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Graves' Disease: Hyperthyroidism, Symptoms, Causes and Treatment

Paula Aragão Prazeres de Oliveira,

Beatriz Nayara Muniz de Oliveira,

Eduarda da Silva Souza Paulino,

Fernanda Carolinne Marinho de Araujo

and Paula Gabriele Tabosa Lyra

Abstract

DG presents with three main presentations: hyperthyroidism with diffuse goiter, infiltrative ophthalmopathy and pre-tibial myxedema. Patients with Graves' Disease can rarely develop severe hyperthyroidism. The hyperthyroidism of Graves' Disease is characterized immunologically by the lymphocytic infiltration of the thyroid gland and by the activation of the immune system with elevation of the circulating T lymphocytes. In GD, goiter is characteristically diffuse. May have asymmetric or lobular character, with variable volume. The clinical manifestations of hyperthyroidism are due to the stimulatory effect of thyroid hormones on metabolism and tissues. Nervousness, eye complaints, insomnia, weight loss, tachycardia, palpitations, heat intolerance, damp and hot skin with excessive sweating, tremors, hyperdefecation and muscle weakness are the main characteristics. In the laboratory diagnosis, biochemical and hormonal exams will be done to assess thyroid hormones and the anti-thyroid antibodies. Additionally, imaging tests may be performed, such as radioactive iodine capture in 24 hours, ultrasonography, thyroid scintigraphy and fine needle aspiration. It is necessary to make the differential diagnosis of Graves' Disease for thyrotoxicosis, subacute lymphocytic thyroiditis and toxic nodular goiter. The treatment of DG aims to stop the production of thyroid hormones and inhibit the effect of thyroid hormones on the body. Hyperthyroidism caused by DG can be treated in the following ways: it may be the use of synthetic antithyroid medicines, thionamides, MMI being a long-term medicine, it allows a single daily dose, and adherence to treatment occurs, a disadvantage is that it cannot be used in pregnant women; beta-blockers, preferably used in the initial phase of DG with thionamides; radioactive iodine therapy (RAI), being the best cost-benefit and preventing DG recurrence; finally the total thyroidectomy, causing the withdrawal of the thyroid gland. Therefore, it should be discussed with the patient what is the best treatment for your case, with a view to the post and against each approach. If the patient develops Graves ophthalmopathy, in lighter cases the artificial tears should be used, and in more severe cases can be used as treatment, corticosteroids, orbital decompression surgery, prisms and orbital radiotherapy. In addition, the patient should keep their body healthy, doing exercise and healthy eating, following the guidance of their doctor.

Keywords: Graves' Disease, Hyperthyroidism, Goiter, Thyroid hormones

1. Introduction

GD presents with three main presentations: hyperthyroidism with diffuse goiter, infiltrative ophthalmopathy and dermopathy (pretibial myxedema). Patients with Graves' Disease rarely may develop severe hyperthyroidism (thyroid storm or thyrotoxic crisis) [1]. Consider tests for thyroid dysfunction for people if there is a clinical suspicion of thyroid disease, but bear in mind that only an isolated symptom may not be associated with this disease [2].

2. Hyperthyroidism

Graves' Disease hyperthyroidism is characterized immunologically by lymphocytic infiltration of the thyroid gland and by activation of the immune system with elevation of circulating T lymphocytes, appearance of autoantibodies that bind to the TSH receptor (TRAb) and that stimulate glandular growth and function [3–5]. The reasons for triggering this autoimmune process have not yet been fully understood, but factors such as susceptibility genetics, constitutional factors such as sex hormones and changes in immune function, and factors environmental factors (stress, iodine intake and the action of infectious agents) [6, 7].

From a clinical point of view, the hyperthyroidism of Graves' Disease is characterized by diffuse enlargement and hyperactivity of the gland thyroid, associated or not with infiltrative ophthalmopathy and, more rarely, localized myxedema. Excess thyroid hormones can lead to the development of serious complications such as congestive heart failure, cardiomyopathy and arrhythmias, mainly atrial fibrillation (10–30%). It is also associated with increased bone resorption, increased calcium and phosphorus excretion in urine and faeces, with a consequent decrease in bone mineral density and risk of fractures in women elderly [1, 3].

Symptoms of Graves' Disease	
Nervousness	Fatigue
Excessive sweating	Increased evacuations
Heat intolerance	Menstrual disorders
Palpitation	Increased appetite

3. Dermopathy (pretibial myxedema)

It affects only 5 to 10% of patients with GD and is almost associated with ophthalmopathy (usually severe) and high levels of TRAb [8]. Exceptionally, it has seen in euthyroid patients with GD [1] or with Hashimoto's thyroiditis [9]. It consists of within the thickening of the skin, particularly within the pretibial area, because of the buildup of the glycosaminoglycans. The evidence is shown in plaques and on them; the skin is type of thickened, with the looks of orange rind and violet color. Sometimes a Dermopathy involves the entire lower leg and should reach the feet. Rarely (less than 1% of cases), it can be seen in other places (hands or shoulders), especially after prolonged trauma [8, 10]. Very rarely, pretibial myxedema is the initial manifestation of GD [1, 11].

4. Goiter

In GD, goiter is characteristically diffuse. May have asymmetric or lobular character, with variable volume. In some patients, there is thrill and murmur over the gland, produced by increased flow of blood, this finding being exclusive to the disease. Any patient with diffuse goiter and hyperthyroidism has GD until they prove the opposite [4, 12]. In the elderly, when present, the goiter tends to be small [1].

5. Ophthalmopathy

The clinical manifestations of hyperthyroidism are due to the stimulatory effect of thyroid hormones on metabolism and tissues. Nervousness, eye complaints, insomnia, weight loss, tachycardia, palpitations, heat intolerance, damp and hot skin with excessive sweating, tremors, hyperdefecation and muscle weakness are the main characteristics [13, 14].

In GD, goiter is singularly diffuse, being present in 97% of cases. Asymmetric or lobular, with variable volume. In some patients, an exclusive finding of the disease is that the increase in blood flow brings the presence of thrill and murmur over the gland. Any patient with diffuse goiter and hyperthyroidism has GD until proven otherwise. In the elderly, when present, the goiter tends to be small [15, 16].

Ophthalmopathy or orbitopathy has an equivalent autoimmune pathogenesis as GD hyperthyroidism and may exacerbate both hypo and thyroid hyperfunction. Antibodies react by causing intraorbital auto-aggression, as in tissue thyroid. Ophthalmopathy can precede hyperthyroidism (20% of the time), succeed it (40%) or appear concomitantly with it (40%) [1, 15].

The cases during which ophthalmopathy, transiently or permanently, isn't in the course of hyperthyroidism are called Graves' euthyroid disease. Clinically evident ophthalmopathy occurs in up to 50% of patients with GD. It stems from the thickening of the muscles extraocular and increased retrobulbar fat, which results in a rise in intraorbital pressure. Consequently, protrusion of the eyeball (proptosis or exophthalmos) and decreased venous drainage may occur, leading to periorbital edema, conjunctival edema and conjunctival hyperemia [16, 17].

The most common ocular manifestations in the GD are the eyelid retraction, the stare or frightened look and the sign of lid-lag (delay in lowering the upper eyelid when the eyeball is moved down). Nevertheless, they occur in any sort of thyrotoxicosis, as they're consequent to adrenergic hyperactivity. On the opposite hand, the finding of periorbital edema and exophthalmos practically confirms the diagnosis of GD. Additionally, diplopia can occur in 5 to 10% of patients, because of the functional impairment of the musculature extrinsic ocular. Ophthalmoplegia and eyelid ptosis also can occasionally be seen. Finally, severe cases, there could also be dysfunction of the nervus opticus, defects in the visual fields, disturbance of vision in color or loss of vision [1, 15–18].

GD exophthalmos is typically bilateral, but it can be unilateral. During this situation, it must be differentiated from a tumor retrobulbar or arteriovenous malformation using computerized tomography or resonance imaging. The most effective way to verify the existence of the property and establish its magnitude is by using Hertel's exophthalmometer. A measurement greater than 20 mm in Caucasians is taken into account abnormal, 18 mm between Orientals and 22 mm in blacks. However, caution is required in borderline interpretations of up to

2 mm. Proposals are often selected as mild (increase of 3 to 4 mm), moderate (5 to 7 mm) and severe (>7 mm) [1, 16, 18].

6. Laboratory diagnosis

6.1 Biochemical and hormonal exams

6.1.1 Thyroid function tests

For adults when secondary thyroid dysfunctions are not suspected, it is appropriate to consider measuring thyroid-stimulating hormone (TSH) itself, then if the TSH is above the reference range, measure free thyroxine (FT4) in the same sample. If the TSH is below the reference range, measure FT4 and free triiodothyronine (FT3) yet in the same sample. In addition, consider measuring both TSH and FT4 for adult patients when secondary thyroid dysfunction (pituitary disease) is suspected in children and young people. If the TSH is below the reference range, measure FT3 in the same sample. Consider repeating the tests for thyroid dysfunction if symptoms worsen or new symptoms develop (but just 6 weeks from the most recent test) [2].

6.1.2 Antithyroid antibodies

The antibodies are often classified a minimum of three general types. Thyroid stimulating antibodies (TSAb, sometimes TSI) interact with the TSH receptor during a positive functional manner and initiate the adenylyl cyclase function and the phospholipase A2 function of the receptor, causing all aspects of thyroid stimulation [12, 19].

Functionally, this is probably identical to the effects induced by TSH itself. Other antibodies can interact with the receptor in a slightly different manner, presumably by binding to different epitopes on the receptor, and can block the binding of TSH to the receptor while not themselves stimulating function. These antibodies are known as thyroid stimulation blocking antibodies, or TBAb [19, 20].

A third set of antibodies can bind to the receptor but neither stimulate nor inhibit its function. These are known as thyrotropin binding immunoglobulins. They are commonly recognized by assays which detect their ability to interfere with the binding of TSH to the receptor, and are identified as TRAb, or TBII [19]. Probably all patients with Graves' Disease have a mixture of all of these antibodies. If TSAb predominates, thyroid stimulation occurs and, if the activity is sufficient, the patient may become hyperthyroid and be characterized as having Graves' Disease. If the antibodies block the action of TSH, they may induce hypothyroidism, in which case the patient might be characterized as having Hashimoto's thyroiditis or idiopathic myxedema [12, 20].

Among patients with GD, up to 50% have anti-thyroglobulin (anti-Tg) antibodies and up to 90% have antibodies antithyroperoxidase (anti-TPO), at lower titers than those observed in Hashimoto's thyroiditis [21]. Although TSH anti-receptor antibodies (TRAb) can be found in normal individuals (exceptionally), in Hashimoto's thyroiditis (in 6 to 60%) and in painless subacute thyroiditis or postpartum thyroiditis (in 5 to 15%), its occurrence in hyperthyroid patients is highly specific for GD (present in 90 to 100% of cases) [13, 14].

A recent meta-analysis showed high sensitivity (97.1 to 97.4%) and specificity (98.3 to 99.2%) for the second and third TRAb assays generations. According to

these data, the probability of a TRAb-positive individual having GD is 1,367 to 3,420 times higher (depending on the type of assay) compared to a TRAb-negative individual [1, 22]. In Europe, around 85% of specialists measure TRAb in the initial diagnostic assessment of GD [23]. A similar approach is reported in Japan and Korea [18, 24]. In Brazil and the USA [16, 18] the guidelines still recommend prioritizing the dosage of TRAb in some specific situations, such as: 1- In the diagnosis of euthyroid GD; 2- in the diagnosis of apathetic hyperthyroidism; 3- In the distinction between GD and postpartum thyroiditis or subacute lymphocytic thyroiditis; 4- In assessing the risk of recurrence of hyperthyroidism after discontinuation of thionamide treatment (elevated titers increase the risk of relapse); and 5- In pregnant women with GD [1].

TRAb at elevated titers at the end of pregnancy implies an increased risk of neonatal hyperthyroidism. On the other hand, its negativity favors the interruption of treatment, aiming to decrease the risk of fetal hypothyroidism [1, 14].

6.1.3 Hematological and biochemical parameters

In GD, leukopenia (common), hypercalciuria and hypercalcemia (occasional), elevated transaminases and hyperbilirubinemia (in the most severe cases). Reduction of total cholesterol and LDL-cholesterol can also be found [1].

6.2 Medical imaging

6.2.1 Radioactive iodine capture in 24 hours (RAIU/24H)

The uptake of radioactive iodine in 24 hours appears high in basically 100% of cases of GD, generating the possibility of its distinction with cases of thyroid acid and thyroid oxycosis secondary to lymphocytic subacute thyroid, in which the RAIU/24 h has low or absent characteristics. In addition the RAIU/24H should only be requested when there is diagnostic doubt between the GD and the mentioned pathologies. A path to differentiation is thyroid ultrasonography with color Doppler or specification of TRAb levels (lower accuracy) [1, 25–29].

6.2.2 Ultrasonography

Ultrasonography has similar sensitivity to RAIU/24 h for the diagnosis of GD (95.4% vs. 97.4%, respectively). Advantages of ultrasonography are absence of exposure to radiation, greater precision within the detection of possible thyroid nodules and cost low. Additionally, color Doppler ultrasonography can differentiate GD (diffusely enlarged hypoechogenic gland) from thyrotoxicosis induced by follicular destruction (reduced glandular volume and blood flow) [1, 30, 31].

6.2.3 Thyroid scintigraphy

Scintigraphy with radioactive iodine (^{123}I or ^{131}I) or technetium should be performed in patients with nodules identified at ultrasonography, to assess whether such nodules are “hot” or “cold” [1].

In clinical practice thyroid scintigraphy is most ordinarily used to differentiate between subacute thyroiditis and Graves' Disease. Additionally, patients with congenital hypothyroidism, functioning thyroid nodule, suspected ectopic thyroid, thyroid carcinoma, and midline neck swelling (thyroglossal cyst) also require thyroid scintigraphy [1].

6.3 Fine needle aspiration

It will be indicated when normal thyroid nodules or hypocaptants are found on scintigraphy. It's been suggested by some studies that such nodules would be at higher risk for malignancy in patients with GD, however newer studies haven't confirmed this possibility [32, 33].

6.4 Differential diagnosis

6.4.1 Graves' Disease versus other causes of thyrotoxicosis

Hyperthyroidism can have several etiologies. In the distinction between these etiologies, some data clinical and laboratory tests are often useful, for instance, the presence of infiltrative ophthalmopathy or pretibial myxedema in patients with hyperthyroidism is sufficient to verify the diagnosis of Graves' Disease (GD) [1, 32]. Furthermore, any patient with diffuse toxic goiter, until proven otherwise, has GD. However, within the absence of ophthalmopathy and dermopathy, the involvement of other pathologies in the genesis of thyrotoxicosis may be considered, especially subacute thyroiditis lymphocytic (TSL) and toxic nodular goiter, the likelihood of TSL, although low, is higher in patients with goiters small, mild and short-lived [1, 32].

Rarely, Graves' Disease and toxic nodular goiter coexists, characterizing the Marine-Lenhart syndrome [1]. This possibility should be suspected whenever the treatment of hyperthyroidism requires high doses of synthetic antithyroid drugs or when relapse happens soon after suspension of an equivalent. In patients with thyrotoxicosis and low ^{131}I uptake, additionally to subacute thyroiditis, other diagnostic considerations include factitious thyrotoxicosis (using thyroid hormones), functioning metastasis from follicular carcinoma and also the rare struma ovary (ovarian teratoma with ectopic thyroid issues), in the latter situation, there's increased RAIU within the pelvic region [34, 35].

6.5 Atypical presentations of Graves' Disease

Occasionally, GD can manifest itself during a very atypical way, making diagnosis difficult. Sometimes she goes with marked muscle atrophy and wishes to be differentiated from a primary nervous disorder. In the elderly, as mentioned, we are able to find apathetic hyperthyroidism, during which the classic manifestations of GD are usually absent, with predominance of cardiac symptoms. Thus, GD should be considered in any patient with atrial fibrillation or heart failure without apparent cause and/or refractory to the standard treatment [1, 36, 37]. GD should also be considered in cases of amenorrhea or infertility, since some young women may present these problems as a manifestation hyperthyroidism. GD can rarely happen, especially in Eastern and Latino men, with a sudden flaccid paralysis and hypokalemia (periodic hypokalemic thyrotoxic paralysis). Such paralysis is typically resolvable spontaneous, are often the initial manifestation of hyperthyroidism and may be treated by potassium supplementation and use of beta-blockers. It's cured by the right treatment of hyperthyroidism [1, 36, 37].

6.6 Treatment

Hyperthyroidism due to Graves' Disease is treated with one among the subsequent approaches: synthesis antithyroid drugs (thionamides), surgical removal of the thyroid gland (total thyroidectomy), or RAI-induced shrinkage of the thyroid

tissue [1, 18, 21]. These options have advantages and drawbacks, they ought to always be presented to the patient, if he has the ability to discern [1, 21]. Treatment should be individualized based on the clinical characteristics, age, etiology, size of goiter, concurrent comorbidities, patient's preference, and special situations like pregnancy [3].

6.7 Medical treatment

6.7.1 Synthesis antithyroid drugs (thionamides)

The available antithyroid drugs are methimazole (MMI), also called thiamazol, carbimazole and propylthiouracil (PTU) [3, 18]. The use of thionamide antithyroid drugs as an initial treatment varies according to geographic location, they are the foremost common treatment of GD in Asia, Europe and Latin America. However, radioiodine is used more often than medications in the United States [21, 38]. These drugs are actively transported into the thyroid where they inhibit iodide oxidation and organification by inhibiting thyroid peroxidase and therefore the coupling of the iodotyrosine to synthesise T4 and T3 [38, 39]. The long duration of MMI (up to 24 hours or more) makes it possible to administer it during a single daily dose, which facilitates the most effective adherence to the treatment [40].

The PTU should be administered, at least initially, in two to three daily doses [1, 41]. Nonetheless, a divided dose could also be more effective initially within the most severe cases. Compared to PTU, MMI makes it possible to get euthyroidism more frequently and faster, additionally being better tolerated and causing less hepatotoxicity [36, 41, 42]. The current guidelines of the American Thyroid Association and also the latest consensus of the Brazilian Society of Endocrinology and Metabology recommends that you must always choose MMI as the first option. Two exceptions to the this rule are the first trimester or pregnancy and severe intolerance to MMI [36, 37].

6.8 Mechanism of action

The mechanism of action of those drugs is the inhibition of synthesis of thyroxine (T4) and triiodothyronine (T3) in the follicular cells, for interference with the organization (formation of MIT and DIT) and coupling (joining MIT and DIT to make T3 and T4) of iodotyrosine, by blocking thyroid peroxidase, and enzyme responsible for the iodination of tyrosine residues in the thyroglobulin [40, 42]. Additionally, PTU, but not methimazole, inhibits the peripheral conversion of T4 to T3, with a consequent drop by serum T3 levels and increased reverse T3 when utilized in high doses (> 600 mg/day) [1]. There's, however, little evidence that this effect is clinically relevant, except possibly in patients with severe thyrotoxicosis [32]. The antithyroid drugs negatively impact the activity and numbers of intrathyroidal T cells, the aberrant thyrocyte expression of MHC class II, also because of the generation of reactive oxygen species, lipid peroxidation, and subsequent oxidative damage [2, 43].

6.9 Posology

For dosage for hyperthyroidism, the severity will follow, the MMI dose is 10 to 40 mg/day, the PTU dose is 100 to 400 mg/day, these are the initial portions. When a more severe case occurs the recommended is a higher MMI dosage of 30 to 40 mg/day, causing faster normalization of thyroid hormones, however, bringing side effects on a larger scale [44, 45].

After treatment, the patient has to be monitored every 4 to 6 weeks, achieving eutyroidism, the dose is gradually decreased, obtaining the lowest possible dose for the patient, in addition, the medical consultations should be quarterly. Usually the preservation dose is 5 to 10 mg/day of MMI, since OCT is 50 to 100 mg/day 2 times/day. Carbimazole corresponds to more than 140% of methimazole relative to dosage. It is important to monitor serum TSH levels, since they are suppressed even after a few months after euthyroidism, being essential to see when there is biochemical hypothyroidism. Therefore, the dosage of TSH at initiation of treatment with thionamides is limited [44, 45].

One type of scheme used in the former was blocking and replacement, an L-thyroxine adjustment and high doses of TAD, however, causes a greater danger of adverse effects. Occasionally combined therapy is used when metimanzol maintenance therapy is difficult to titrate, so 10 mg/day of MMI is used in combination with 12.5 to 25 µg/day of L-thyroxine [44, 45].

6.10 Effectiveness of treatment

Among patients who tolerate and take thionamides properly, the overwhelming majority will achieve hormonal normalization, but recurrences are frequent. Relapses are common in the first year, especially in the first six months post-treatment suspension. They rarely manifest after 4 to 5 years. Patients at increased risk of recurrence are those with severe hyperthyroidism, larger goiter, orbitopathy, duration of treatment <12 months, elevated T3:T4 ratio, TSH persistently suppressed and, above all, high concentrations of TRAb at the beginning or at the end of treatment [1, 21, 30, 40, 46]. In case of recurrence, a second course of treatment with DAT could also be attempted, but usually opts for an additional sort of therapy, preferably radioactive iodine [1, 25].

7. Factors affecting the long-term response to thionamides

One factor may be time, there are still conflicts about the appropriate duration of therapy, but it seems to be 12 to 18 months. Patients treated for one semester have less favorable results when compared to those treated for 1 to 2 years [47, 48].

A metanalysis was performed and one of the interpretations of the study was that the rate of remission in adults does not improve when treatment is performed for a period longer than one and a half years. Another factor is the dose of thionamide. According to studies, the definitive remission rate appears to be similar with the use of low or high doses of TAD. On the other hand the higher doses are indicated for patients with more severe hyperthyroidism, and through their use it was also possible to observe the reach of euthyroidism more quickly [10, 14]. Classically, it is known through studies that children and adolescents compared to adults have considerably lower remission rates [49, 50].

Another factor was demonstrated by most of the reverse relationship studies between the initial size of the bucket and the possibility of remission. Patients with large buoyancy (≥ 80 g) are the least likely to relapse, the same occurring in cases with persistently suppressed TSH at the end of treatment [51]. It also has TSH anti-receptor antibody factor (TRAb); their levels at diagnosis and end of treatment are linked to higher relapse rate compared to low expression of these antibodies [52].

Thyroid function at baseline levels of T3 > 500 ng/dl are associated with increased likelihood of disease reappearance [51, 53]. And a very high rate of relapse of hyperthyroidism occurred in the postpartum period in women who were in remission during pregnancy; a higher probability was also related to

ophthalmopathy, as was the use of iodine or drugs that have it in their composition. Some studies have also found smokers, mostly male, as part of this higher-risk group. Patients with a high chance of recurrence should be evaluated more frequently and shorter intervals after stopping antithyroid drugs (TDD). On the other hand, mild disease carriers, small bulges and negative TRAb have a remission rate > 50%, making the use of TDD potentially more favorable in this patient group [1, 8, 14, 53–55].

8. Long-term thionamide treatment

In cases of patients, from young people to the elderly, who do not opt for definitive therapies in the face of the reappearance of the disease, such as surgery or radioiodine, it is reasonable to consider other treatment routes, such as long-term maintenance [14, 50, 55, 56].

Researchers examined studies in the Ovid MEDLINE, Ovid Embase and Scopus databases, on GD until 2020, and evaluated the effectiveness of long-term antithyroid drugs in achieving and maintaining euthyroidism compared to the state of euthyroidism during the treatment of hypothyroidism after ablative therapies. They cited a retrospective study that concluded that long-term antithyroid drugs were effective in maintaining euthyroidism. And it has been seen that the risk of hypothyroidism is greater after treatment with radiation compared to antithyroid drugs. Bearing in mind that when considering a health-related quality of life, long-term antithyroid drugs are possibly an economical alternative, despite the fact that radioactive iodine is considered the most affordable first-line treatment [57].

9. Adverse effects of thionamide

The effects are most common in the first half of treatment. The most common are allergic in origin such as itching, rash, fever and even arthralgia. And also very frequent epigastralgia. Subdivisions in two groups: mild reactions (allergic reactions, gastric intolerance, neutropenia, fever, hair loss/alopecia, anaemia and decreased or even palate loss) and severe reactions (thrombocytopenia, medullary aplasia, cholestatic hepatitis, agranulocytosis, hepatocellular necrosis, hypoglycemia, ANCA-positive vasculitis, polyarteritis and glomerulonephritis [30, 50].

In cases of mild side effects the switch to another thioamide can be done cautiously or even the concomitant use of an antihistamine solves the rashes within a few days. Patients who develop severe reactions such as vasculitis, hepatitis or agranulocytosis should no longer be medicated with another compound in the same group [55, 58].

They may possibly also have cramps, muscle pain, edema, general fatigue and toxic psychosis rarely occurs. Other serious adverse reactions include polyarthritis, lomerulonephritis and lupus-simile syndrome, more common with PTU than with MMI [55, 58].

10. Beta blockers

Especially useful in the initial phase of GD treatment with amides, when euthyroidism has not yet been achieved. Its main indication is the elderly with symptomatic thyrotoxicosis and other thyrotoxic patients with high resting heart rate or who have a presence of cardiovascular disease. Caution should be paramount as high doses can

cause a decrease in serum T3 levels. Usually the medication is stopped in the third or fourth week. There is also an option to use selective B-1 drugs [24, 30, 51].

10.1 Potassium iodide

Since the arrival of antithyroid drugs, iodine has ceased to be used as primary therapy for GD. Its main limitation is the escape of the inhibition of the synthesis of thyroid hormones by iodine, a phenomenon referred to as the Wolff-Chaikoff [1, 32, 41].

10.2 Radioactive iodine (radioiodine)

Radioiodine is definitely administered orally, in solution or capsules, and has low cost. This treatment is proper to patients with persistent hyperthyroidism after completion of a 12–18 month first course of antithyroid drugs therapy, those with a recurrence or relapse of thyrotoxicosis, individuals with poor compliance on ATD, patients with major ATD-induced effects and subjects who choose this approach. It is often used either as initial therapy or after treatment with medication. Antithyroid drugs, when used, are generally discontinued for 3 to 7 days before radioiodine therapy, since the effectiveness of radioiodine could even be diminished when antithyroid drugs are given concurrently [59]. Compared to other sorts of treatment of GD, ^{131}I is taken into account to be the foremost cost-effective [3, 41, 60, 61]. The goal of radioiodine therapy is induced hypothyroidism so as to prevent a recurrence of Graves' Disease. This goal is achieved in approximately 80% of patients [58].

11. Dose

Most specialists choose to use fixed doses for their high simplicity (from 10 to 20 mCi). However, the dose is usually calculated in microcuries (μCi) or megabecquerels (MBq) per gram (g) of thyroid tissue, from thyroid size and in the capture of radioactive iodine of 24 hours. Generally, 160 to 200 $\mu\text{Ci/g}$ is recommended to leave the treatment safe and ensure it, the two squirrels being [1, 41, 56, 62].

12. Effectiveness

The rate satisfactory response to radioiodine therapy, with the resultant appearance of hypo or euthyroidism, is approximately 80 to 90% [1]. An oversized goiter with hypoechogenicity at US, the presence of anti-TPO antibodies and high doses of ^{131}I increase the likelihood of hypothyroidism [1]. In many patients, normalization of thyroid function tests and symptoms occurs within the period of 4 to 8 weeks. Hypothyroidism can appear after 4 weeks, but more commonly it occurs between 2 and 6 months [1, 21]. With the use of fixed or calculated doses, the efficacy appears to be an equivalent [3, 21]. Higher doses provide success earlier and, generally, more expressive therapeutic, lower doses (< 10 mCi), tend to result in failure rates and more pronounced recurrence [3, 21, 63].

13. Factors that influence the response to radio

Among the varied factors which will interfere with the response to ^{131}I , the quantification of the goiter appears to be the foremost important. Smaller goiters

are the ones that respond best and those the most often progress to hypothyroidism, especially with fixed doses. Also it had been demonstrated that patients with HLA-DR3 would have greater resistance to radioiodine therapy [23, 32, 40]. Clinical features most related to therapeutic failure include: male gender, smoking, large goiter (> 50 g): RAIU/24 h very high (>90%) and a marked increase in T3 levels (> 500 ng/ml) [64]. Persistence of levels of elevated TRAb and increased thyroid blood flow at Doppler also increases the likelihood of relapses [1].

14. Complications

Hypothyroidism is the main adverse effect of radioiodine therapy, being the frequency in the short term, depending on the dosage used, and may be more than 12 to 20 mCi than with 8 to 10 mCi. However, the amount of patients with hypothyroidism does not depend on the dose of ^{131}I , reaching a minimum of 80% of these adequately treated patients. A frequency of hypothyroidism is observed in about 50% in the first year, followed by 5% per year, at doses between 12 and 15 mCi. However, hypothyroidism due to ^{131}I may be transient, occurring in about 25% of patients who acquired hypothyroidism in the first 6 months after dosing. If the patient is severely symptomatic, L-thyroxine and discontinue treatment 6 months later, checking the maintenance of the disease. Hypothyroidism may develop or persist after one year, it is almost always permanent. In addition, one of the complications of radioiodine therapy is actinic thyroid or radiation, transient and occurs in approximately 3% of treated patients. It may cause pain in the anterior cervical region, lasting up to 4 weeks, and sometimes exacerbation of hyperthyroidism due to the release of t3 and t4 into the bloodstream. Elevation of thyroid hormones is reported in up to 10% of patients and should result in actinic thyroiditis or increased TRAb, observed 3 to 6 months after taking ^{131}I [1, 14, 39].

15. Radioiodine and thyroid eye disease

When radioiodine therapy (RAI) is used, in a delimited group as in smokers, an adverse effect is thyroid eye disease. This issue may occur because of glucocorticoid therapy and the next conditions are considered; smoking, active ophthalmopathy or severe hyperthyroidism. Moreover, in these cases, prior to RAI, the correct is to achieve euthyroidism with thionamide, preferably MMI, possessing the most prolonged radioprotective effect on propylthiouracil. However, for patients with severe DG and risk for vision disorders, radiotherapy is not recommended by choosing thioamides. Different corticotherapy regimens, such as prednisone 0.2 mg/kg/day, were analyzed one day after administration of radioactive iodine and held the dosage for 6 months, this decreased the dosage and discontinued at most within two months. There is evidence that thyroid eye disease may worsen in patients who may develop hypothyroidism after treatment. Therefore, in the face of thyroid hypofunction tests, revising the introduction of L-thyroxine early. Soon after 7 days of radiotherapy in patients with registered hyperthyroidism, MMI should be reintroduced [1, 14, 24, 65, 66].

16. Preparation for radioactive iodine with thionamides

The danger of worsening hyperthyroidism or thyrotoxic crisis triggering induced ^{131}I is <1%. In Brazil and Europe, radioiodine without prior treatment with

thioamides is usually common, not in the USA. However, this should be avoided in cardiopathic patients with severe hyperthyroidism and the elderly. Due to the assumed radioprotective effect of PTU, preference should be given to MMI, therefore, it should be administered until it reaches euthyroidism, with the drug discontinuation 5 to 7 days prior to the ^{131}I dose, its reintroduction 4 to 7 days after it. In addition, patients using PTU, a 25% increase in radioiodine dose is recommended. Another important point is that patients with an iodine allergy have no contraindication for ^{131}I [1, 14].

17. Contraindications

The use of ^{131}I in pregnant or lactating patients is contraindicated. Women or men who intend to have children within the next 6 months are also advised not to be given radioactive iodine. However, there is insufficient evidence of the risk of teratogenicity with radioiodine. Other equivalent contraindications are: severe inflectional ophthalmopathy and patient refusal [3, 14, 57, 66].

18. Radioiodine and thyroid nodules

Radioiodine treatment is indicated for ablation of autonomous tissue and reduction of thyroid volume. There is disagreement whether nodules have a greater chance of malignancy in GD cases. It is then suggested that non-functioning nodules >1 to 1.5 cm undergo a fine needle suction puncture (PAAF) prior to administration of I [14].

19. Monitoring after radioactive iodine

Thyroid function should be monitored 1–2 months after radioactive iodine therapy. Some suggest that it be checked after 15 days and then monthly or every 2 months; Such guidance is aimed at the early detection of hypothyroidism, especially in patients at risk of developing or worsening orbitopathy. If the patient is still thyrotoxic within two months of therapy, thyroid function should be monitored every 4–6 weeks until the patient is euthyroid or hypothyroid, remember that it may take up to 6 months or more for TSH to normalise. Substitution of levothyroxine should be initiated as soon as hypothyroidism occurs before laboratory tests proving the condition, immediately introducing L-thyroxine replacement. Patients with relapse or persistent hyperthyroidism after 6 months may re-receive radioactive iodine or those with minimal response to treatment ≤ 3 months [14, 50, 56].

20. Thyroidectomy

Thyroidectomy is the oldest treatment for GD. The main objective is the rapid and definitive control of effects of excess thyroid hormones. That is achieved by removing all or almost all of the functioning tissue of the thyroid gland. Indications for surgery in the treatment of GD do not are well established in the literature, being classified by some authors in absolute and relative indications. The indications considered absolute are large goiter with compressive symptoms, suspicious nodule or malignant, pregnant woman who does not get control with DAT, refusal of treatment with ^{131}I , woman planning pregnancy within six to 12 months

and intolerance to DAT. At relative indications are large goiter, ophthalmopathy severe, poor adherence and lack of response to treatment with DAT [56, 62, 67].

The standard procedure is total thyroidectomy (TT), which provides a cure rate of around 100% for hyperthyroidism of the DG [14, 65]. The risk of recurrence is almost 0% after TT, while subtotal thyroidectomy (TST) implies a probability of 5 to 20% (8%, on average) of persistence or recurrence of hyperthyroidism in 5 years [65]. Furthermore, with the exception of hypothyroidism early, as rates of complications with TT and TST may be comparable when the patient is operated on by a surgeon experienced (more than 100 thyroidectomies/year): transient hypocalcemia, 9.6 vs. 7.4%; definitive hypoparathyroidism, 1.6 vs. 1.0%; recurrent laryngeal injury, 0.9 vs. 0.7%, respectively [65]. In a recent meta-analysis and systematic review, the risk for hypoparathyroidism (transient or permanent) survived the older ones with TT. In a few centers, there is underwent an endoscopic thyroidectomy [38].

21. Preoperative management and follow-up of patients who receive thyroidectomy

Before surgery, patients should be euthyroid. Pretreatment with ATD reduces the risk of thyroid storm precipitated by surgery, and β blockers control hyperthyroid symptoms. Pretreatment with inorganic iodide, such as potassium iodide (50 mg iodide, three times daily, for 7–10 days before surgery) can also be considered in patients with Graves' Disease [67]. Inorganic iodide reduces thyroid hormone release and thyroid vascularity [68], which in turn decreases intraoperative blood loss. After surgery, levothyroxine replacement should be started and TSH concentration monitored 6–8 weeks after surgery. Oral calcium and calcitriol supplementation can be used before surgery and according to postoperative serum calcium concentrations [69].

22. Side effects

Surgical complications are rare, occurring in 1–3% of patients [60]. The most frequent complication is hypocalcemia due to permanent hypoparathyroidism, followed by permanent recurrent laryngeal nerve injury. The risk of these complications is lower when thyroidectomy is done by a high-volume thyroid surgeon [59, 61].

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Author details

Paula Aragão Prazeres de Oliveira^{1*}, Beatriz Nayara Muniz de Oliveira²,
Eduarda da Silva Souza Paulino², Fernanda Carolinne Marinho de Araujo²
and Paula Gabriele Tabosa Lyra²

1 Centro Universitário Maurício de Nassau-UNINASSAU, Disciplina de
Endocrinologia, Recife, Pernambuco, Brazil

2 Centro Universitário Maurício de Nassau-UNINASSAU, Medicina,
Recife, Pernambuco, Brazil

*Address all correspondence to: endopaulaoliveira@gmail.com

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