

Comparative analysis of the new guidelines and consensuses for the management of hypothyroidism, thyroid nodules, and differentiated thyroid cancer

Análise comparativa das novas diretrizes e consensos para o manejo do hipotireoidismo, nódulos tireoidianos e câncer diferenciado de tireoide

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In this edition of the *Brazilian Archives of Endocrinology and Metabolism*, a clinical practice guideline and a consensus on thyroid disorders are published. First, the Thyroid Department of the Brazilian Society of Endocrinology (SBEM) updates the Brazilian consensus on thyroid nodules and differentiated thyroid cancer (1), initially published in 2007 (2). Then, for the first time, the Clinical Practice Guideline for the Management of Hypothyroidism is published by a *task force* commissioned by the Latin American Thyroid Society (LATS) (3). Those publications are hallmarks for clinical practice not only in Latin America, but also worldwide, and serve as guidelines for the management of thyroid nodules, differentiated thyroid cancer, and hypothyroidism.

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THE CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF HYPOTHYROIDISM

The LATS clinical practice guideline for the management of hypothyroidism is published in this issue, just a few months after a similar guideline is published by the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) (4). Each guideline employs advanced techniques for the selection of high-quality and relevant publications, which are graded by levels of evidence (1 to 5 in the LATS guideline; 1 to 4 in the AACE/ATA guideline). The final recommendations are then based on the levels of evidence provided by the literature, complemented with the experts' opinions (from A to D in both guidelines). Although some fine differences exist in the methodologies employed for outlining the grades of recommendations, it is most likely that the final result was not affected by them.

The AACE/ATA guideline has been officially endorsed by several medical associations worldwide, including the LATS. Therefore, it is expected that both guidelines have more similarities than discrepancies. Some of the common key recommendations from the LATS and the AACE/ATA clinical practice guidelines are:

For the diagnosis of hypothyroidism, both guidelines acknowledge serum TSH level as the first-line diagnostic test. For case-finding, the LATS guideline recommends only TSH initially, followed by free T4 if TSH is abnormal and confirmed after 2-3 months. However, if a patient has clinical findings or high probability of hypothyroi-

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dism, both TSH and free T4 can be measured concomitantly. The AACE/ATA guideline is not clear whether free T4 should be measured concomitantly, or only after altered TSH levels are confirmed. Total serum or free T3 are not useful for the diagnosis of hypothyroidism, and clinical assessment alone without thyroid function tests is not sufficient for the diagnosis of hypothyroidism. However, the LATS guideline does acknowledge the importance of certain clinical manifestations that increase the likelihood of hypothyroidism. Therefore, although thyroid function tests are crucial for the diagnosis of hypothyroidism, clinicians should not forget the importance of a detailed clinical examination. Also, cases of incongruent thyroid hormones levels may occur, and clinicians should be aware of those situations in order to avoid misdiagnosis and mistreatment (5).

Anti-thyroid peroxidase antibody (TPOAb) measurements are suggested (LATS, grade C) or should be considered (AACE/ATA, grade D) to define thyroid autoimmunity. In groups at risk for autoimmunity, the LATS guideline increases their recommendation grade to B. The AACE/ATA guideline also recommends measuring TPOAb to predict the onset of overt hypothyroidism in patients with subclinical hypothyroidism, and when evaluating patients with recurrent miscarriage. Both guidelines acknowledge the importance of measuring TPOAb, and their usefulness in defining thyroid hormone therapy. Measurement of TSH-receptor antibodies is discussed only by the AACE/ATA guideline: their measurement is recommended in hypothyroid pregnant women with history of previously treated Graves' disease, because they are predictors of fetal and neonatal thyrotoxicosis.

Source of controversy amongst several medical associations, universal screening is not recommended by either guideline; patients with certain clinical conditions, as well as women of fertile age upwards (especially women over 60 years) and pregnant women, should be considered for thyroid testing. Both guidelines recommend case-finding rather than screening for pregnant women. There is much controversy regarding universal screening *vs.* case-finding of thyroid disorders in pregnant women (6), and the screening recommendation might change in the future, when better trials evaluating the rates of obstetrical complications and the childrens IQ become available. Regarding the elderly, the AACE/ATA guideline is more specific and acknowledges that screening for hypothyroidism should be considered in patients over the age of 60 years. These

recommendations differ from the older ATA guidelines published in 2000, when frequent early screening was recommended beginning at age 35, and every 5 years thereafter (7).

For case-finding, according to the AACE/ATA guideline, the normal TSH reference range varies according to age; if that information is not available, an upper limit of normality of 4.12 mU/L should be considered. In the LATS guideline, the normal reference range is 0.45-4.5 mU/L, and a higher cutoff should be considered for elderly patients. This recommendation is very important for the day-to-day clinical practice, and is based on strong level A evidence. In pregnant women, both guidelines recommend the use of reference value ranges specific for each trimester for the diagnosis of hypothyroidism.

Both guidelines recommend against the assessment of thyroid function in hospitalized patients, unless there is an index suspicion of thyroid dysfunction. However, the LATS guideline suggests that, if hypothyroidism needs to be ruled out, TSH, T4 and TPOAb should be measured concomitantly.

The use of ultrasound is not discussed in the AACE/ATA recommendations. The LATS guideline recommends US for patients with hypothyroidism (overt or subclinical) and negative antibodies (to diagnose autoimmune thyroiditis), for patients with subclinical hypothyroidism (to assess the risk of progression to overt hypothyroidism), and in patients with abnormal thyroid palpation. Whereas ultrasound is a powerful therapeutic tool, its widespread use should be limited in order to avoid excessive increases in medical costs and in the diagnosis of incidentalomas, which *per se* require additional workup.

Both guidelines recommend treatment with levothyroxine for patients with serum TSH levels > 10 mU/L, but the level of recommendation is higher for the LATS guideline (A), *versus* B for the AACE/ATA guideline. Similarly, both guidelines recommend that patients with serum TSH levels above the reference range (up to 10 mU/L) and normal free T4 (*i.e.*, subclinical hypothyroidism) should be treated with levothyroxine if they have increased cardiovascular risk, with higher recommendation level in the LATS guideline (A). The level of recommendation for treating symptomatic middle-aged patients with subclinical hypothyroidism is lower in the LATS than in the AACE/ATA guideline, as well as for treating patients with positive TPOAb and thyroid ultrasonographic findings

typical of autoimmune thyroiditis (D). The LATS panel recommends against routinely treating elderly patients with subclinical hypothyroidism, but acknowledges the possibility of treating those patients > 65 years old if the aim is to improve cognitive function.

Treatment of patients with subclinical hypothyroidism remains an area of uncertainty. For instance, it has been recently shown that the cardiovascular consequences of subclinical hypothyroidism in elderly may be minimal, and that routine treatment may not lead to predictable benefit (8). To specifically address the management of patients with subclinical hypothyroidism, SBEM has published its own consensus (9). In regards to the normal TSH reference range, that consensus is in concordance with the LATS panel, suggesting the normal range between 0.45-4.5 mU/L for healthy non-pregnant adults, rather than an age-specific range or an upper limit of 4.12 mU/L in the absence of age-specific reference values. Specific to that consensus, TSH values up to 20 mU/L are accepted as the upper limit for TSH; values beyond 20 mU/L, regardless of free T4, would then lead to the diagnosis of overt hypothyroidism. Therefore, this consensus is far more conservative is the diagnosis of overt hypothyroidism. The diagnosis of hypothyroidism made by the adoption of TSH higher levels up to 20 mU/L (with normal free T4 values) might lead to the underdiagnosis of that condition. However, this approach protects the patients against untimely and precocious thyroid hormone replacement that normalizes the levels of TSH; it also encourages the clinician to repeat the evaluation of thyroid function. The cardiovascular consequences of subclinical hypothyroidism are reviewed in the consensus, as are the outcomes following treatment. That leads to the recommendation of treating all patients with TSH levels ≥ 10 mU/L, and tailoring therapy in patients with lower TSH levels. Table 1 compares the recommendations from the LATS and the AACE/ATA guidelines, and the SBEM consensus. The recommendations for the treatment of patients with subclinical hypothyroidism is fairly similar across the guidelines, but all of them acknowledge that a widely accepted, strongly substantiated consensus is far from being reached; large, randomized, long-term prospective studies evaluating the outcomes of levothyroxine treatment in these patients are needed.

Levothyroxine is the treatment of choice, and it is recommended that the same preparation of levothyroxine is used throughout the treatment, to avoid variations

in bioequivalence. Combination therapy with levothyroxine and triiodothyronine are not recommended by the guidelines. The European Thyroid Association partly disagrees with that recommendation, and suggests that levothyroxine plus triiodothyronine might be considered as an experimental approach in compliant patients who have persistent complaints despite serum TSH values within the reference range (10).

The AACE/ATA guideline goes further and recommends against the use of iodine supplementation in patients from iodine-sufficient areas, desiccated thyroid, 3,5,3'-triiodothyroacetic acid (TRIAC), thyroid-enhancing preparations (such as L-tyrosine), thyromimetic preparations (such as Asian Ginseng), selenium, and dietary supplements or *nutraceuticals* for the treatment of hypothyroidism.

Both guidelines recommend treatment with full replacement doses (1.6 to 1.8 mcg/kg ideal body weight) in healthy young adults. Regarding patients older than 50-60 years, the AACE/ATA guideline is less conservative, and recommends initial doses of 50 mcg, instead of 12.5-25 mcg/day. For treating subclinical hypothyroidism, the LATS panel recommends a calculated initial dose of 1.1 to 1.2 mcg/kg ideal body weight, whereas the AACE/ATA panel recommends a fixed dose of 25-75 mcg, depending on the degree of TSH elevation. Both guidelines agree on the importance of the timing of levothyroxine administration, but the AACE/ATA guideline is more specific regarding the need to take the medication at least 4 hours after the last meal, if taken at bedtime.

Regarding the target TSH levels after levothyroxine is initiated in non-pregnant patients with overt hypothyroidism, the LATS guideline recommends considering age-dependent target TSH levels: the target TSH should be 1-2.5 mU/L for patients < 60 years, 3-4 mU/L for patients between 60-70 years, and 4-6 mU/L for those older than 70 years. The AACE/ATA guideline recommends that TSH levels are kept within the reference range or between 0.45-4.12 mU/L. In fact, the AACE/ATA panel discusses the lack of evidence supporting the benefits of targeting specific TSH values, which goes against the recommendations of the LATS panel.

In pregnant women with hypothyroidism, the AACE/ATA guideline recommends that levothyroxine dose should be titrated according to trimester-specific TSH reference range; if trimester-specific reference range is unavailable, levothyroxine should be titrated

Table 1. Recommendations for the treatment of patients with subclinical hypothyroidism, according to the LATS and the AACE/ATA guidelines, and the SBEM consensus

	TSH 4.5-10 mU/L			TSH ≥ 10 mU/L		
	LATS	AACE/ATA	SBEM	LATS	AACE/ATA	SBEM
Age ≤ 65 years						
Without comorbidities	No	No	No	Yes	Yes	Yes
Risk to progression to overt hypothyroidism	Consider treatment	Consider treatment	Consider treatment	Yes	Yes	Yes
Preexisting cardiovascular disease or cardiovascular risk	Consider treatment particularly if TSH ≥ 7 mU/L	Consider treatment	Consider treatment if TSH ≥ 7 mU/L	Yes	Yes	Yes
Hypothyroidism symptoms	Therapeutic test should be considered in middle-aged patients	Consider treatment	Therapeutic test should be considered	Yes	Yes	Yes
Age > 65 years						
	No	Not addressed	No	Yes	Yes	Yes
Pregnant women						
With positive TPOAb	Yes	Consider treatment	Insufficient data to recommend for or against; the consensus accepts that treatment should be initiated	Yes	Yes	Yes
With negative TPOAb	Insufficient data to recommend for or against; if not treated, monitor every 4 weeks up to 16-20 weeks, and at least once between 26-32 weeks	Consider treatment	Insufficient data to recommend for or against; the consensus accepts that treatment should be initiated	Yes	Yes	Yes

to keep TSH levels below 2.5 mU/L, 3 mU/L, and 3.5 mU/L during the first, second and third trimesters, respectively. In the current guideline, the LATS panel does not present recommendations regarding the treatment of pregnant women, nor regarding the treatment of patients with central hypothyroidism.

For monitoring treatment, the LATS panel recommends measuring serum TSH 6-8 weeks after any levothyroxine dose change, whereas the AACE/ATA panel acknowledges that TSH can be measured sooner, 4-8 weeks after initiation, or after a dose change. After euthyroidism is reached, both panels recommend TSH measurements every 6 to 12 months; free T4 measurements have a role only in the early stages of dose adjustments, and can be left out after euthyroidism is achieved.

Despite some discrepancies, both guidelines are in agreement with the most recent evidence from the literature. They are important for guiding clinicians in the management of hypothyroidism, but clinical judgment

should always prevail. There are still many areas of controversy such as the need for broader screening, the management of subclinical hypothyroidism, and the benefit of designing levothyroxine therapy based on age-specific TSH targets. Those areas should be addressed by large randomized clinical trials.

THE UPDATE OF THE BRAZILIAN CONSENSUS ON THYROID NODULE AND DIFFERENTIATED THYROID CANCER

Clinicians can count on many guidelines and consensuses addressing the management of thyroid nodules (TN) and differentiated thyroid cancer (DTC). In 2009, the ATA published a revised version of its 2006 guideline (11). Similarly, SBEM now publishes a revised version of its own 2007 consensus (1). The degrees of recommendation employed by both societies is slightly different: the ATA panel presents seven degrees of recommendation ranging from “strongly recom-

mends” to “strongly recommends against”, with a seventh recommendation (“neither for nor against”); the SBEM panel presents only four degrees of recommendation based on the level of evidence. Therefore, direct comparison of the degrees is not possible, and the recommendations should be interpreted with caution.

The initial biochemistry workup of patients with TN is similar for both societies: TSH measurement is fundamental. The SBEM panel does not recommend the measurement of thyroglobulin and of calcitonin, whereas the ATA panel does not have a recommendation for nor against its measurement. Both panels agree that US is fundamental for all patients with thyroid nodules, and that computerized tomography, magnetic resonance, and FDG-PET are rarely necessary.

The indication for fine needle aspiration biopsy (FNAB) is fairly similar in both guidelines. Functioning nodules or purely cystic nodules should not be biopsied. Also, regardless of size, both panels recommend the biopsy of all non-functioning nodules only if there are abnormal cervical lymph nodes or evidence extra-thyroid invasion. For subcentimeter nodules, in the absence of high-risk history, both panels agree that the biopsy should be decided upon based on ultrasonographic findings. In case of subcentimeter nodules with high-risk history, the ATA panel strongly recommends biopsy if there are also suspicious ultrasonographic findings, and no recommendation is provided if there are no abnormal ultrasonographic findings in subcentimeter nodules with high-risk history. The SBEM panel recommends the biopsy of subcentimeter nodules if there is high-risk OR suspicious findings, but also accepts follow-up with US, postponing FNAB when size increases to more than 1 cm. The recommendations for the biopsy of nodules ≥ 1 cm are similar in both guidelines, and depend on echogenicity, nodule type (solid, cystic, spongiform), and ultrasonographic findings. According to the ATA, all solid nodules ≥ 1 -1.5 cm should be biopsied (> 1 cm if hypoechoic; ≥ 1 -1.5 cm if iso- or hyperechoic), whereas SBEM recommends the biopsy of all nodules ≥ 1 cm if they are hypoechoic; if solid nodules are iso- or hyperechoic, they should be biopsied if ≥ 1.5 cm, even in the absence of abnormal ultrasonographic findings. By restricting FNAB of subcentimeter nodules to specific cases, both panels miss the diagnosis of some microcarcinomas. However, both panels consider that missing the diagnosis of microcarcinomas has no clinical impact on the patient prognosis, because those tumors have slow progression and their cure is not compromised by delayed treatment.

The SBEM panel suggests that FNAB-guided US is useful only when initial results are inadequate, whereas the ATA panel specifically recommends US guidance for FNAB when nodules are non-palpable, predominantly cystic, or posteriorly located in the thyroid lobe, and in cases when FNAB needs to be repeated for an initial non-diagnostic result. There are studies showing that US-guided FNAB decreases the rates of inadequate and false-negative results, and improves accuracy, sensitivity and positive predictive value (12-14). When available onsite, FNAB guided by US might be the procedure of choice, without incurring in excessive increase in costs.

The approach following FNAB is the same in both guidelines, in case of malignant (Bethesda VI), suspected for malignancy (Bethesda V), follicular neoplasm (Bethesda IV), benign (Bethesda II), and inadequate/non diagnostic results (Bethesda I). In cases of follicular lesion or of atypia or indeterminate significance (Bethesda III), the SBEM panel recommends FNAB to be repeated in 3-6 months, and indicate surgery or follow-up, depending on the degree of suspicion, ultrasonographic findings, and nodule size. The ATA panel recommends surgery depending on the size of the lesion and other risk factors; both panels suggest that the use of molecular biomarkers should be considered, with a strong recommendation by the SBEM panel. The use of those biomarkers may become a safe and inexpensive alternative to surgery (15), but further evaluation is needed. Their use needs to be individually assessed, and cost-effectiveness should also be considered (16). Also, in cases of follicular lesion or of atypia or indeterminate significance, FDG-PET is not recommended by the SBEM panel; the ATA panel does not have a position on that issue.

Regarding the management of DTC, both panels recommend total thyroidectomy to patients with diagnosis of DTC, suggesting that lobectomy may be performed in cases of low-risk papillary carcinoma. The recommendations for lymph node dissection are similar in both panels, as is the recommendation for using the AJCC/UICC (TNM) staging system. Prophylactic central neck dissection may be considered in cases of advanced tumors (T3 or T4).

The need for postoperative radioactive (RAI) remnant ablation is source of much controversy amongst thyroidologists. RAI ablation is not recommended in cases of very low risk (T1N0M0) by both panels, but the SBEM panel suggests that the decision to ablate cases of low risk (T1N0M0 with multifocal involvement or

T2N0M0) should be made based on the levels of post-surgical stimulated thyroglobulin (Tg). Even though low serum Tg level at the time of ablation is predictive of the absence of residual disease, measuring stimulated Tg post-surgically increases costs and is not widely available. Ablation is strongly recommended by both panels (levels A/B) only in cases of patients with persistent tumor, metastasis, or high/intermediate risk of recurrence. The ATA panel is more detailed in regards to ablation recommendations, and may be more useful to guide clinicians. Nevertheless, the degrees of the recommendations are not strong, and are mostly based on the expert opinions. There is a tendency, however, to recommend remnant ablation only to patients with high-risk, when the benefits outweigh the risks. There are concerns regarding the side effects caused by RAI in a population that is relatively young and that has a long life expectancy despite the risk of cancer recurrence.

Both panels strongly recommend ablation following recombinant human TSH (rhTSH) stimulation, rather than thyroid hormone withdrawal. Clearly there are many benefits of rhTSH administration, particularly regarding the patient well-being, but it should be noted that ablation success rates are the same when compared with those achieved by ablation following thyroid hormone withdrawal. In patients with tumor persistence, and in children or teenagers, thyroid hormone withdrawal is still preferred.

Regarding the recommended RAI activity, there is a tendency to use lower doses in low-risk patients. The SBEM panel is more specific, and recommends 30 mCi to low-risk patients; the ATA panel is more flexible, and suggests that 30 to 100 mCi may be administered. In that regard, the low dose recommended by the SBEM panel seems to be more adequate because it is based on strong evidence that it lowers the risks and side effects associated with RAI, without compromising effectiveness in low-risk patients (17). Pre-ablation low-iodine diet is recommended by both panels.

Before ablation, neither panel recommends performing whole body scan (WBS) at that time, unless in the absence of data on surgical extension, or on tumor pathology results. There is much controversy on whether the pre-dose WBS reduces the efficacy of RAI ablation due to the stunning effect, and whether it changes the outcomes in patients whose surgical and pathology data are known (18). On the other hand, post-ablation WBS is recommended for all patients by both panels.

The follow-up of patients with DTC submitted to surgery and RAI ablation is initially based on neck US and measurements of Tg (baseline and stimulated by thyroid hormone withdrawal or rhTSH) and TgAb, and subsequent approaches may be considered based on their results. In case of patients with Tg > 1 ng/mL (while on levothyroxine) and normal US, the SBEM panel recommends first imaging with thorax computerized tomography or FDG-PET, whilst the ATA panel suggests diagnostic WBS. Given the fact that diagnostic WBS is performed with lower activities of RAI and is less sensitive than therapeutic RAI, the SBEM recommendation may be more adequate. The usefulness of the diagnostic WBS, even after stimulation with rhTSH, is questioned by both panels. Regarding the follow-up and management of treated patients (including TSH suppression and management of patients with metastasis), both panels agree on many issues. However, there is some concern on whether clinicians from developing countries are able to apply all recommendations in settings of limited resources.

In conclusion, the guidelines addressing the management of hypothyroidism and the consensus on thyroid nodules and cancer provide valuable information for clinicians managing those disorders. From a decision-making perspective, the presented recommendations should be followed as guidelines rather than blindly accepted, and factors inherent to the patients and to the clinical setting should be taken into account. There are still many unanswered questions that need to be addressed in large prospective controlled trials.

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