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Consensus

Management of thyroid dysfunctions in the elderly. French Endocrine Society consensus 2019 guidelines. Short version☆

La version courte du consensus « Management of thyroid dysfunctions in the elderly »

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The elderly population is classically defined by the World Health Organization (WHO) and in the international literature, including in endocrinology, as aged more than 65 years; "geriatrics" begins with 75 year-old patients with multiple pathology. The prevalence of loss of functional autonomy due to comorbidities increases sharply after 85 years of age.

In the French population, life-expectancy is increasing by 3 months every year, and the over-65-year-old population is now 18% of the general population, and 9% in over-75-year-old subjects in France.

1. Q.1. Whom to screen for thyroid dysfunctions?

The symptoms of thyroid dysfunctions are relatively non-specific in the elderly, who tend to show fewer symptoms overall (Carlé et al. [1]). A high level of clinical vigilance is required not to overlook thyroid dysfunction. However, this needs weighing against the risk of over-prescription of thyroid examinations, which often reveal transient biological abnormalities that are actually secondary to other general diseases or medical treatments, and unrelated to any thyroid pathology, and almost always without any clinical impact, giving rise to unnecessary treatment and pointless and costly iterative check-ups.

Guideline 1.1 Hormonal thyroid exploration is indicated in previously unknown atrial fibrillation, cognitive disorder of recent onset, unexplained depression or other signs of thyroid dysfunction (Grade 1+++).

Guideline 1.2 Thyroid function screening is not indicated in the elderly (Grade 1++).

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In case of symptoms prompting thyroid function assessment that finds normal TSH level, there is no reason to repeat the assay within 6 months or a year in the absence of new clinical events.

Guideline 1.3 In the absence of new clinical events, there is no reason to repeat hormonal thyroid exploration that came out normal (Grade 1+++).

Thyroid function tests are often non-specifically disturbed in general non-thyroid diseases, especially in acute phase. Thyroid function evaluation is better avoided in case of intercurrent pathology without strong suspicion of thyroid dysfunction if a diagnosis of thyroid dysfunction would alter the ongoing treatment (for example, for recent atrial fibrillation). Thyroid evaluation work-up is better performed outside of the acute episode. This is especially true for hospitalized patients. There are no data determining a particular interval to be respected, but work-up in practice is usually repeated at a 4–12 month interval, although this depends on the context and particularly on the progression of the thyroid dysfunction.

Guideline 1.4 Except if diagnosis of thyroid dysfunction would alter ongoing treatment, thyroid function assessment is best not performed during acute episode of intercurrent diseases, and especially during unscheduled hospital stay (Grade 1+++).

2. Q.2. How to screen for thyroid dysfunction in the elderly?

Small changes in free T4 (FT4) concentration are accompanied by much greater changes in TSH levels. This remains true in the elderly, whatever the relation between the two (linear, sigmoid or logarithmic) (Rothacker et al. [2]) and is a good reason for assaying TSH concentration for thyroid exploration in this age group, except in case of central pathology (hypothalamic or pituitary diseases).

Interpreting TSH in the elderly should always take account of variations that may be due to medication or non-thyroid pathologies.

Guideline 2.1 Diagnosis of thyroid dysfunctions is based on TSH assay alone in first line (Grade 1+++).

Guideline 2.2 There is no reason in first line to perform free T4 or free T3 assay, screen for antithyroid antibodies or perform thyroid ultrasound scan (Grade 1++).

3. Q.3. What are the TSH reference values in the elderly?

The reference range for a biological parameter is a statistical notion (range including 95% of subjects without the pathology in question) and does not in itself determine what is pathological, and should therefore not be used alone for treatment decision-making.

Guideline 3.1 The lower limit of normal for TSH assay is usually 0.4 mIU/L. This threshold is relatively unaffected by age (Grade 2+).

For the upper limit, the TSH distribution is skewed rightward, and no universal threshold can be set. Given the above-mentioned reservations, we propose a pragmatic solution: for over-60 year-old patients, the upper limit of normal range is the patient's age (decade) divided by 10: e.g., TSH $\leq$ 7 for a 70 year-old, or $\leq$ 8 mIU/L for an 80 year-old subject.

Guideline 3.2 The upper limit of normal range for TSH increases with age. For simplicity, it is recommended in clinical practice in over-60 year-old subjects to use the patient's age (decade) divided by 10: e.g., $\leq$ 8 mIU/L for an 80 year-old subject (Grade 2+).

4. Q.4. What procedure in patients with low TSH level?

4.1. Q.4.1 What diagnostic procedure in patients with low TSH level?

Guideline 4.1.1 Low TSH level should be systematically assayed except in the context of clinical emergency (Grade 1++).

The inter-assay interval depends on the clinical situation, initial TSH value and cardiovascular context.

Guideline 4.1.2 In case of TSH > 0.1 mIU/L, only TSH control is recommended; in case of TSH < 0.1 mIU/L, control should associate FT4 assay and FT3 assay if FT4 is normal (Grade 2+).

FT3 assay should be interpreted in the light of the clinical context and ongoing medications.

4.2. Q.4.2 What procedure if TSH level later normalizes?

Guideline 4.2 There is no need for systematic control of TSH in the absence of clinical signs (Grade 1++).

Very few patients with isolated low TSH level go on to develop hyperthyroidism within 5 years, and most recover a normal thyroid function.

In case of low TSH after iodine overload, any further iodine injection requires control of thyroid function test (cf. Guideline 4.6.2).

4.3. Q.4.3 What complementary examinations are needed in case of confirmed thyrotoxicosis?

Thyrotoxicosis consists in the clinical and biological consequences of excess thyroid hormone in tissues. The term "hyperthyroidism" refers for situations of hyperfunction of the thyroid gland. In the elderly, the most frequent cause of thyrotoxicosis is overdose of levothyroxine.

4.4. Q.4.4 What specificities of hyperthyroidism treatment and follow-up in the elderly?

Autonomous pathology (multinodular goiter, toxic adenoma) is more frequent than Graves' disease. In elderly patients with Graves' disease, prolonged synthetic antithyroid therapy is often unsuited.

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Guideline 4.3.1 Etiological assessment depends on the clinical context and treatment objectives, but in most elderly patients treatment options are relatively unaffected by the etiology of the hyperthyroidism. Work-up in first line comprises thyroid scintigraphy (Tc99 or I-123 as available) to provide etiologic and pre-treatment data (Grade 2+). It should not postpone treatment initiation.

Guideline 4.3.2 The usefulness of anti-TSH receptor antibody assay is to be assessed according to context and the likelihood of Graves' disease (Grade 2+).

Guideline.4.3.3 Thyroid ultrasound scan should not be performed in first line, as it is uninformative on etiology and is associated with a risk of over-diagnosis of thyroid nodule. It is to be reserved to particular situations: clinical abnormalities on neck palpation or pre-treatment work-up (notably before radioiodine therapy), or in the context of amiodarone-related thyrotoxicosis (Grade 2+).

Definitive treatment is usually to be preferred, notably iodine^{131} if not contraindicated.

Guideline 4.4.1 In elderly subjects with permanent atrial fibrillation, tachy-arrhythmia, ischemic cardiopathy or risk of acute coronary syndrome, or with cardiovascular symptomatology triggered or aggravated by their hyperthyroidism, the objective is definitive treatment, with iodine^{131} ablation in first line after medical control of thyrotoxicosis (synthetic antithyroid drugs) (Grade 2++).

Guideline 4.4.2 In fragile patients without serious cardiovascular pathology with moderate hyperthyroidism and contraindications to total thyroidectomy or if iodine^{131} is unavailable, long-course low-dose synthetic antithyroid drugs may be used (Grade 2++).

Guideline 4.4.3 In the absence of contraindications, total thyroidectomy is indicated in case of large goiter, signs of compression and/or thyroid cancer (Grade 1++).

In over-65 year-old patients with large multinodular goiter (>40–60 mL) and TSH < 0.4 mIU/L, radical treatment such as total thyroidectomy is recommended in the absence of major cardiovascular risk factors. If surgery is contraindicated, repeated low-dose iodine^{131} can restore normal thyroid function and reduce goiter volume (by 40% in 6–12 months). Surgery is also indicated in some other situations: thyroid cancer, primary hyperparathyroidism (Kahaly et al. [3], Ross et al. [4], Biondi and Cooper [5]).

4.5. Q.4.5 What procedure in case of persistent low TSH level with normal FT4?

This situation corresponds to subclinical hyperthyroidism. In the literature, TSH level sometimes normalizes at a variable delay of some months to some years, and progression to over or clinical thyrotoxicosis is rare (Das et al. [6]). There is, however, a risk of complications: notably cardiovascular with atrial fibrillation.

Guideline 4.5.1 Persistent low TSH level with normal FT4 and FT3 concentrations requires endocrinologic opinion (Grade 1++).

Guideline 4.5.2 In case of low TSH level with normal FT4 and FT3 concentrations, thyroid scintigraphy is recommended to identify autonomization (toxic adenoma, multinodular goiter) and assess comorbidities and risk of complications, notably cardiovascular and bone diseases (Grade 2+).

In the absence of evidence from randomized clinical trials, management is founded on expert consensus. The aim is more to prevent complications such as atrial fibrillation (AF) than to treat the disease itself: a large majority of patients are asymptomatic, and their biological abnormality is revealed fortuitously.

4.6. Q.4.6 Should subclinical hyperthyroidism in the elderly be treated?

Decision factors to treat or not to treat comprise: patient age, etiology of hyperthyroidism, TSH level (< or >0.1 mIU/L), and risk of complications (notably AF). The international guidelines (European Thyroid Association, American Thyroid Association) are not fully concordant: roughly, the ETA recommends treating all "older" subjects (>65 years) (Kahaly et al. [3]), while the ATA recommends treating all over-65 year-old patients with TSH < 0.1 mIU/L (Ross et al. [4]); for those with moderately decreased TSH level (0.1–0.4 mIU/L), treatment is indicated in case of osteoporosis, atrial fibrillation or cardiopathy.

In the absence of interventional studies assessing the risk/benefit ratio, and taking account of:

- the lack of evidence that treating subclinical hyperthyroidism significantly reduces the risk of atrial fibrillation;
- the risk of definitive hypothyroidism following treatment for hyperthyroidism, and;
- several reports that achieving normal thyroid function during levothyroxine treatment is difficult in the elderly, with high rates of low or high TSH levels (Canaris et al. [7], Somvaru et al. [8]), we recommend a cautious attitude weighing risk and benefit for each individual.

Guideline 4.6.1 The decision between treatment and surveillance for subclinical hyperthyroidism is to be discussed with the individual patient and/or family, taking account of expected benefit (basically, reduced risk of atrial fibrillation) and possible risk (basically onset of definitive hypothyroidism).

Advanced age, the degree in TSH decrease (arbitrary threshold generally set at 0.1 mIU/L), etiology of hyperthyroidism (autonomous pathologies with greater risk of progression to over or clinical thyrotoxicosis) and comorbidities (cardiopathy or osteoporosis) are elements that encourage the offer of treatment. Their absence prompts discussion with the patient of regular monitoring (Grade 2+).

Following contrast medium injections, especially in patients with advanced age, goiter or history of thyroid dysfunction, there is clear risk either of thyrotoxicosis episodes or of inducing hyperthyroidism.

The literature data fail to identify any particular protocol for preventing iodine overload due to contrast medium injections. A single prospective randomized study reported preventive benefit for synthetic antithyroid drugs and sodium perchlorate (Nolte et al. [9]), providing rapid urinary elimination of the iodine excess and thus avoiding overload.

A few days' treatment around the radiology examination, using synthetic antithyroid drugs or sodium perchlorate (if available) could be implemented, with empiric dosage and duration, according to the 2010 Société française d'endocrinologie – Groupe de recherche de thyroïde – Société française de radiologie guidelines for iodized contrast medium injection in thyroid pathology. Thyroid function should be checked a few weeks after the radiology examination. If contrast medium is expected to be re-administered, as

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in oncologic surveillance, and the risk of thyrotoxicosis is significant, iodine^{131} ablation may be considered some time after contrast medium injection.

Guideline 4.6.2 In case of known thyroid pathology, and notably multinodular goiter, and especially if TSH level is transiently low, prophylactic treatment may be implemented around iodized contrast medium administration (Grade 2+).

Guideline 4.6.3 When a form of treatment has been chosen, modalities are the same as for over hyperthyroidism (Grade 2++).

Guideline 4.6.4 If surveillance without treatment is chosen, it is based on TSH and FT4 monitoring (plus FT3 if FT4 is normal) at 3 months then every 6 months, during all life. A clinical check-up should also be made, notably to ensure maintained sinus rhythm (Grade 2+).

Guideline 4.6.5 Amiodarone is a frequent cause of thyrotoxicosis (and hypothyroidism) in the elderly. Treatment does not differ from that in younger patients (Grade 2++). However, given the potential severity of thyrotoxicosis and the complexity of management, an endocrinologic opinion is indispensable (Grade 2+++).

Management of thyroid dysfunctions occurring during amiodarone treatment was the focus of very recent ETA guidelines (Bartalena et al. [10]). This will not be dealt in this manuscript, as patient age does not affect diagnosis or treatment modalities.

5. Q.5 What procedure in case of high TSH level in the elderly?

5.1. Q.5.1 What diagnostic attitude in case of high TSH level?

Guideline 5.1 All high TSH level should be controlled: within the month in case of clinical signs, and within 3 months in the absence of symptoms or if the TSH level is < 10 mIU/L (Grade 2+).

In the Framingham study, prevalence of hypothyroidism (TSH > 10 mIUL) was 4.4% in over-60 year-old patients (5.9% in women, 2.3% in men) (Sawin et al. [11]).

5.2. Q.5.2 What examinations are mandatory or contributive in case of high TSH level (checked on repeat assay?

No examinations alter treatment for elderly patients with high TSH level: antithyroid antibody screening, FT4 assay, lipid profile, or thyroid ultrasound (except in case of abnormal neck palpation).

On the practical level, no additional examination modifies the management of elderly patients with high TSH level, in particular: the search for antithyroid antibodies, the free T4 assay, the lipid profile, thyroid ultrasound (except abnormality of cervical palpation). These examinations are useless and are not recommended in practice in the elderly with hypothyroidism.

Guideline 5.2 No complementary examinations are needed for high TSH level in elderly patients (Grade 2+).

5.3. Q.5.3 What are the indications for treating hypothyroidism?

Subclinical hypothyroidism has less impact in the elderly than in younger subjects (Barbesino [12]). Several older studies, with relatively small series, demonstrated normalization of TSH levels over time in about half of patients with "subclinical hypothyroidism" (Tabatabaie and Surks [13], Mooijaart et al. [14]).

Guideline 5.3.0 Levothyroxine therapy should be initiated only when hypothyroidism is confirmed by high TSH level on two assays (Grade 2+++).

Although formal proof is lacking, the present group recommends levothyroxine therapy when TSH is > 20 IU/L in two samples. In the absence of proven benefit (Stott et al. [15]), given the risk of thyrotoxicosis, the group advises against treatment when TSH is < 10 mIU/L on several successive controls. When TSH is 10–20 mIU/L, treatment should be considered on a case-by-case basis with the patient and family, depending on context, comorbidities, clinical signs, expected benefit, baseline TSH and progression over successive controls.

Guideline 5.3.1 Levothyroxine replacement therapy is indicated in case of TSH > 20 mIU/L in at least two controls (Grade 2+).

Guideline 5.3.2 There is no evidence of favorable risk/benefit ratio for replacement therapy in case of TSH < 10 mIU/L (Grade 2+).

Guideline 5.3.3 In patients with TSH level between 10–20 mIU/L on several assays, levothyroxine replacement therapy should be considered on a case-by-case basis, taking account of the patient's wishes, expected benefit and TSH progression (Grade 2+).

5.4. Q.5.4 What are the follow-up modalities during hypothyroidism treatment in the elderly?

Guideline 5.4.1 Treatment is based on levothyroxine at a substitutive dose of 1.1–1.3 μg/kg/day (Grade 2+).

Guideline 5.4.2 There are no indications for associating levothyroxine + triodothyronine (T3) (Grade 2+++).

Guideline 5.4.3 Levothyroxine should be introduced progressively, especially if TSH is significantly elevated and the patient's cardiovascular status is unknown (Grade 1+++).

Guideline 5.4.4 Surveillance of levothyroxine treatment for primary thyroid failure is based on TSH alone. Checks should be conducted between 6 weeks and 3 months after achieving replacement dose or any dose adaptation (Grade 1+++).

Guideline 5.4.5 The treatment objective is to have TSH level within the normal-for-age range (cf. Guideline 3.2), avoiding risk of overdose if TSH < 1 mIU/L; e.g., the upper limit of normal is 7 mIU/L for 70–79 years and 8 mIU/L for > 80 years (Grade 2+).

Guideline 5.4.6 Once normal thyroid function is achieved, annual checks of TSH level are sufficient (Grade 2+).

Guideline 5.4.7 When a treatment known to impact levothyroxine bioavailability is introduced or withdrawn, TSH level should be checked after 6 weeks (Grade 2++).

Guideline 5.4.8 If levothyroxine therapy is not indicated, TSH level should be assayed every 6 months for 2 years to assess the kinetics of progression. If TSH level is stable, annual checks are sufficient (Grade 2+).

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6. Q.6 Can levothyroxine therapy be withdrawn?

Hypothyroidism is usually definitive. In the elderly, some patients have often been taking levothyroxine for many years, frequently at low-doses, and the initial reasons for prescription may be unknown. It may sometimes be justifiable to try reducing and withdrawing a non-beneficial treatment, although obviously making sure that there was no formal indication of levothyroxine treatment (total thyroidectomy, previous iodine^{131} therapy, proven auto-immune hypothyroidism), informing the patient and securing consent. Treatment may then be withdrawn, but a TSH assay should be check at 4–6 weeks.

> Guideline 6 If the indication for levothyroxine therapy is not clear, withdrawal may be attempted, with the patient's consent and TSH check at 4–6 weeks (Grade 2+).

7. Q.7 When should an endocrinologic opinion be sought?

Whether endocrinologic opinion should be sought depends on the context and is at the physician's discretion. Given the possible complexity of situations and treatment considerations, the present group recommends endocrinologic opinion for all patients with prolonged low TSH level. Specialist opinion should also be sought in the following situations:

- at diagnosis:
  - signs of severity (coronary context, auto-immune polyendocrinopathy, over hypothyroidism, myxedema coma, etc.),
  - discordance between clinical and biological findings,
  - according to etiology: iatrogenic, central hypothyroidism,
  - discussion of treatment objectives;
- during follow-up:
  - doubt regarding treatment objectives,
  - difficulty in interpreting results (central hypothyroidism),
  - onset of unfavorable symptoms,
  - lack of improvement (treatment resistance, drug interactions, malabsorption, poor adherence, etc.),
  - poor tolerance,
  - need to change levothyroxine formulation (e.g., impossibility of oral administration).

> Guideline 7 Endocrinologic opinion should be sought in proven hyperthyroidism or persistent low THS level. Grade 2++.

Disclosure of interest

J. Abeillon: HAC, Sanofi, Uni-pharma.
A. Cailleux: Sanofi, HAC.
P. Caron: Merck-Serono, HAC, Genevrier, Uni-pharma.
B. Goichot: Merck-Serono, Uni-pharma, HAC.
L. Groussin: Merck-Serono, HAC.
M. Klein: Merck-Serono, Genzyme, HAC, Sanofi.
R. Leroy: Merck-Serono, HAC, Sanofi.
V. Raverot: Abbott Diagnostic, Roche Diagnostic, IDS, HAC.
L. Vija: Merck-Serono, Genzyme, HAC, Sanofi.
The other authors declare that they have no competing interest.

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