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Graves' disease, multinodular goiter and subclinical hyperthyroidism

Maladie de Basedow, goitres multinodulaires et hyperthyroïdie infra-clinique

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Abstract

Subclinical hyperthyroidism is a common clinical entity, defined by serum TSH below the reference range, with normal FT4 and FT3 levels in an asymptomatic patient. Whether or not subclinical hyperthyroidism should be treated remains a matter of debate. Cross-sectional and longitudinal population-based studies demonstrate association of subclinical hyperthyroidism with risk of atrial fibrillation and osteoporosis, and with cardiovascular and all-cause mortality. However, there are no randomized clinical trials addressing whether long-term health outcomes are improved by treating subclinical hyperthyroidism; in the absence of evidence one way or the other, it seems appropriate to use decision trees taking account of TSH concentration and presence of risk factors (age >65 years or post-menopause, osteoporosis and cardiac disease).

Keywords: Subclinical hyperthyroidism; thyroid; TSH; multinodular goiter

Résumé

L'hyperthyroïdie infra-clinique est une entité clinique fréquente. L'hyperthyroïdie infra-clinique est définie biologiquement par la présence, chez un patient asymptomatique, d'une concentration de TSH infranormale, mais avec la persistance de concentrations normales de T4L et T3L. Que l'hyperthyroïdie infra-clinique doive être ou non traitée reste un sujet de débat. Les études transversales (*cross-sectional studies*) et les études longitudinales basées sur le suivi de populations ont permis de démontrer qu'une hyperthyroïdie infra-clinique est associée à une augmentation des risques de fibrillation auriculaire et d'ostéoporose, ainsi qu'à une augmentation de la mortalité cardiovasculaire et de la mortalité globale. Cependant, on ne dispose pas d'essais cliniques randomisés permettant de savoir si le traitement de l'hyperthyroïdie infra-clinique améliore de manière durable ces différents paramètres. Par conséquent, en l'absence de preuves en faveur ou en défaveur du traitement de l'hyperthyroïdie infra-clinique, il semble opportun de s'inspirer des algorithmes qui prennent notamment en compte la concentration de TSH et la présence de facteurs de risque (âge > 65 ans, ostéoporose, ménopause et présence d'une pathologie cardiaque).

Mots clés : Hyperthyroïdie infra-clinique ; thyroïde ; TSH ; goitre multinodulaire

Definition

Subclinical hyperthyroidism (SCH) is defined by biological criteria regardless of the presence of clinical signs of hyperthyroidism. SCH is biologically determined by a concentration of TSH below the normal with concentrations of free T4 (FT4) and free T3 (FT3) within normal limits (1). SCH can further be divided according to its biological severity, into two categories: grade I SCH with lowered but still largely measurable TSH concentration (typically between 0.1 and 0.39 mU/l) and grade II SCH with low or

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undetectable TSH concentration (typically <0.1 mU/l) (2). The measurement of TSH is very sensitive for diagnosing even mild thyroid dysfunction. Minimal variations in hormonal impregnation will cause a rather large modification in TSH concentration. Therefore changes in the concentration of FT4 within the normal range will result in increases or decreases in the TSH concentration that may be outside reference values (3,4). The term of “subclinical” can be misleading as it suggests the absence of symptoms and signs of thyroid hormone excess while they may be present but undiagnosed or not attributed to SCH like atrial fibrillation or osteoporosis. Giving an absolute biological definition of subclinical thyroid disease is difficult since every individuals may have their own standards evolving in a much narrower range than the accepted norms for a population (5). For all these reasons the diagnosis of SCH may occur in different situations: (i) for an individual presenting clinical signs of hyperthyroidism, (ii) for an individual without clinical signs of hyperthyroidism but with a medical condition that can be affected by SCH, (iii) during a routine biological screening that included thyroid hormone tests. The clinical benefits of screening for subclinical thyroid disease is a matter of debate (6,7).

Etiologies of subclinical hyperthyroidism

The first step is to exclude an exogenous SCH (iatrogenic) due to excessive intake of thyroid hormones. This may be intentional (in the follow-up of a thyroid cancer) or unintentional (too high L-thyroxin dosage in the substitution treatment of hypothyroidism) (8). Importantly, a lowered TSH concentration does not always imply a diagnosis of SCH and its interpretation should always take into account the general clinical context of the patient (1,3,4). A lowered concentration of TSH without SCH can be observed during central hypothyroidism, in acute non-thyroid disease or secondarily to some medications (glucocorticoids, dopamine etc.). A low concentration of TSH (but most often >0.1 mU/l) can also be observed in smokers and in some ethnic groups (9) (Table 1).

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Except for the situation of pregnancy, which will not be discussed here, endogenous SCHs can be of two types: transient or persistent (Table 2).

Transient SCHs are mainly due to clinical hyperthyroidism in the early phase of treatment, to thyroiditis (subacute, silent, postpartum) or to iodine contamination in the presence of autonomous tissue. The etiologies of persistent SCH are the same as those of clinical hyperthyroidism: Graves' disease (although its expression is usually clinically obvious), toxic autonomous nodule or multinodular goitre. Few studies have systematically analysed the relative proportions of the different causes of SCH. These proportions vary according to the age and sex of the patients, the iodine intake of the studied population and threshold of TSH set to define SCH. In countries where iodine intake is important, such as Japan, approximately 65% of SCHs are attributable to Graves' disease (10), while this proportion is less than 15% in populations where iodine intake is lower (11,12). Age is also an important factor, as Graves' disease classically occurs before the age of 60, while toxic multinodular goitre is the predominant cause observed in older subjects.

Prevalence

The prevalence of SCH varies across the different studies from 0.4% to 11% (4). It mainly depends on the TSH threshold used to define SCH (for most studies: 0.1 or 0.4 mU/l), as well as the age, sex and iodine intake of the study population. The prevalence increases with age and is greater in iodine deficient areas.

Development of subclinical hyperthyroidism due to Graves' disease or toxic autonomous nodules

The mode of development of SCH is very different in autonomous nodules compared to Grave's disease. The classical presentation of Graves' disease is a sudden onset clinical hyperthyroidism caused by the presence of antibodies stimulating the TSH receptor. The subclinical presentation, although less common, is increasing and would now account for

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almost 20% of Graves' disease cases according to a recent Italian study (15). It could be related to a lower volume of the thyroid (15). Similar to the classical presentation of Graves' disease, remissions are frequently observed.

Hyperthyroidism due to autonomous toxic nodules may occur in two slightly different types of pathologies: autonomous toxic nodules within a multinodular goitre (toxic multinodular goitre) or an isolated autonomous toxic nodule. The pathogenesis of goitres is linked to genetic factors and environmental issues that are not yet fully identified (16). Iodine deficiency is by far the most frequently mentioned cause in the pathogenesis of goitres, consistently with the observation of a higher prevalence of goitres in areas with even mild iodine deficiency compared to countries with high iodine intake, such as the United States or Switzerland. According to the SU-VI-MAX study, the prevalence of goitre in France is about 11% among men and 14% among women (17). Iodine deficiency however is not the only factor involved and genetic factors may play an important role, as suggested by the family predisposition that is frequently observed. Tobacco and multiparity are also contributing factors. Simple goitres usually appear in adolescence or among young adults, especially women. Most goitres grow very slowly. Over the years and decades, goitres increase in size and will progress to become nodular with the development of autonomous areas, most often secondary to activating mutations of the TSH receptor (18). Once the number of autonomous cells reaches a critical mass, the concentration of TSH decreases, becomes infra-normal and SCH can appear. The development of SCH in a patient with a toxic autonomous nodule follows the same pathophysiological pathway: activating mutation of the TSH receptor, development of a clone of autonomous cells which, having reached a critical mass, leads to a decrease in TSH concentration (Figure 1). In a single recent study, it was found that the median size for an autonomous nodule to lead to a decrease in TSH concentration is about 3 cm (19).

Progression towards clinical hyperthyroidism

Based on the few large prospective studies, the annual rate of progression from SCH to clinical hyperthyroidism varies from 0.3% to 41% (3,20,21). The great variability in the results underlines the heterogeneity in the methodologies that were used and the populations that were studied. Based on the most recent studies, 1% to 5% of SCHs on average evolve annually to clinical hyperthyroidism. The progression rate is higher among patients with autonomous nodules (isolated or within a multinodular goitre) than in those with Graves' disease. Progression to clinical hyperthyroidism is usually slow in the presence of autonomic nodules, unless the iodine intake increases abruptly (iodine-induced hyperthyroidism). This situation is most often observed following an iodine overload after an injected CT scan or the intake of iodine containing medications (22). In Graves' disease, the progression to clinical hyperthyroidism is rare but can be rather brutal. Regardless of the underlying pathology, the rate of progression to hyperthyroidism also depends on the concentration of TSH at the time of the diagnosis: in grade I SCH, the risk of progression to clinical hyperthyroidism is lower. The concentration of TSH can also spontaneously normalize in 25% to 50% of cases (23,24).

Complications of subclinical hyperthyroidism

In the absence of major intervention trials, most of the described effects of SCH are reported from observational studies and must be interpreted with caution due to the important heterogeneity in their design and methodology. Indeed, the underlying disease, the severity of SCH, and the population characteristics of the populations vary in these studies where the diagnosis often relies on a single dosage of TSH concentration and the duration of the disease is unknown. This high heterogeneity may explain the conflicting results. The main and consensual described effects of SCH are on the cardiovascular system, bone mineral density and quality of life.

Cardiovascular complications

- Functional and structural alterations

The effects of hyperthyroidism on the myocardium and on the heart rate are well known (25). Even in euthyroidism situation, the concentration of FT3 is associated with cardiac parameters such as left ventricle size or heart rate (26). Compared to euthyroid controls, patients with SCH have a higher heart rate and increased frequency of both atrial and ventricular ectopic beats (27–30). Some studies have also reported changes in echocardiographic parameters (increase in the left ventricle mass, diastolic dysfunction etc.) (28,29) although these effects have not always been confirmed in population studies (31,32). On the other hand, multiple studies show a link between SCH and the risk of heart failure, especially in the elderly and in subjects with grade II SCH (33,34).

- Atrial Fibrillation

The association between atrial fibrillation (AF) and SCH was first observed in 1994 after the 10-year follow-up of subjects from the Framingham cohort. An increased risk of AF was found for SCH subjects compared to euthyroid controls with a stronger association for those with a TSH concentration lower than 0.1 mU / l (grade II SCH) (35). In another large study including 613 SCH and 725 hyperthyroidism patients, the risk of AF was strongly increased for subjects with SCH compared to the euthyroid controls (relative risk of 5.2). Interestingly, the relative risk of AF was no different from that observed in subjects with clinical hyperthyroidism (36). These results were later confirmed in cross-sectional studies (37) and prospective studies (38) with a higher risk of AF for patients with the lowest TSH concentrations (37–39).

- Cardiovascular events and mortality

An association between SCH and an increase in cardiovascular mortality and overall mortality has been reported in some prospective studies (40–42) contrasting with other

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findings (38). However, a meta-analysis based on 5 prospective cohort studies confirmed an increased risk of cardiovascular events, cardiovascular mortality and overall mortality (hazard ratio of 1.2 for overall mortality) for subjects with SCH, with a greater effect when the TSH is lower than 0.1 mU/l (43).

Bone mineral density, risk of fracture

Thyroid hormones have an activating effect on bone resorption and hyperthyroidism is a known risk factor for osteoporosis (44). Regarding SCH, studies have more conflicting results. While most studies show a decrease in bone mineral density in SCH postmenopausal women (45), SCH does not seem to alter bone density in men or premenopausal women (46,47). A recent meta-analysis concluded to a small association between SCH and a lower bone mineral density (in hip measurements) (48). Regarding the risk of fractures, data are also conflicting. A study that included postmenopausal women with grade II SCH (TSH <0.1 mU/l) showed a significantly increased risk of hip and vertebral fractures compared to the controls (relative risk of respectively 3.6 and 4.5) (49) when another study with a higher TSH threshold (0.45 mU/l) reported an increased risk only in the male population (50). A recent meta-analysis of 13 prospective studies confirmed an association between SCH and an increased risk of vertebral fracture (hazard ratio of 1.5) and hip fracture (hazard ratio of 1.4) with stronger associations when TSH was lower than 0.1 mU / l and when the exogenous origin of SCH (thyroid hormones intake) had been excluded (51).

Metabolic effects

Clinical hyperthyroidism leads to weight loss, decreased blood cholesterol levels and may contribute to insulin resistance (52,53). Recent data suggest that SCH may have similar effects (54). Many cross-sectional studies have reported correlations between thyroid hormones and metabolic parameters such as body weight, fasting glucose and cholesterol (55,56). In one of the few studies including patients with subclinical thyroid disorders, a

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positive correlation was found between TSH and body mass index (BMI) with a difference in BMI of 1.9 kg/m^2 between the group with the lowest level of TSH and the one with the highest level (55). Once again, the lower concentrations of TSH are associated with greater metabolic effects (54).

Symptoms, quality of life, and cognitive function

SCH can be associated with clinical symptoms of hyperthyroidism, such as palpitations, tremors, sweating, anxiety and impaired quality of life linked to these symptoms (28,29).

Hyperthyroidism is associated with impaired cognitive function and screening for thyroid dysfunction is recommended for patients with cognitive impairment. Regarding the association between cognitive impairment, dementia and SCH, until recently study results seemed very inconclusive (57). More recent data (58) and a meta-analysis including only prospective cohort studies indicate a small association between SCH and the risk of dementia (risk ratio of 1.67) although decrease in Mini Mental State Evaluation was not significantly faster in SCH subjects (59).

Therefore, despite the deceptive term "subclinical", SCH has consequences which are mainly cardiovascular (cardiac structural and functional changes, increased risk of atrial fibrillation, increased cardiovascular mortality). SCH also leads to a decreased density of bone minerals and increases the risk of fractures. It may affect the quality of life and have metabolic effects. The consequences of SCH are mainly observed in older individuals and when the TSH is lower ($<0.1 \text{ mU/l}$).

Treatment of subclinical hyperthyroidism

The three main therapeutic options, antithyroid drugs (thiamazole, carbimazole), radioiodine therapy and surgery should be used following the same criteria as in clinical hyperthyroidism.

Antithyroid drugs.

Their indication is mainly limited to Graves' disease. Their side effects are well known: leukopenia, agranulocytosis, cutaneous allergies, arthralgia, hepatitis, amongst others. When SCH is caused by a toxic multinodular goiter (TNG) or a toxic adenoma, thyroid dysfunction is typically persistent and the risk of recurrence after a long term therapy is above 95% (60). However, antithyroid drugs still have a place in the treatment of SCH due to thyroid autonomy, albeit in limited cases, in the following situations: 1) as a lifelong treatment at the lowest efficient dose in elderly nursing home patients with urinary incontinence or the inability to comply with radioprotection measures, 2) as a pretreatment before RAI therapy or surgery in particularly fragile patients with cardiac disease, 3) as a temporary treatment for patients at risk of acute exacerbation due to iodine overload (61,62)

Radioiodine therapy.

It is the treatment of choice for subclinical hyperthyroidism in elderly subjects. In multinodular goitres (MNG), the treatment is based on the fact that ^{131}I is preferentially picked up by the autonomous cells, which leads to a gradual destruction of the autonomous areas and progressive restoration of euthyroidism. Difficulties are sometimes encountered when treating patients with MNG, especially large ones, because of low (sometimes <30% at 24h) and heterogeneous ^{131}I uptake, resulting in high calculated therapeutic doses of ^{131}I that may exceed recommendations for ambulatory treatments (15 mCi ~ 555 MBq). In order to increase the uptake of radioiodine and thus reduce the administered dose or increase its effectiveness, recombinant TSH (rhTSH) has been used at doses between 0.1 and 0.9 mg, 24 to 72 hours before treatment with ^{131}I . The administration of rhTSH enables at least doubling of the ^{131}I intake at 24h, resulting in a greater goitre volume reduction (63–67) and more frequent occurrence of hypothyroidism (52% of cases after 5 years against 13% in the ^{131}I

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alone group (68)). RhTSH is however generally not covered by health care in this indication, and other studies have analysed the effect on ^{131}I intake of an antithyroid drug pre-treatment to increase the TSH concentration. A recent randomized study has shown that in patients with SCH due to MNG, 30 mg/day of thiamazole administered for 6 weeks and stopped 72 hours before treatment with ^{131}I allowed doubling of the ^{131}I intake at 24 hours (from 32% to 63%) and therefore reduction of the therapeutic calculated dose without altering the effectiveness of the treatment (69). **In subclinical Graves' disease, radioactive iodine is also a valuable option in patients > 65 year old to avoid the risk of recurrence in fragile patients. Radioactive iodine must be avoided in woman still wishing to become pregnant and in patients with active orbitopathy.**

Surgery

Surgery is the treatment of choice for compressive multinodular goitre or in nodules with suspected malignancy (i.e. non-oval shape, irregular margins, microcalcifications, marked hypoechogenicity) (70). Thyroidectomy will be total in the presence of bilateral multinodular goitre but a simple lobectomy may be a valid option in the case of a unilateral goitre or a single toxic nodule. The complications of thyroidectomy and especially lesions of the recurrent nerve depend on the experience of the surgical team. In expert hands, the risk of permanent complications following total thyroidectomy (recurrent nerve paralysis, hypoparathyroidism) is very low (71,72). This complication rate is lower than 1-2% and decreases with systematic identification of recurrent nerves and of the parathyroid glands. These results are however not applicable to less experienced teams, for which complication rates can be more important in less extensive surgery (73,74). Moreover, the indication of lobectomy must be balanced with the risk of nodular recurrence in the contralateral lobe, which may lead to new invasive investigations (fine needle aspiration), or even reoperation. However, even if nodular recurrence after lobectomy is common, it is rarely clinically

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significant and according to a recent study reoperations are rare (75). Lobectomy does not rule out the need for postoperative supplementation, since approximately 20% of patients develop hypothyroidism (often subclinical) (76). Nevertheless, it allows easier control of the thyroid function after total thyroidectomy (75).

Effects of the treatment of subclinical hyperthyroidism

In the absence of major intervention trials, there is little evidence of the effectiveness of the treatment outside the normalization of thyroid function. However, a few studies have analysed the changes occurring after treatment of SCH.

Cardiovascular parameters

Although with a limited sample size, several studies report changes in cardiovascular parameters after treatment of SCH. A prospective study showed an improvement in echocardiographic parameters and a decrease in the frequency of ectopic heart beats after treatment of SCH with antithyroid drugs (28). Similarly, 3-4 months after ¹³¹I treatment of SCH, heart rate decreased and cardiac parameters measured by heart MRI improved compared to euthyroid controls, (77). There are, however, no data regarding the effectiveness of treatment on the risk of atrial fibrillation, on cardiovascular events and on mortality.

Bone mineral density and body composition

There is some evidence of improvement of bone mineral density after treatment of SCH. In a non randomized controlled intervention study including postmenopausal women with SCH (TSH <0.2 mU/l), bone mineral density increased (+1.5%) 2 years after normalization of TSH by radioiodine therapy, whilst it dropped (-2%) in the control untreated group (78). A similar increase in bone mineral density increase was found in another prospective study after SCH treatment compared to euthyroid controls (79), suggesting a prevention of the SCH-induced bone mineral loss with treatment. There are however no data on the effect of treatment of SCH on the prevention of fractures.

Metabolic and body weight and parameters.

Metabolic parameters are rarely reported in the interventions studies but recent data suggest an impact of endogenous SCH treatment on body weight and cholesterol. In a small prospective study with exogenous SCH patients (post-thyroid cancer therapy), no weight gain or blood cholesterol and glucose changes were reported 6 months after restoration of euthyroidism (80). However, the small number of patients (n = 12) may account for this apparent lack of metabolic effects. In two other intervention studies, weight gain and increased LDL cholesterol levels were observed after correction of SCH, suggesting a direct effect of SCH on weight and metabolism (54,79). In a study with a large number of patients, metabolic effects of total thyroidectomy for multinodular goitre were retrospectively analysed in patients with preoperative SCH (n = 74) compared with preoperative euthyroid controls. After an average of 26 months of follow-up, weight gain (+3.1 kg) and increase in LDL cholesterol (+16 mg/dl) were observed and were significantly higher in the SCH group, with a greater increase in patients with grade II SCH (Figure 2) (54). No effects on glucose tolerance were reported in these studies.

Proposed management algorithm for SCH (Figure 3)

Considering the rather conflicting literature on a common pathology and the absence of large trials on the efficacy of SCH treatment (81,82), the European Thyroid Association (ETA) published in 2015 a series of recommendations (3) similar to those of the American Thyroid Association (83). Although there is no strong evidence and no consensus, the guidelines can be synthesized in the following way. To care properly for a patient with a lowered TSH concentration, 6 main questions must be answered.

1 / Does the patient have persistent SCH?

- To screen for SCH, it is recommended to measure the TSH concentration.
- If the concentration of TSH is low, thyroid hormones (FT4 and FT3) must be measured.

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- Situations where TSH is lowered unrelated to SCH must be ruled out: medications, acute non-thyroid disease, pituitary insufficiency etc.
- The persistence of SCH must be verified by monitoring TSH concentration after 2-3 months.

2 / What is the degree of severity of SCH?

- The concentration of TSH is used to determine the severity of SCH and distinguish between grade I SCH (TSH: 0.1-0.39 mU/l) and grade II SCH (TSH <0.1 mU/l).

3 / What is the etiology of SCH?

- Patient history, age and cervical palpation may guide the diagnosis.
- Cervical ultrasound with colour Doppler-assessment of vascularity is useful if thyroid nodules are suspected.
- Thyroid scintigraphy can highlight the presence of autonomous areas with hyperfixation.
- The measurement of anti-TSH receptor antibodies may help confirm an autoimmune cause of SCH.

4 / Is this SCH harmful for the patient?

- Although this distinction is debatable, it is generally considered that subjects with a concentration of TSH <0.1mU/l are more at risk than those with a concentration TSH \geq 0.1 mU/l.
- Another important parameter to consider is the age of the patient. Morbidity associated with SCH is low in premenopausal women and in men under 60-65 years old.
- The presence of cardiovascular risk factors could also make the SCH more deleterious. In menopausal women the realization of a bone densitometry may help to better characterize the fracture risk.

5 / Should the patient be treated?

- To answer this question, one must first assess the prognosis of this SCH. If it is linked to Graves' disease, spontaneous normalization is possible. On the other hand, if it is caused by autonomous areas within a multinodular thyroid, the chances of spontaneous remission are low, especially if the concentration of TSH is <0.1 mU/l.
- The risk of progression to clinical hyperthyroidism must be taken into account and is more important in the case of a multinodular goitre than in Graves' disease.
- The concentration of TSH must be taken into account. The lower it is, the more likely it is that treatment will be useful. And, of course, the cornerstone of the decision to treat is based on the estimation of the risk for the patient to remain with an untreated SCH.

- Elderly patients

- It is strongly recommended to treat patients over 65 years old with grade II SCH to prevent progression to clinical hyperthyroidism and hopefully decrease the risk of atrial fibrillation, cardiovascular mortality and bone fractures.
- In patients over 65 but with grade I SCH, treatment may be considered to reduce the risk of atrial fibrillation, particularly in patients with a high cardiovascular risk (history of cardiovascular disease, kidney failure, diabetes etc.).

- Young patients

- In patients younger than 65 years old, treatment will be offered to patients with grade II SCH with cardiovascular risk factors or comorbidities.
- In patients younger than 65 years old, treatment of grade II SCH may be considered if the disease is persistent and / or symptomatic, especially if the etiology is clearly demonstrated (positive anti-TSH receptor antibodies or identification of autonomous nodules in thyroid scintigraphy).

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- Treatment of grade I SCH is not recommended in young, healthy individuals, given the possibility of spontaneous remission, the low risk of developing clinical hyperthyroidism and the scarcity of evidence for an increased morbidity induced by grade I SCH in young subjects.
- Simple observation is recommended for patients with a grade I SCH with normal thyroid morphology and no cardiac or bone frailty.
- In case of a surveillance approach, thyroid function should be monitored every 6-12 months or sooner in case of clinical evolution. Iodine containing medications and iodine contrast products should be avoided if possible given the risk of inducing hyperthyroidism.

6 / Which treatment to choose?

A non-contrast CT scan or an MRI can be performed in the presence of a bulky multinodular goitre to evaluate its potential compressive character. In cases of suspicious nodules, a fine needle aspiration will be proposed.

- In the case of SCH induced by Graves' disease, radioiodine therapy and antithyroid drug therapy are two acceptable options. Antithyroid drugs will be the first choice in young subjects and in patients with identified cardiovascular disease. If the objective is a definitive treatment with a low risk of recurrence, the choice of therapy will be ^{131}I .
- In the case of a SCH induced by a single toxic autonomous nodule or a multinodular goitre, there is no place for long term antithyroid drug therapy since long term remission will not be achieved. The treatment of choice will generally be ^{131}I . Since these patients are usually older, surgery will be considered only in the presence of a compressive goitre or suspicious nodular lesions within the thyroid gland.

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The authors declare that they have no competing interest.

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Figures legends

Figure 1 – Illustration of the evolution of thyroid function (A) and thyroid scintigraphy (B) in a patient developing hyperthyroidism induced by an autonomous nodule.

Stage 0: Normal thyroid hormones production and scintigraphy.

Stage 1: Autonomous adenoma appears on scintigraphy as a small hyperfixating nodule relative to extranodular tissue. Thyroid hormone production is normal with a low proportion produced by the autonomous tissue. The concentration of TSH decreases a little but remains normal. The production of thyroid hormones by the normal tissue decreases slightly.

Stage 2: The autonomous adenoma increases in size and now appears more clearly as a hot nodule on scintigraphy. The uptake of the extranodular tissue decreases further. Secretion of thyroid hormones remains normal but an important proportion comes from the autonomous tissue. The TSH concentration remains normal but decreases more and more.

Stage 3: The autonomous adenoma always increases in size. The extranodular tissue is no longer fixating. Thyroid hormones production is normal or very slightly increased and comes essentially from the autonomous nodule. The concentration of TSH is undetectable.

Stage 4: The autonomous adenoma continues to grow. The extranodular tissue is not fixating. Thyroid hormones production is increased (thyrotoxicosis). The concentration of TSH remains undetectable.

Figure 2 – Relation between pre-operative TSH levels and BMI (A) and LDL-cholesterol changes after total thyroidectomy (B).

Data are expressed as the means \pm SEM. P for trend < 0.01

Figure 3 – Proposed algorithm for the management of a patient with subclinical hyperthyroidism

Tables

Table 1. - Causes of low serum TSH concentrations not due to subclinical hyperthyroidism

- Serum TSH concentration below the reference range, but corresponding to a normal concentration for this person because the normal values only refer to 95% of the population.
- Low TSH concentration due to pituitary insufficiency.
- Low TSH concentration observed at the end of the first trimester of pregnancy.
- Low TSH concentration due to non-thyroid disease ("euthyroid sick syndrome") or treatment with high doses of glucocorticoids or dopamine.
- Low TSH concentration observed in some disease-free thyroid diagnosed subpopulations; smoking, elderly and certain ethnic groups.
- Low TSH concentration observed in the context of iodine overload

Table 2. - Most common causes of subclinical hyperthyroidism

Persistent

Exogenous

- Iatrogenic (intentional or unintentional)

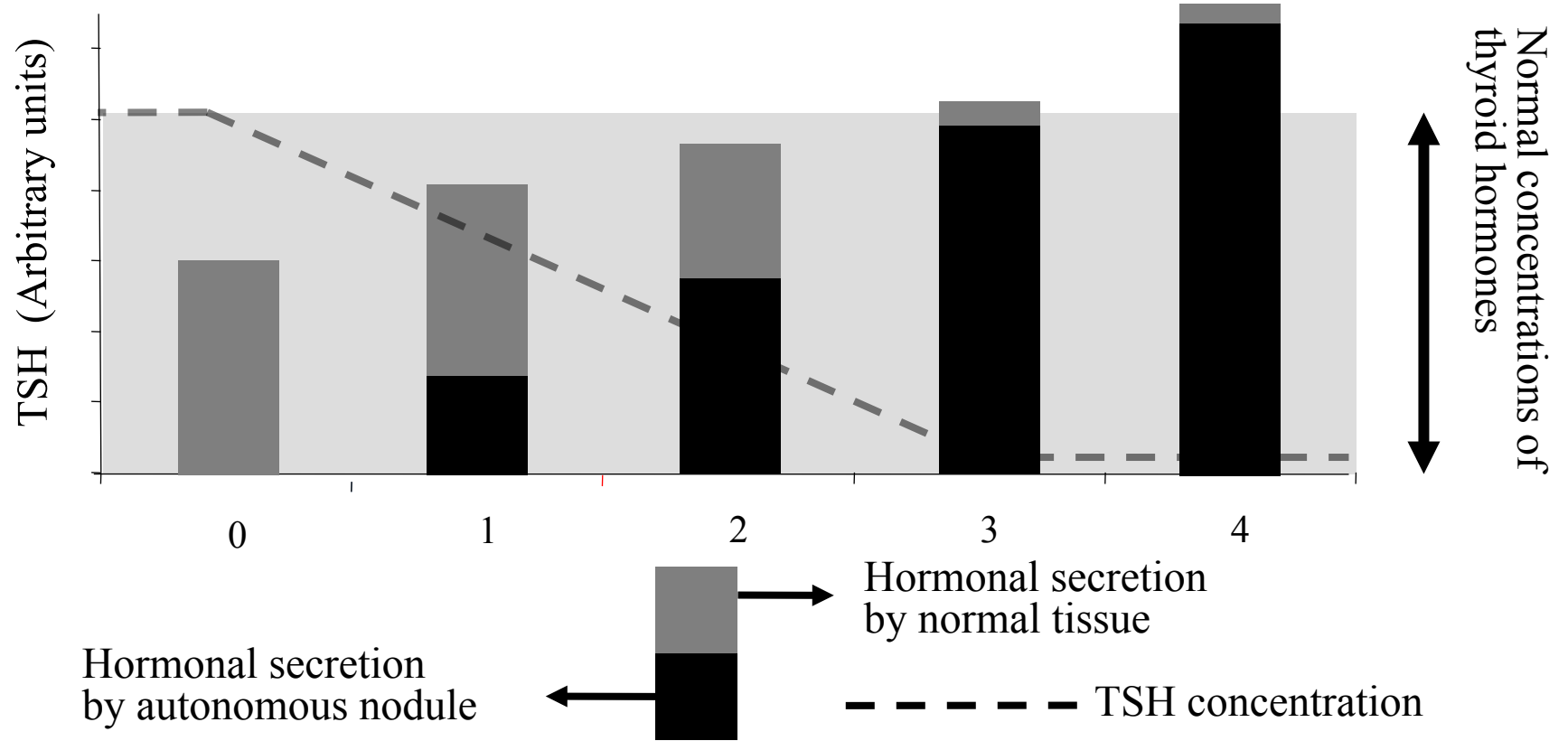
Endogenous

- Toxic multinodular goitre
- Solitary nodule (solitary autonomic nodule)
- Basedow's disease

Transient

- Hyperthyroidism treated with antithyroid drugs or radioactive iodine therapy
- Iodine contamination in the presence of autonomous tissue
- Various forms of thyroiditis (subacute thyroiditis, silent thyroiditis, postpartum thyroiditis etc.)

A



B

