A review of treatment options for Graves’ disease: why total thyroidectomy is a viable option in selected patients

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Graves’ disease is the most common cause of hyperthyroidism. If left untreated, patients may have multiple systemic complications such as cardiac, reproductive, and skeletal disease. Thionamides, such as methimazole and propylthiouracil, and I131 iodine ablation are the most commonly prescribed treatment for Graves’ disease. Total thyroidectomy is often overlooked for treatment and is usually only offered if the other options have failed. In our case, we discuss a patient who was admitted to our medical center with symptomatic hyperthyroidism secondary to long-standing Graves’ disease. She had a history of non-compliance with medications and medical clinic follow-up. The risks and benefits of total thyroidectomy were explained and she consented to surgery. A few months after the procedure, she was biochemically and clinically euthyroid on levothyroxine. She had no further emergency room visits or admissions for uncontrolled thyroid disease. Here we review the advantages and disadvantages of the more typically prescribed treatments, thionamides and I131iodine ablation. We also review the importance of shared decision making and the benefits of total thyroidectomy for the management of Graves’ disease. Given the improvement in surgical techniques over the past decade and a significant reduction of complications, we suggest total thyroidectomy be recommended more often for patients with Graves’ disease.

Keywords: hyperthyroidism; thionamides; methimazole; propylthiouracil; iodine ablation; thyroid surgery

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Received: 23 May 2016; Revised: 6 July 2016; Accepted: 8 July 2016; Published: 7 September 2016

Graves’ disease, the most common cause of hyperthyroidism, is an autoimmune disease resulting in overproduction of thyroid hormone. If left untreated, patients with Graves’ disease may experience multiple systemic complications including cardiovascular, respiratory, metabolic, reproductive, and skeletal dysfunction (1). Patients may also have neuropsychiatric manifestations of the disease such as emotional lability, anxiety, restlessness, and insomnia. It is not uncommon for these symptoms to increase gradually over time even before the patient is diagnosed with the disease, negatively impacting their quality of life (2). Therefore, diagnosis and symptom relief are the priority in management, followed by definite treatment with thionamides, iodine ablation, or total thyroidectomy. The most common treatment of choice for patients with Graves’ disease varies based on location; long-term use of thionamides is favored in Europe. In the United States, thionamides (methimazole and propylthiouracil) are initiated short term and then patients are frequently offered iodine ablation (3). Total thyroidectomy is usually only considered if patients have contraindications or failure with other treatments (4). Here we present a patient who was offered thyroidectomy after long-term methimazole therapy. We review the advantages and disadvantages of the most commonly prescribed treatments and when to consider total thyroidectomy.

Case presentation
A 30-year-old Hispanic female with a history of Graves’ disease presented to our medical center with chief complaints of increased tremors, palpitations, heat intolerance, abdominal pains, diarrhea, and shortness of breath for approximately 2 weeks. Her symptoms were associated with unintentional weight loss of approximately 5 kg and dysphagia. On presentation, her vital signs were remarkable for a blood pressure of 135/83 mm Hg and a pulse of 115 beats per minute. Her electrocardiogram was consistent with sinus tachycardia. Her physical exam was
remarkable for mild bilateral exophthalmos, tremor, and a
diffusely enlarged goiter without any distinct nodules or
bruits.

The patient was already well known to our institution.
She had been diagnosed with Graves’ disease approxi-
mately 12 years ago in Puerto Rico and now resided in
the United States. She was started on methimazole in
Puerto Rico and the same treatment was continued after
she established care in our outpatient medical clinic. She
often forgot to take methimazole two to three times a day
as prescribed and was non-compliant with follow-up
visits. As a result, she was frequently admitted to our
hospital as well as to other local hospitals for complaints
due to uncontrolled hyperthyroidism.

Her thyroid function tests revealed thyroid stimulating
hormone (TSH) < 0.01 mIU/L (reference range 0.27–4.2
mIU/L) and free T4 > 7.7 ng/dl (reference range 0.93–1.7
ng/dl). Serum B-hCG was negative. She was treated with
hydration, methimazole, and propranolol and her symp-
toms improved significantly. Ultrasound of the neck was
consistent with a diffusely enlarged thyroid gland, each
lobe approximately 7 cm in its longest dimension (Fig. 1).
Non-contrast computerized tomography (CT) scan re-
vealed subglottic tracheal compression (Fig. 2).

After consultation with the endocrinologist, total thy-
roidectomy was discussed and she agreed. To minimize risks
for thyroid storm, she remained inpatient while awaiting
surgery and was maintained on methimazole 10 mg three
times daily and propranolol 20 mg three times daily for
approximately 1 week. Prior to surgery, repeat free T4
was 1.46 ng/dl and her vital signs were stable with a blood
pressure of 117/53 and a pulse of 64 beats per minute.
She had an uncomplicated post-operative course and was
discharged on levothyroxine. Her thyroid pathology was
consistent with follicular hyperplasia and the gland was
markedly enlarged at approximately 90 g. She was exten-
sively counseled on the importance of compliance with
levothyroxine and precautions for pregnancy were empha-
sized. Within 3 months after surgery, TSH was 2.3 mIU/L
on levothyroxine 125 mcg daily. She had no further
emergency room visits or hospital admissions for sympto-
matic thyroid disease and her exophthalmos remained stable.

Discussion

Graves’ disease is the most common cause of hyperthy-
roidism. The diagnosis can often easily be made based on
eye findings, a goiter, and the typical signs and symptoms
of hyperthyroidism such as palpitations, tremors, uninten-
tional weight loss, heat intolerance, and increased irrit-
ability. In the presence of typical signs and symptoms, a
suppressed TSH, elevated free T4 and increased radio-
iodine uptake confirm the diagnosis. Thyroid ultrasound
consistent with increased vascularity of the gland and
positive thyroid receptor antibodies also provide strong
supporting evidence for Graves’ disease (5).

Thionamides are generally well tolerated, although
rash, musculoskeletal pains, and gastrointestinal upset

Fig. 1. Thyroid ultrasound significant for bilateral lobe
enlargement.

Fig. 2. CT scan of neck significant for tracheal compression
and narrowing due to thyroid enlargement.
may occur. Significant complications reported with these
drugs are liver toxicity (more common with propylthiour-
acil) and agranulocytosis. The risks for these complications
usually occur within the first few months of treatment,
although they can occur at any time. Propylthiouracil-
related liver toxicity has been reported to occur in 1% of
treated patients and the incidence of agranulocytosis is
less than 1%. So although these complications are rare,
they can be life-threatening (7, 8).

Iodine ablation with 131I is another treatment often
used for Graves’ disease. 131I is given orally as an
outpatient in a single dose, which makes it an attractive
treatment option. However, patients must be compliant
with numerous precautions such as avoiding contact with
children and pregnant women for up to 1 week after
treatment and limiting close contact with non-pregnant
adults. Radiation is in the patients’ secretions so they must
be careful about eating, cleaning, and toileting. After
treatment, frequent thyroid function testing is required to
monitor for changes in thyroid function as it may take up
to 6 months to see the full effects of treatment. Approxima-
tely 10% of patients will have 131I treatment failure and
will have to undergo iodine precautions and treatment
again. After treatment with 131I, patients may feel worse
before they feel better; they may have transient worsening
of disease and require treatment with beta-adrenergic
blocking agents or treatment with thionamides. Patients
may also develop painful radiation thyroiditis and require
glucocorticoid therapy (9).

Thyroidectomy is another option for the treatment of
 Graves’ disease but is often overlooked. According to
United States data published by the American Thyroid
Association, only 2% of patients with Graves’ disease and
only 7% of patients with Graves’ and thyromegaly are
treated with surgery. Surgery is usually only considered if
patients develop significant side effects from thionamides
or have contraindications to radioactive iodine (4). A 2011
survey investigating clinical practice patterns of providers
who care for patients with uncomplicated Graves’ disease
found less than 1% of respondents prefer surgery for their
patients with uncomplicated Graves’ disease (10). But there
are many situations in which thyroidectomy is reasonable
to consider.

Graves’ ophthalmopathy is one of the most frequently
observed extra-thyroidal manifestation of Graves’ disease,
ranging from mild to severe. Even patients who do not
have obvious eye findings may in fact have some degree of
ophthalmopathy on magnetic resonance imaging (MRI)
of the orbits. The primary goal for Graves’ ophthalmopathy
is long-term euthyroidism, but this can be difficult to
achieve. Thionamide failure and hyperthyroidism recur-
rence lead to reactivation of autoimmunity and there-
fore possible worsening of eye disease. Iodine ablation
has been associated with exacerbation and progression
of Graves’ ophthalmopathy, particularly in patients that
smoke. Thyroidectomy is the only option that offers
rapid resolution of hyperthyroidism, and studies show
that Graves’ ophthalmopathy stabilizes or even improves
after surgery. So for patients with moderate to severe
Graves’ ophthalmopathy, thyroidectomy is an appropriate
management (11).

Females with Graves’ disease who are pregnant may also
benefit from surgical management. If hyperthyroidism is
uncontrolled during pregnancy, there is an increased risk
for premature labor and fetal demise (12). If thionamides
are unable to control the hyperthyroidism, or the patient
is unable to tolerate thionamide therapy, thyroidectomy
is recommended. It is usually performed in the second
trimester when the pregnancy is more stable with little
risk to the fetus. Propylthiouracil has been preferred over
methimazole in the first trimester of pregnancy because of
decreased risk for teratogenicity. However, recent studies
have demonstrated almost 10% risk for birth defects with
both propylthiouracil and methimazole (13). Given these
data, female patients may consider thyroidectomy prior to
attempting pregnancy so they can avoid exposure to any
thionamide during pregnancy.

There are other concerns for female patients with
Graves’ disease who are planning pregnancy in the near
future. Treatment with both thionamides and iodine
ablation may take many months or even years to establish
euthyroid state. Initiating treatment with thionamides or
iodine ablation may significantly delay female patients’
plans for pregnancy. Furthermore, 131I crosses the plas-
centa and can result in fetal hypothyroidism or cretinism
as well as cause other teratogenic effects. So it is critical
that patients avoid pregnancy for at least 6 to 12 months
after 131I (5). Delaying plans for pregnancy can be
frustrating, especially for patients of advanced maternal
age. For such patients, thyroidectomy is preferred.

Thyromegaly is another indication for thyroid surgery,
especially thyromegaly causing mechanical obstruction
and dysphagia. Evidence for obstruction can be obtained
clinically and confirmed by non-contrast CT scan of the
neck focusing on tracheal abnormalities. Although iodine
ablation can decrease gland size, it improves compressive
symptoms in less than 50% of patients (9). Therefore,
thyroidectomy is often the best treatment for these patients
because it will provide the quickest relief for patients’
compressive symptoms and hyperthyroidism with virtually
no risk of hyperthyroid recurrence.

The management of thyroid nodules in the setting of
Graves’ disease, especially those above 1 cm, can be
challenging and is another instance in which thyroidect-
omy may be preferred. The incidence of thyroid cancer
in nodules in the setting of Graves’ disease has been
reported to be as high as 15 to 20% (14). When fine needle
aspiration of thyroid nodule is suspicious or confirmed
for malignancy, thyroidectomy is the only treatment
option that allows for simultaneous treatment of both
the thyroid cancer and hyperthyroidism. So thyroidectomy is an attractive treatment option for patients with Graves’ disease and thyroid nodules.

The extent of surgery, sub-total thyroidectomy versus total thyroidectomy, was once a topic for debate in the surgical management of Graves’ disease. Permanent hypocalcemia and recurrent laryngeal nerve palsy are all well-known complications from both procedures. Sub-total thyroidectomy was at one time the preferred approach because complications were less frequent, but was associated with approximately 6 to 28% risk for hyperthyroidism relapse (15). Multiple studies including a long-term, 15-year study evaluating more than 1,400 patients who underwent surgery for Graves’ disease found the frequency of permanent hypocalcemia and permanent recurrent laryngeal nerve palsy to be quite low, from 1 to 3%, and not statistically different in patients who underwent total thyroidectomy versus sub-total thyroidectomy. Therefore, total thyroidectomy has become the surgery of choice for Graves’ disease. The most common complication is transient symptomatic hypocalcemia, occurring in 6 to 20% of patients, and is easily managed with calcium and vitamin D supplementation (4, 14–17).

Thyroid storm is also a possible complication from thyroidectomy but the risks for this can be greatly reduced with proper planning. Prior to surgery, patients should be biochemically and clinically optimized and euthyroid prior to surgery using thionamides and β-blockade. Inorganic iodine may also be started preoperatively and continued postoperatively in high-risk patients. When adequate preparations are made, thyroid storm is rarely seen (12).

In conclusion, total thyroidectomy is a safe and effective treatment option for patients with Graves’ disease and is recommended for patients such as ours who are young females of child-bearing age, have thyromegaly, or have Graves’ ophthalmopathy. Of course, not all patients are good operative candidates due to comorbid conditions, advanced age, or other factors. Therefore, a candid discussion with patients reviewing the risks and benefits of all treatment options is very important. There is no one perfect treatment, so patients should decide which option is best for them given their personal circumstances and lifestyle. Although it is invasive, patients seeking the fastest results and most rapid resolution to their disease may prefer thyroidectomy over thionamides and iodine ablation. To achieve best possible outcomes and lowest risks for complications, patients desiring surgery should be referred to a high-volume thyroid surgeon whenever possible (17).

Acknowledgements

The authors thank Dr. Sara Wallach, Chief and Chairperson of the Department of Medicine at Saint Francis Medical Center, for her assistance with journal selection as well as her support for the department of endocrinology at our institution. They also thank Dr. Praneet Iyer for his technical support and assistance in preparing this manuscript for submission.

Conflict of interest and funding

We have not received any funding from any sources for this project, nor do we have any conflict of interest. This manuscript is not being considered for publication elsewhere.

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