1.1 ± 0.5 d low dose S: 1.4 ± 0.5 d PTH based S: 2 ± 0.4 d, $p < 0.001$	[73]
Jin (2023)	Single blind RT, 209 pts with thyroid cancer	103 pts: OC 600 mg/d + alfacalcidol 1 mcg/d for 2 d 106 pts: placebo	Hypocalcemia POD1 OC+alfacalcidol group: 41.7% Placebo: 65.9%, $p < 0.05$ Hospitalization after TTx OC+alfacalcidol group: 2.79 ± 1.15 d Placebo: 3.55 ± 1.89 days, $p < 0.05$ No differences in mean postoperative Ca levels (POD1 and W 3) and hospitalization length in the hTx	[74]
Yosef (2025)	Retrospective cohort study, 1219 pts (11% GD)	491 pts: alfacalcidol 1 mcg/d for 5 d 728 pts: NS	No differences in the incidence of short (14.5 vs 15.7%) and long-term (3.9 vs 4.2%) postoperative hypocalcemia Thyrotoxicosis was associated to postoperative hypocalcemia	[72]

Abbreviations: Cholecal: cholecalciferol; GD: Graves' disease; NS: not supplemented; OC: oral carbonate calcium; OR: odds ratio; POD: postoperative day; PTH: parathyroid hormone, pts; RCT: randomized control trial; S: supplemented; hTx: hemithyroidectomy; VitD: Vitamin D supplementation (both cholecalciferol and activated formulations); p, comparison between groups of treatment.

compared to controls (13% vs. 36%) [67]. In a RCT of 219 patients operated on for various thyroid disorders, perioperative alfalcidol supplementation reduced the incidence of transient postoperative hypocalcemia and related symptoms [68] (Table 3). A prospective case-control study compared surgical outcomes of 45 GD patients treated with 3 g calcium carbonate daily for two weeks before surgery to those of 38 GD patients and 40 non-GD euthyroid controls not pretreated with calcium [69]. Preoperatively, serum calcium and parathyroid hormone (PTH) concentrations were similar in the three groups, VitD was not measured. Postoperatively, serum calcium levels were slightly, but significantly lower, and hypocalcemia-related symptoms significantly more frequent in the untreated groups [69]. Serum VitD deficiency may be a risk factor for postoperative hypocalcemia, as shown by a prospective clinical trial of 130 patients with nontoxic nodular goiter [70] and by two systematic reviews of observational studies (not limited to GD) [65,71]. Conversely, a retrospective study of 1219 patients (GD, only 11%) submitted to thyroidectomy showed that preoperative treatment with alfalcidol (1 mcg/day for 5 days) did not reduce the incidence of postoperative hypocalcemia [72]. In a study of 300 patients (130 with autoimmune thyroid disorders), the group receiving preoperative treatment with 1 mcg calcitriol the day before surgery, 1 mcg calcitriol 4 h after surgical procedure, 1 mcg calcitriol plus 3 g calcium carbonate starting on the day after surgery had a decrease in postoperative symptomatic hypocalcemia compared to the groups given a lower preoperative dose of calcitriol (0.5 mcg) or no preoperative treatment [73]. The incidence of post-thyroidectomy chronic hypoparathyroidism did not significantly differ in the three groups [73]. In a RCT study of 209 thyroid cancer (not GD) patients, a short preoperative course (two days) of alfalcidol (1 mcg/day) and calcium carbonate (600 mg/day) was associated with a significantly reduced incidence of postoperative (day 1) hypocalcemia and a shorter hospital stay compared to placebo-treated patients [74]. A systematic review and meta-analysis of 39 RCTs and 37 observational studies (mainly of low quality) concluded that the combination of VitD and calcium supplementation was more effective than calcium supplementation alone or no supplementation in preventing post-thyroidectomy transient hypocalcemia [75]. Surprisingly, a retrospective study of 397 patients showed that VitD deficiency might be a 'protective' condition hypothetically due to an earlier parathyroid function recovery after surgery [76]. The results of the above studies are not unequivocal for several reasons, including the retrospective design and the small sample size of many studies, the frequently low quality of systematic reviews and meta-analyses, the frequent lack of specific evaluation of GD patients. These uncertainties are mirrored by the recommendations of major scientific societies. The American Thyroid Association guidelines recommend that calcium and 25OH-VitD should be assessed preoperatively and repleted if necessary or given prophylactically (strong recommendation, low-quality evidence) [34]; the European Thyroid Association guidelines recommend that vitD deficiency should be corrected to reduce the risk of postoperative hypocalcemia (strong recommendation, high-quality evidence) [11]; the American Endocrine Surgeons guidelines state that prior to

surgery for GD calcium and 25OH-VitD may be assessed and repleted or supplemented prophylactically (strong recommendation) [18].

Summary: Restoration of euthyroidism by ATDs is the standard of preoperative care for GD patients. Surgery can be performed in patients with only partially controlled hyperthyroidism if the surgeon and the anesthesiologist are highly expert in this clinical setting. The preoperative administration of KI in euthyroid patients under ATD treatment is controversial (and infrequently used), but it is certainly useful (together with other treatments) in patients with uncontrolled hyperthyroidism, because it inhibits T4-to-T3 conversion. Evidence concerning preoperative supplementation with calcium and/or VitD in the absence of VitD deficiency is controversial, but current guidelines substantially agree that calcium and VitD should be assessed preoperatively and repleted, if necessary.

4. Complications of thyroidectomy

Main complications of thyroid surgery are hypoparathyroidism, RLN injury, and neck hematoma.

4.1. Hypoparathyroidism

The prevalence of all-cause chronic hypoparathyroidism is between 6.4 and 37 per 100,000 [77]. Post-surgical hypoparathyroidism accounts for 75% of all cases and, although occurring mainly after thyroid surgery, may develop after parathyroidectomy or other neck surgeries [78,79]. Postoperative hypoparathyroidism may be caused by either accidental removal of one or more parathyroid glands or their devascularization during thyroidectomy [77]. The number of postoperatively functioning parathyroid glands is relevant, since the risk of postoperative hypocalcemia is 16% if 1–2 parathyroid glands are preserved, 6% for three glands, and 2.5% for four glands [79]. Recent guidelines recommend that circulating PTH values should be measured within 12–24 h after total thyroidectomy, because a value >10 pg/ml virtually excludes subsequent permanent hypoparathyroidism [78,79]. It is worth noting that some patients with early postoperative PTH value <10 pg/ml may recover normal parathyroid function over time [80]. In addition to other factors, including female sex, young age, preoperative VitD deficiency, GD *per se* is a risk factor for postoperative hypocalcemia [65,81] (Figure 4). The higher frequency of hypoparathyroidism in these groups may reflect the prevalence of GD among women and younger individuals. Other factors possibly contributing to the increased frequency in women include smaller parathyroid gland size, the presence of estrogen receptors in normal parathyroid tissue, and postmenopausal changes, such as reduced vitamin D levels, increased bone turnover, decreased bone mineral density and loss of the modulating effect of estrogens on bone metabolism [82].

The relationship between obesity and the risk of postoperative hypoparathyroidism remains debated, as several studies have reported no significant association. However, in a large systematic review and meta-analysis, obesity was associated with a significant reduced risk (odds ratio, 0.79) of

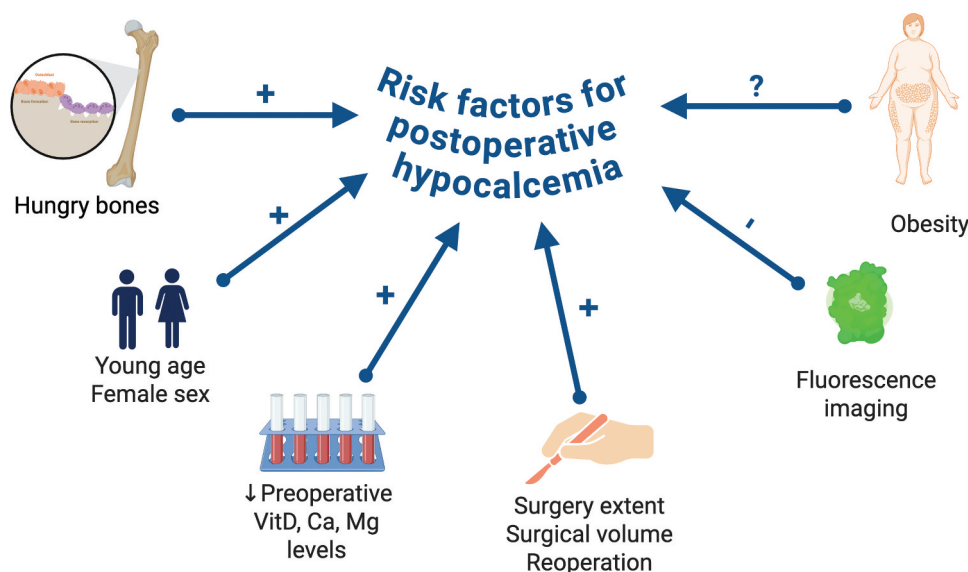


Figure 4. Risk factors for post-thyroidectomy hypocalcemia. Ca: calcium; Mg: magnesium; VitD: vitamin D; +: increased risk of postoperative hypocalcemia; -: reduced risk of postoperative hypocalcemia. Created in BioRender, Gallo, D. (2026) <https://BioRender.com/er1y3yb>.

postoperative hypoparathyroidism [83]. In a retrospective analysis of 352 patients undergoing total thyroidectomy, the protective effect of a higher body mass index was independent of either VitD levels or the number of visualized parathyroid glands [84]. Potential explanations include a protective role of the cervical fat pad during surgical dissection and the positive association between PTH levels and adiposity ('Obesity paradox').

Postoperative hypoparathyroidism may be transient or permanent, the latter being defined by the persistence of hypocalcemia in the presence of undetectable/low/inappropriately normal circulating PTH values ≥ 12 months after surgery [78,79]. The latter time-point seems more reliable than the 6-month time-point. In fact, a review of 8,832 thyroid surgeries from several series showed that early postoperative hypocalcemia occurred in 2981 patients (33.8%); of the latter, 73.9% recovered normal parathyroid function within 6 months, but an additional 7.4% normalized between 6 and 12 months [78].

Fluorescence-based imaging techniques for identifying parathyroid glands and their vessels intraoperatively have been developed. Near-infrared autofluorescence (NIRAF) can help obtain an earlier and more frequent identification of the parathyroid glands and decrease the rate of accidental parathyroidectomy. A meta-analysis of nine RCTs including 1363 patients submitted to total thyroidectomy for both benign and malignant thyroid disorders showed that the use of NIRAF reduced the rate of early postoperative hypocalcemia, but not the incidence of permanent hypoparathyroidism [85]. Contrast-enhanced fluorescence imaging (indocyanine green [ICG] angiography) helps identify parathyroid glands' vessels at the beginning of surgery [86]. A recent systematic review and meta-analysis of 28 studies (including nine RCTs) showed that fluorescence imaging (either NIRAF, ICG, or both) may reduce early (day 1) postoperative hypocalcemia and short-term hypoparathyroidism [87]. Both NIRAF and ICG angiography may be useful in detecting parathyroid gland(s) viability

and vascular integrity, guiding the decision of whether proceeding to selective parathyroid gland autotransplantation. These techniques require a fluorescence system but may be helpful, especially in low-volume institutions. Recent guidelines state that 'standardization of the technique, as well as long-term randomized controlled studies, are required to truly assess any sustained beneficial effect of NIRAF [and ICG angiography] on parathyroid function' [79].

Treatment of post-surgical chronic hypoparathyroidism relies on the use of calcium and activated VitD metabolites [88]. Typical doses of VitD metabolites are: calcitriol [1,25(OH)₂D]: 0.25–2 mcg once or twice daily; alfacalcidol [1 α (OH)D₃]: 0.5–4 mcg once daily; dihydrotachisterol: 0.3–1 mcg once daily [79]. In the liver alfacalcidol is rapidly activated to 1,25(OH)₂D, and dihydrotachisterol to 25(OH)D dihydrotachisterol [79]. Dietary calcium intake should be optimized and supplemented, if serum calcium target levels are not reached, with either calcium carbonate (taken with meals) or calcium citrate (taken independently of food intake), in doses ranging 0.5–3 g daily, monitoring serum calcium and phosphorus levels, and urinary calcium excretion [77]. If serum magnesium is low, magnesium deficiency should also be corrected because it can worsen hypocalcemia. In some cases, thiazide diuretics are used to decrease urinary calcium excretion, thereby reducing the risks of kidney complications, such as kidney stones and nephrocalcinosis [77]. Early postoperative severe and symptomatic hypocalcemia should be promptly corrected by intravenous calcium gluconate. PTH replacement therapy is an important issue. For the time being, the pegylated form of PTH(1–34), palopegteriparatide, is the only PTH replacement therapy approved by the European Medicines Agency and the Food & Drug Administration for chronic hypoparathyroidism [79], but long-term data are still limited. Ongoing studies are evaluating parathyroid allotransplantation, parathyroid cell transplantation, and parathyroid organoids, but results are too preliminary to foresee their possible use in clinical practice.

4.2. Recurrent laryngeal nerve injury

RLN injury is a major complication of thyroidectomy with significant implications for patient voice function, airway protection, and HR-QoL. It may be transient, due to vocal folds edema following endotracheal intubation, or permanent. Early postoperative fiberoptic laryngoscopy is more reliable than symptomatic voice assessment in diagnosing RLN injury [89], with a sensitivity and negative predictive value of 92% and 98%, respectively [90]. Transient RLN injury usually resolves in few days, but sometimes it takes weeks to months for a full recovery. GD *per se* is an independent risk factor for RLN injury [91]. As shown by a systematic review and meta-analysis of 10 studies (mostly retrospective) including 108,153 patients, obesity is associated with a 15% increased risk of RLN injury [83]. A careful surgery technique with direct visualization of the nerve has been the standard of care for avoiding this complication, but since many years intraoperative neuromonitoring (IONM) has been introduced to decrease the risk of RLN injury [92]. Results of several systematic reviews and meta-analyses have provided conflicting results on IONM true effectiveness, possibly because of methodological bias, including lack of i) differentiation between continuous and intermittent IONM, ii) analysis of different stimulation amplitudes, and iii) evaluation of neuromuscular blockade. A recent systematic and meta-analysis included 103 studies (RCTs, prospective studies, and retrospective cohorts) involving 132,212 patients submitted to thyroidectomy, irrespective of diagnosis, surgical approach, and extent of surgery [93]. This study showed a 38% reduction in transient unilateral RLN injury and a 51% reduction in permanent RLN injury using IONM; in addition, continuous (rather than intermittent) IONM, lower amplitude (<2 mA), and avoidance of neuromuscular blockade had a protective effect on RLN injury [93]. In a recent, large-volume single-center retrospective analysis of 1263 total thyroidectomies, IONM was associated with a significant reduction in permanent RLN injury and a faster recovery from transient RLN injury [94]. IONM has been reported to reduce also the risk of damage to the external branch of the superior LN during superior thyroid pole dissection [95].

Voice rehabilitative therapy due to unilateral RLN injury is frequently followed by full recovery of normal vocal fold function [90].

4.3. Postoperative hematoma

Postoperative neck hematoma is an infrequent, but serious and potentially life-threatening complication of thyroidectomy, and a relevant cause or readmission/reoperation. Analysis of an Austrian database of 30,142 thyroidectomies over a 30-year period evidenced postoperative bleeding in 519 cases (1.7%) [96]. Similar incidence rates were found in a study of the UK Registry of Endocrine & Thyroid Surgery (449 cases out of 39,014 thyroidectomies, 1.2%) [97], in a report from a Serbian tertiary center (72 cases out of 6938 procedures, 1.04%) [98], and in a Japanese report (incidence rate, 1.85%) [99]. Identified risk factors include male sex, older age, retrosternal goiter, preoperative antiplatelet/anticoagulant therapy, postoperative heparin therapy, total thyroidectomy,

reoperation [96–98], and obesity [83]. Postoperative bleeding occurs within 6 h in 80% of cases [93], within 24 h in 95% of cases [97]. Reoperation may be needed in about 1% of cases, tracheostomy may rarely be required, mortality rate is about 0.1% [99]. Most relevant to this review article, GD *per se* is a significant risk factor for postoperative bleeding. A systematic review and meta-analysis of 11 studies (10 retrospective, one prospective; 48,381 patients, including 3185 GD patients) showed that GD was the only indication for thyroid surgery having an increased risk for postoperative neck hematoma [100]. More recently, in a North American surgical cohort of 17,906 patients (1207 with GD), GD had the highest odds of postoperative neck hematoma (odds ratio, 1.65, 95% CI, 1.10–2.46) and hypocalcemia (odds ratio, 2.04, 95% CI, 1.66–2.50) compared to other indications for thyroid surgery [81]. The reasons underpinning this increased risk are unclear but may include the increased thyroid vascularization in GD. Although overnight thyroidectomy has been reported in a retrospective study to lead to higher patient satisfaction compared to a 3-day hospital stay [101], the possible increased risk inherent to GD suggests caution in the adoption of outpatient/overnight thyroidectomy in GD, or, at least, a very careful selection of patients (young patients, well controlled hyperthyroidism, no coagulation abnormalities) in high-volume centers. In this regard, it is worth noting that in the above mentioned North American study, most GD patients with a postoperative neck hematoma were inpatients, suggesting that patients, such as GD patients, bearing a higher risk of postoperative neck hematoma, are likely monitored as inpatients after thyroidectomy [81]. This is very important in the elderly, because of the slight increase in the risk of hematoma and RLN injury, as shown in a recent systematic review and meta-analysis of 11 studies (10 retrospective and 1 prospective) including >100,000 patients aged ≥ 65 years [102].

Measures to minimize the risk of postoperative neck hematoma include intraoperative careful hemostasis, postoperative maintenance of normal blood pressure, control of pain, cough, nausea and vomiting.

Summary: Surgery is the main cause of chronic hypoparathyroidism. Its diagnosis relies on circulating PTH values <10 pg/ml 12–24 h after surgery. It may be transient or permanent (if persisting ≥ 12 months after surgery). Fluorescence-based imaging techniques (NIRAF, ICG angiography) may help reduce the incidence of postoperative hypoparathyroidism. IONM reduces the risk of RLN injury. Postoperative neck hematoma is a rare, but serious complication of thyroid surgery. Most importantly, GD *per se* represents an independent risk factor for postoperative occurrence of hypoparathyroidism, RLN injury, and neck hematoma, suggesting the adoption of an inpatient approach in high-volume institutions.

5. Relation between thyroidectomy and Graves' orbitopathy

The choice of the optimal treatment of GD in the presence of GO, as well as the effects of treatments for hyperthyroidism on GO are highly debated, as recently reviewed [9]. In general, particular attention has been paid to the possible deterioration or *de novo* occurrence of GO after RAI treatment, which

has been demonstrated in RCTs in patients with mild and active GO [103,104]. It is widely recognized that ATDs are neutral as to the course of GO [105], and restoration of euthyroidism by ATDs and its stable maintenance may be associated with beneficial effects on GO [9].

As far as the effects of surgery on the course and outcome of GO are concerned, in a RCT study, 168 Graves' patients were divided into two groups, group 1 (age, 20–34 years) and group 2 (age, 35–55 years) [103]. Group 1 patients were treated with either ATDs ($n=27$) or subtotal thyroidectomy ($n=27$); at the end of follow-up GO developed or progressed in 4 of 27 medically-treated patients (15%) and 3 of 27 surgically-treated patients (11%), with no significant difference between the two groups [103]. Among the older age patients (group 2), progression/development of GO occurred in 4/38 patients treated with ATDs (10%) and 6/37 patients submitted to subtotal thyroidectomy (16%), differences between the two groups being insignificant also in this case [103]. In a case-control study, 30 patients with GD and absent/mild GO submitted to near-total thyroidectomy were matched with 60 patients treated with ATDs: GO progressed in one patient with preexisting GO in the surgical group (3%) and developed in two patients medically treated (3%) [105]. In a prospective database cohort study of 48 GD patients treated by either total ($n=46$) or subtotal ($n=2$) thyroidectomy, among 20 patients with GO prior to surgery, stabilization/improvement of the disease was reported after surgery at the end of follow-up [106]. In a recent Bayesian meta-analysis of 22 cohort studies (17 retrospective, 5 RCTs) including 131,297 GD patients, the risk of GO progression/development after thyroidectomy was lower than using ATDs (hazard ratio, 0.54) or RAI treatment (hazard ratio, 0.62); however, when only RCTs were considered, no differences were detected between ATDs and thyroidectomy [107]. In a RCT of 42 patients with moderate-to-severe and active GO treated with intravenous glucocorticoids (IVGCs) and randomly assigned to either ATD treatment ($n=24$) or total thyroidectomy ($n=18$), no significant differences between the two groups were observed as to the outcome of IVGC treatment [108]. In a retrospective cohort study of 92 patients treated with IVGC for moderate-to-severe and active GO, early thyroidectomy was associated with a slightly higher rate of GO inactivation compared to ATDs [109]. In a retrospective study of 80 GD patients initially treated with ATDs, 40 were submitted to surgery and 40 to RAI treatment [110]. Before the definitive treatment, active GO was present in 13 patients of the surgical group and in 4 of the RAI group; at the end of follow-up, eye involvement was reported in only 5 patients treated surgically, but in 7 patients treated with RAI (110). As shown by two RCTs [111,112] and two retrospective studies [113,114], thyroidectomy followed by RAI remnant ablation (so-called total thyroid ablation) is associated with an earlier response to IVGC therapy for moderate-to-severe and active GO compared to total thyroidectomy alone, although this difference does not persist at a longer follow-up [114].

Summary: Thyroidectomy has no negative impact on development of GO or progression of mild GO. In patients with moderate-to-severe and active GO, early thyroidectomy (with or without RAI remnant ablation) may be associated with an

earlier response to immunosuppressive treatment, but large, multicenter, prospective studies are needed to substantiate this benefit.

6. Cardiovascular outcomes in Graves' patients after thyroidectomy

Hyperthyroidism (both subclinical and overt) increases the risk for all-cause mortality, cardiovascular (CV) morbidity and mortality, and MACE [115]. It is worth noting that the risk for mortality and MACE, including AF and arterial embolism, is highest in the first three months after diagnosis, but it remains higher than in controls during long-term (>2–3 years) follow-up [116,117]. The CV risk is higher in untreated than in treated patients and increases per every 6 months of decreased/suppressed TSH, i.e. of a suboptimal control of hyperthyroidism [15,16]. In a nationwide register-based Danish study of >30,000 GD patients, mortality in GD, particularly in males, was increased compared to the control population [118]. The association of hyperthyroidism with all-cause mortality, acute myocardial infarction, and CV disease was supported by additional large dataset-based studies [117,119]. This suggests that, in addition to prompt restoration and stable maintenance of euthyroidism, a definitive treatment for hyperthyroidism might be indicated particularly in at-risk groups (elderly, obese, smokers, patients with diabetes, hypertension, dyslipidemia, severe/unstable hyperthyroidism). In a Finnish large comparative cohort study, hospitalizations due to all CV complications were more frequent in patients treated with RAI than in patients submitted to thyroidectomy [120]. However, this difference held true only if RAI treatment did not cause permanent hypothyroidism [120], which should represent the deliberate goal of both RAI treatment and thyroidectomy. A registry-based study from Sweden [121] reported that in hyperthyroid patients (particularly men) thyroidectomy was associated with a long-term reduction in overall mortality compared to patients treated with RAI, possibly due to faster eradication of hyperthyroidism by surgery. In a retrospective, population-based study from Korea, GD patients treated surgically had a similar risk of AF compared to controls, while the risk was higher in patients treated with ATDs or RAI [122]. Interestingly, longer duration of ATD treatment increased the risk of AF [122], suggesting the opportunity of an early definitive treatment in at-risk patients. Likewise, in a retrospective study of 1371 GD patients from the Mayo Clinic, ATD treatment was associated with a higher risk of late AF than RAI treatment or thyroidectomy, although this difference did not persist at multivariable regression analysis [123]. This suggests but does not prove that the longer time required to restore euthyroidism using ATDs, compared to the other two treatments, may be an important risk factor for late AF. In a recent analysis of the UK Biobank, surgically-treated patients had a significantly reduced all-cause mortality compared to ATD-treated patients, who had a significantly higher risk of AF, likely reflecting periods of poorly controlled hyperthyroidism [124]. These results are in keeping with a large health insurance database study from Taiwan of 144,062 newly diagnosed hyperthyroid patients (precise etiology of hyperthyroidism not defined), showing that

hyperthyroid patients submitted to thyroidectomy had a lower rate of MACE, all-cause mortality, heart failure, and CV mortality than ATD-treated patients [125].

Summary: The above studies are predominantly retrospective, observational, or registry-based and are subject to confounding by indication. However, they overall suggest that early correction of hyperthyroidism by total thyroidectomy may decrease the CV risk associated with thyroid hormone excess. This is particularly relevant in at-risk GD patients, who may benefit from early eradication of hyperthyroidism, thereby preventing the risk of dangerous periods of fluctuations of thyroid status and relapsing hyperthyroidism.

7. Quality of life after thyroidectomy

GD and, in general, hyperthyroidism heavily impact on HR-QoL, impairing physical and social function, mental health and overall wellbeing. Impairment of HR-QoL is often detectable years after hyperthyroidism has been cured [126,127]. In some instances, hyperthyroidism may not only affect social relations but may also have deleterious effects on economic status ([128]. A review of 75 studies showed that 18–66% of hyperthyroid patients (both toxic nodular goiter and GD) had limitations in daily activities and general health perception, with social and emotional impairment [127]. Not surprisingly, GO, when present, is an important contributor to the impairment of HR-QoL, because of the changes in appearance and functioning of the eyes [129]. Relevant psychosocial consequences of GO include impaired self-perception, restrictions in daily activities, sick leave absence, early retirement, job loss [130]. In a survey of 443 respondents to a home-made questionnaire, 179 of 394 respondents with GO (45%) felt depressed and/or anxious, 174 (44%) mentioned concern about their appearance, 73 (19%) were socially isolated, 192 (49%) complained of decreased confidence and well-being, with impact on reading, driving and socializing [131].

Evaluation of the effects of GD therapies on HR-QoL is difficult because of the retrospective design of most studies, presence/absence of comorbidities, age, presence/absence of preexisting GO, confounding by indication. In a prospective RCT of 174 GD patients, >90% were satisfied or very satisfied with the treatment for hyperthyroidism, with no difference between ATD vs. RAI or thyroidectomy, also regarding work ability and social life [128]. A follow-up study of the same cohort 14–21 yr later again found no differences in the outcome of patients submitted to either therapy, although all patients, irrespective of the treatment for hyperthyroidism, complained of a decreased vitality and mental QoL, possibly related to an imperfect control of thyroid function, perception of disease, psychological vulnerability, missing expectations, or other factors [126]. In a non-RCT of 1186 patients evaluated 6–10 years after diagnosis, HR-QoL was similar in patients treated with ATDs or surgery, and slightly worse in patients receiving RAI treatment [132].

Conventional transcervical thyroidectomy for benign and malignant disorders leaves a visible scar causing not only a cosmetic concern, but, possibly, sensory disturbances, including hyposthesia, paresthesia and discomfort [133]. It is not surprising that a visible scar may have a negative impact on HR-QoL

[134], although evidence is not unequivocal. Interestingly, a recent cross-sectional survey study of 1334 patients submitted to transcervical thyroidectomy showed that scar perception improved progressively within the first two years after surgery and was a primary driver of the associated improvement in HR-QoL [134]. Improvement in scar perception-related HR-QoL was associated with age (>40 years) and sex (males >females), suggesting that young patients, particularly women, prioritize appearance [134]. Remote access thyroidectomy offers the potential for an improved cosmetic outcome by avoiding a visible scar. A recent systematic review and meta-analysis included three studies which compared transcervical thyroidectomy to either transoral endoscopic thyroidectomy or transaxillary thyroidectomy [135]. Although the individual studies favored remote-access thyroidectomy in terms of HR-QoL improvement, their meta-analysis showed that differences with transcervical thyroidectomy were insignificant, possibly due to heterogeneity and small sample size of the studies [135].

Hyperthyroidism is usually characterized by weight loss, while restoration of euthyroidism is associated with weight regain, sometimes in excess of the pre-illness weight. Severity of hyperthyroidism appears to be a risk factor for excessive weight regain [136]. Obesity has a negative impact on HR-QoL [137]. A systematic review and meta-analysis of 17 studies with 3164 patients (only five studies [$n = 431$] included patients with hyperthyroidism) submitted to total thyroidectomy, with a mean follow-up of about two years, reported an estimated overall weight gain of 2.13 Kg, but this effect was significantly more pronounced in hyperthyroid patients, whose weight gain was 5.19 Kg after surgery [138]. The weight gain was negatively associated with age, but not with sex [138]. Weight gain after thyroid surgery (not limited to GD), even in the presence of good control of post-surgical hypothyroidism, is a relevant cause of patient dissatisfaction and reduced HR-QoL [139]. A recent cross-sectional analysis of a prospectively completed database of 108 hyperthyroid patients (etiology not specified), 74% of whom treated with ATDs alone, showed that, despite normal TSH values in about 80% of patients, there was a mean weight increase of 7.2 Kg (mean percent weight gain, 8.8%) over a 41-month duration of disease [140]. Weight gain was an independent predictor of poorer HR-QoL outcomes, specifically in cosmetic complaints, tiredness and overall HR-QoL domains [140]. Mechanisms underpinning weight increase after correction of hyperthyroidism, including the use of thyroidectomy, remain unclear. In a recent small longitudinal study, weight gain after thyroidectomy for GD was largely attributable to a significant increase in skeletal muscle mass (but not in fat mass) compared to pre-surgical analysis of body composition [141]. In any case, given its effects on HR-QoL and the long-term consequences of overweight/obesity, weight control should be part of a comprehensive management of GD, including patients treated surgically [142].

Summary: HR-QoL is severely affected in GD patients, especially if complicated by GO. Restoration of euthyroidism is usually followed by an improvement in the HR-QoL, although the latter may remain suboptimal years after treatment of hyperthyroidism and irrespective of the type of treatment. Scar perception is a relevant and surgery-specific factor

influencing post-surgical HR-QoL, which may be reduced by minimally invasive or remote access procedures. Excessive weight regain after treatment of hyperthyroidism is an important factor affecting HR-QoL, but is not specific for thyroidectomy.

8. Management of post-thyroidectomy hypothyroidism

Hypothyroidism is the unavoidable consequence of total thyroidectomy, and is not a complication, but rather the desired goal in GD patients. Ideally replacement treatment should: i) restore biochemical and tissue euthyroidism, avoiding overtreatment and undertreatment; ii) abolish signs and symptoms of hypothyroidism, thereby normalizing HR-QoL; iii) avoid iatrogenic thyrotoxicosis. The current standard of care is levothyroxine (LT4) monotherapy, a synthetic form of the main (pro)hormone synthesized by the thyroid gland [143,144]. The other thyroid hormone, liothyronine (LT3), which is metabolically active, mostly (80%) derives from peripheral deiodination of T4 mediated by deiodinases (DIO), but is in part (20%) synthesized by the thyroid gland [145]. Thus, to mimic physiology, replacement therapy in athyreotic patients should in principle rely on the combination of both LT4 and LT3 [146]. However, for the time being, combination therapy is controversial, due to the conflicting results of published studies.

Treatment of hypothyroidism is not as easy as it might appear. Optimal timing of initiation of therapy is unsettled. Guidelines either do not provide clear indications [11,34] or indicate to wait for one week after surgery [18]. Based on the observation that serum free T3 levels rapidly decline on day 1 postoperatively, others propose an earlier institution of treatment to prevent even short periods of hypothyroidism [147]. Many patients are either under- or overtreated [148], and both conditions are associated with an increased CV risk and excess mortality [148]. About 10–15% of LT4-treated patients are dissatisfied and complain of symptoms, such as fatigue, low energy, brain fog, memory deficit, low mood, resulting in decreased HR-QoL [149,150]. This has been attributed to psychosocial factors, unrealistic patient expectations, comorbidities [151]. In patients whose hypothyroidism represents the progression of chronic autoimmune (Hashimoto's) thyroiditis or the consequence of total thyroidectomy for Graves' disease, autoimmunity might play a role in this dissatisfaction, although the underpinning mechanisms are unclear [150]. Studies in athyreotic animals showed that euthyroidism can be restored in all tissue only by combination therapy [152]. Thus, persisting symptoms reported in some athyreotic patients treated with LT4 might also be contributed to by imperfect restoration of biochemical and tissue euthyroidism. In a study of 1181 athyreotic patients with normal serum TSH values under LT4 treatment, about 15% of patients had serum free T3 (FT3) below the normal range, while 7% had serum FT4 values above the upper normal range, with a resulting decrease in the FT3/FT4 ratio [153]. Another study also showed that, compared to preoperative FT4 concentrations, postoperative higher serum FT4 levels were required to reach

the preoperative serum TSH levels; however, this was not associated with decreased serum FT3 levels [154]. Athyreotic LT4-treated patients carrying type 2 DIO Thr92Ala polymorphisms have lower postoperative serum FT3 concentration compared to wild-type allele patients [155]. Carriers of the above type 2 DIO homozygous polymorphism were reported to have an impaired HR-QoL at baseline in the General Health and Anxiety/Depression domains and showed a greater improvement in HR-QoL if treated with the combined therapy [156]. According to a small Danish study, carriers of the type 2 DIO Thr92Ala and monocarboxylate transporter (MCT)10 polymorphisms more frequently preferred the combined treatment [157]. These findings are not unequivocal, since in a Dutch large, population-based cohort study of 12,625 participants, the Thr92Ala type 2 DIO polymorphism had no effect on thyroid parameters, HR-QoL, and cognitive functioning [158]. Several clinical trials (mostly with a parallel or crossover design) evaluated combination therapy to LT4 monotherapy, with inconsistent results as to improving symptoms and HR-QoL in patients dissatisfied with LT4 alone. In a recent double-blind, placebo-controlled RCT, 141 athyreotic patients were treated with either LT4 + LT3 (in refracted doses) or LT4 monotherapy; the dose of LT3 was calculated to maintain a T4:T3 ratio of 13:1 to 20:1 [159]. At six months, no significant differences in the HR-QoL and serum sex-hormone binding globulin (a peripheral tissue surrogate marker of thyroid hormone action) were found; no patient preferred the combined treatment despite the increase in FT3/FT4 ratio; dose adjustment during the study period was greater in the combination therapy group [159]. At variance, a recent systematic review, meta-analysis, meta-regression of 11 RCTs (eight crossover) including 1135 patients reported patient preference for the combined therapy over LT4 monotherapy [160]. Likewise, a systematic review and meta-analysis of 18 studies showed that a higher proportion of patients (43%) preferred the combined treatment compared to LT4 monotherapy (23%), with >30% of patients having no preference [161]. Accordingly, it has been emphasized that the choice of replacement regime for hypothyroidism should be the result of a patient-centered shared decision-making process [162]. Recent data from a multisource systematic review and meta-analysis of 52 studies (21 RCTs, 4 cohort studies, 27 case reports) reported that LT3 use, if regulated, i.e., not associated to suprathreshold doses, compounding errors, or misuse for weight loss and bodybuilding, is not bound to an increased risk of adverse events and death [163]. The use of LT3 (in combination with LT4) has been insofar hampered by the short life of the current preparations, requiring multiple daily administration, possibly impacting on patient compliance with therapy, and potentially causing dangerous daily fluctuations in serum FT3 levels. This limitation might be overcome by slow-release LT3 formulations providing stable FT3 concentrations. For the time being, while waiting for larger, multicenter, better designed RCTs, according to current guidelines LT4 monotherapy remains the gold standard treatment for hypothyroidism under most circumstances ([143]. A survey of >6000 specialists from 28 European countries confirmed that LT4 monotherapy is the prevalent initial treatment for hypothyroidism [151]. In selected patients with persistent symptoms despite

biochemical euthyroidism, a trial of combination therapy may be a valid option [164].

Recent guidelines have updated the issue of treatment of hypothyroidism with LT4 as monotherapy [144,165]. A detailed description of the recommendations is beyond the scope of this review article. The main key-points are hereby summarized: i) LT4 tablet should be taken on an empty stomach at least 30 min (ideally 60 min) before breakfast or at bedtime (≥ 3 hours after dinner); ii) if the patient is switched to another brand, thyroid status should be checked after 6 weeks; iii) the daily dose of LT4 should be comprised between 1.5–1.7 mcg/kg in patients with thyroid *in situ*, 1.8–2.0 mcg/kg in athyreotic patients, with the aim of maintaining serum TSH within the normal range; iv) if the daily dose exceeds the common doses, patient compliance, drug or nutrients interference, comorbidities should be searched for; v) in obese patients the lean mass is the major determinant of LT4 dose; vi) switching to the (more expensive) liquid solution or soft gel formulations of LT4 can be considered in the presence of malabsorption; vii) liquid formulations may be preferentially used in the unconscious or enterally fed adult patient and in the infant [144,165].

Summary: Hypothyroidism is the desired goal of total thyroidectomy in patients with GD. The current standard of care of hypothyroidism is LT4 monotherapy, although a more physiological replacement should be based on a combination of LT4 and LT3. In selected patients with persistent symptoms of hypothyroidism and dissatisfaction with LT4 monotherapy, small doses of LT3 may be added. Large, multicenter RTCs are warranted to establish whether the combined therapy is superior to LT4 monotherapy.

9. Conclusions

This review analyzed pros and cons of thyroidectomy for the management of hyperthyroidism due to Graves' disease.

All available treatments for GD are imperfect, because they do not target relevant pathogenetic step of the disease. Compared to ATDs and RAI treatment, thyroidectomy is the least used first-line treatment, but it is useful and effective not only in patients with relapsing hyperthyroidism, but also as the initial therapy in patients in whom prompt eradication of the disease is warranted because of high cardiovascular risk. If surgery is selected, total thyroidectomy, rather than more conservative approaches, is the procedure of choice, because it eliminates the risk of a recurrence of hyperthyroidism. Thyroidectomy bears a low risk of complications if performed by a high-volume surgeon.

Whenever possible, hyperthyroidism should be controlled by ATDs prior to surgery. Recent studies have challenged the preoperative use of KI, which is still useful in patients whose hyperthyroidism is only partially controlled. VitD deficiency should be corrected prior to surgery, to reduce the risk of postoperative hypocalcemia;

Fluorescence-based techniques (NIRAF, ICG angiography), through visualization of parathyroids and their vessels, seem to reduce the risk of postoperative hypocalcemia, while intraoperative neuromonitoring helps reduce the risk of RLN injury.

GD *per se* represents a risk factor for the occurrence of the main surgical complications, hypocalcemia, RLN injury and postoperative neck hematoma.

Hypothyroidism is the desired goal of thyroidectomy in GD. The current standard of care is represented by LT4 monotherapy.

10. Expert opinion

The available treatments for GD have drawbacks and limitations. Pharmacological treatment with ATDs is not devoid of toxicity and is bound to a high rate of relapses (about 50%) [7]. Recent studies showed that after prolonged (>5 years, up to 20 years) ATD treatment achieves remission of hyperthyroidism in a larger proportion (around 80%) of patients, but not in all of them [9]. RAI treatment and total thyroidectomy, particularly the latter, are extremely effective in eradicating hyperthyroidism, but inevitably cause hypothyroidism and the related need for lifelong thyroid hormone replacement therapy (7). Therapy of hypothyroidism is not that simple because potentially dangerous periods of overtreatment and undertreatment are not infrequent [148]. On the other hand, the risks of uncontrolled/relapsing hyperthyroidism for the CV system, mortality, fertility, cancer, GO should not be overlooked, and definitive eradication of hyperthyroidism may represent the best way to prevent them, especially in at-risk patients, who are old, obese, smokers, diabetic, or with concomitant/preexisting CV disorders.

In view of the above uncertainties, the choice between very long-term (maybe lifelong) ATD treatment or lifelong thyroid hormone replacement therapy (after RAI or thyroidectomy), one disease (hyperthyroidism) or another disease (hypothyroidism), should be patient-centered within a thorough, shared decision-making process. In particular, a multidisciplinary approach is mandatory for the GD patient who is candidate for surgery, to achieve a meticulous preoperative control of hyperthyroidism (endocrinologist), a safe surgical procedure (skilled high-volume surgeon and anesthesiologist), expertise in the early postoperative management of complications (surgeon and endocrinologist), lifelong thyroid hormone replacement therapy (endocrinologist) and management of chronic hypoparathyroidism (endocrinologist).

In clinical practice and in keeping with current guidelines [11,18], under most circumstances and unless the patient is willing to go immediately for a definitive treatment, our approach in patients with newly diagnosed GD is to use ATDs as the first-line treatment for an 18–24-month course. Persistence of detectable, but declining serum TSHR-Ab levels around the end of the ATD course may suggest continuing ATD treatment beyond 18–24 months. If hyperthyroidism is poorly controlled or unstable in an apparently compliant patient during the first ATD course (and TSHR-Ab levels remain very high), we propose the patient to go for a definitive treatment before the end of the drug treatment course. If hyperthyroidism relapses after the first ATD course, we thoroughly discuss with the patient the pros and cons of the two options, i.e., a second course of ATDs or a definitive treatment.

11. Five-year view

Pilot studies for the treatment of GD have been carried out with the goal of restoring immune tolerance, contrasting B lymphocytes, blocking stimulatory TSHR-Ab or interfering with their binding to the TSH receptor, and blocking recycling of TSHR-AB [see refs. [166,167] for recent reviews]. Results of these studies are promising, but very preliminary. It seems unlikely that in the next five years we will witness a definitive answer to the question of how to 'cure' GD. We will have to keep on using current therapies for (many?) years to come before surgeons or nuclear medicine specialists go out of the business in the field of GD. As far as surgical treatment of GD is concerned, we expect that further refinement of surgical techniques contributes to improving the outcomes of thyroidectomy, already excellent in the hands of skilled surgeons.

Author contributions

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