Subclinical Hyperthyroidism

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Definition

Subclinical hyperthyroidism has been biochemically defined by values of serum TSH below the lower range of reference with thyroid hormones within the normal range [1].

Subclinical hyperthyroidism is also known as subclinical thyrotoxicosis, a broader term that refers to inappropriately high thyroid hormone action in tissues. Subclinical thyrotoxicosis therefore includes both the "exogenous" and the "endogenous" forms. Exogenous subclinical thyrotoxicosis is due to administration of thyroid hormones, while the endogenous form can be explained either by the "release of stored thyroid hormones" or by a "true form of hyperthyroidism with increased synthesis and secretion of thyroid hormones by the thyroid gland" [2].

Endogenous subclinical thyrotoxicosis due to the release of stored thyroid hormones is usually transient, while the endogenous subclinical thyrotoxicosis due to the "true form of hyperthyroidism with increased synthesis and secretion of thyroid hormones by the thyroid gland" is usually of a permanent nature. From now on we shall refer to permanent endogenous subclinical thyrotoxicosis with the term "Shyper."

Two categories of Shyper can be defined according to levels of TSH below the lower normal limit [1]:

Grade 1 Shyper: the one that is between the functional sensitivity of the second TSH generation methods, 0.1 mIU/L, and the lower limit of the reference range of TSH, usually considered as 0.39 mIU/L

Grade 2 Shyper: is the category defined by TSH levels below 0.1 mIU/L

Etiology

As stated endogenous subclinical thyrotoxicosis can be transient or persistent [3]. The causes of Shyper are the same as those of overt hyperthyroidism: Graves' disease and autonomously functioning thyroid nodules (AFTN). AFTN include the solitary toxic adenoma (TA) and toxic multinodular goiter (TMNG).

Graves' disease has an autoimmune origin where thyrotropin receptor antibodies (TRAbs) stimulate the thyroid gland to produce thyroid hormone [4], while AFTN is mainly caused by the gradual progression of hormone secretion from autonomous nodules with somatic gain-of-function mutations in the TSH receptor or the stimulatory Gs alpha subunit [5, 6].

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Table 1 Differential diagnosis of Shyper with other causes of low TSH [1]

1. Delay in the recovery of thyrotrophs after treatment for hyperthyroidism (delayed readjustment of the thyroid axis)
2. Pregnancy (in 1° trimester)
3. Non-thyroidal illness (NTI)
4. Drugs (dopamine, corticoids, somatostatin analogues, dobutamine, amphetamine, bexarotene, bromocriptine)
5. Central hypothyroidism (in general with low or normal T4)
6. Psychiatric diseases
7. Age-related reduced thyroid hormone clearance
8. Presence of heterophile antibodies (HAMA)

Transient endogenous subclinical thyrotoxicosis, on the other hand, is mainly due to different types of thyroiditis, including subacute, (viral or DeQuervain's), silent, and postpartum thyroiditis [7, 8], and recent excess iodine intake, such as in type 2 amiodarone-induced thyrotoxicosis [9], or other drugs such as interferon-alpha [10]. Treatment of overt hyperthyroidism with antithyroid drugs or radioiodine can also origin transient endogenous subclinical thyrotoxicosis [3].

Exogenous subclinical thyrotoxicosis can result from an unintentional over-replacement of thyroid hormones in hypothyroid patients [11, 12], the surreptitious intake of thyroid hormones in non-approved indications such as obesity [13], or intentional TSH suppression therapy in differentiated thyroid cancer [14] or in patients with nontoxic multinodular goiters although this procedure is no longer recommended [15].

The differential diagnosis of Shyper with other causes of low TSH levels is described in Table 1.

Epidemiology

Although the prevalence of Shyper might be estimated about 4.2% [16], it really depends upon the considered levels of TSH, the iodine intake, and the age of the analyzed population. Population studies in iodine-sufficient areas show a prevalence of Shyper that spans from 0.7% in case of Shyper 2 and up to 1.8% for Shyper 1 [17], while in elderly subjects living in an iodine-deficient area, the proportion of Shyper might increase up to 15% [18].

With regard to age differences, it has to be considered that TMNG is more prevalent in aged patients, while Graves' disease is more frequent in younger populations [19].

Unfortunately, the exogenous form is by far the most frequent cause of subclinical thyrotoxicosis. It has been reported that up to 40% of hypothyroid patients under levothyroxine therapy are over-replaced and have TSH below the lower limit of TSH [11]. In a more recent communication, however, a lower prevalence (9.6%) of iatrogenic thyrotoxicosis was found for those patients on thyroid hormone participating in the Baltimore Longitudinal Study of Aging. Exogenous thyrotoxicosis accounted for approximately half of both prevalent and incident low TSH events [12].

Natural History (Progression to Overt Hyperthyroidism)

One important aspect to consider for the management of Shyper is the possibility of progression to an overt form of hyperthyroidism. However this depends mainly on the cause of Shyper and on the initial level of TSH.

In Graves' disease, TSH values have better chance of reverting to normal values or to progress rapidly to clinical hyperthyroidism unlike TMNG that usually has a more indolent course [20]. Nevertheless, caution should be taken in these patients because despite their low progression to overt disease, certain situations such as an iodine load in a contrast study may precipitate severe hyperthyroidism [21]. Furthermore, the size of the hot nodule is also related to overt thyrotoxicosis. A nodule with a diameter of 3 cm or larger has been associated to 20% of overt thyrotoxicosis in 6 years [22].

With regard to the initial level of TSH suppression, some reports suggest that Shyper may spontaneously resolve, especially if the levels of TSH are low but detectable [23–25]. Likewise, in aged patients with TSH between 0.1 and 0.4 mIU/L and in whom AFTN was the main

cause of Shyper, the progression toward clinical hyperthyroidism was described to be unfrequent (approximately 1% per year) [26]. Furthermore, in another study performed in patients above 60 years old followed for 10 years, only 4.3% developed overt hyperthyroidism [27]. On the other hand, in patients with TSH <0.1 mIU/L or grade 2 Shyper, a higher rate of progression to overt hyperthyroidism (hazard ratio 3.4, confidence interval 1.6–7.0) was reported [28].

According to the variable evolution that Shyper may have, in untreated patients it has been recommended to monitor with TSH and free T4 or T3 every 6–12 months or sooner if there is a change of the clinical picture [1]. This procedure will inform about persistence, progression, or disappearance of the disease.

Biochemical and Morphologic Diagnosis

TSH and Thyroid Hormones Determination

The determinations of TSH and total and/or free thyroid hormones are used for the diagnosis of Shyper.

Serum TSH is used as the first-line diagnostic test for Shyper because even a small elevation in serum free T4, that is still within the normal range, will cause a decrease in serum TSH outside its reference range. This is explained by an inverse log-linear relationship between TSH and the concentrations of free thyroxine (T4). This relationship determines that small linear increases in free T4 concentrations are associated with an exponential decrease in TSH concentrations [29].

Although TSH is a very robust assay, given the inherent biological variability of TSH and potential episodes of silent thyroiditis and systemic illness, several authoritative guidelines advice to assure the diagnosis of Shyper with 1 second determination of TSH after 2–3 months [1] or 3–6 months [2]. Although an extended interval to reassess TSH is optimal, certain clinical circumstances such as atrial fibrillation, cardiac disease, or other serious medical conditions may compel physicians to repeat the TSH determination in a shorter lapse of time.

In the second hormone assay, it has been recommended to measure free T4 and free triiodothyronine (T3) or total T3 to discard overt hyperthyroidism, central hypothyroidism, or non-thyroidal illness (NTI) [1]. Moreover, in T3 toxicosis, free T4 might be normal, while high levels of free T3 might discriminate Shyper from overt free T3 toxicosis [30].

TRAbs can also be included in the second determination for cases in which it is deemed necessary to distinguish between Graves' disease and TMNG [31]. They are especially useful when a thyroid scan and uptake are unavailable or contraindicated (e.g., during pregnancy and nursing). In iodine-deficient areas, however, the differential diagnosis might be difficult since approximately 17% of patients with scintigraphic criteria for TMNG may be positive for TRAb reflecting an overlap between both diseases [32].

In order to distinguish Graves' disease or AFTN from thyroiditis, the ratio of total T3 to total T4 can be useful. In true hyperthyroidism more T3 is synthesized than T4 with a ratio (ng/mcg) that is usually >20, while it is <20 in painless or postpartum thyroiditis [33].

In hospitalized patients, diagnosis of Shyper can be a challenge, because a suppressed TSH is less specific than in ambulatory patients and because free T4 assays are not reliable in that setting. Considering that TSH levels can become transiently subnormal in the acute phase of NTI, the degree of TSH suppression might be of aid for diagnosis. TSH levels <0.01 mIU/L may indicate true hyperthyroidism, while a low but detectable TSH may imply a transient TSH reduction or the result of the use of dopamine and steroids [34].

Several biochemical markers such as alkaline phosphatase, sex hormone-binding globulin (SHBG), liver enzymes, osteocalcin, cholesterol, etc. can be employed to study the peripheral action of thyroid hormones [35, 36]. However, their use is not recommended in Shyper due to their lack of accuracy.

Nuclear and Imaging Studies

Scintigraphy or thyroid scan and a 24-h radioactive iodine uptake (RAIU) test are very valuable methods for the etiologic diagnosis.

A RAIU should be performed when the clinical presentation of thyrotoxicosis is not clearly diagnostic of Graves' disease and other causes of thyrotoxicosis have to be distinguished. Furthermore, a thyroid scan should be added in the presence of thyroid nodularity [2] in particular in grade 2 Shyper to guide clinicians in the choice of treatment [1].

The use of thyroid scintigraphy with the objective to identify autonomous tissue has been also recommended, despite normal TSH levels, in patients with MNG from regions of long-standing insufficient iodine supply [37, 38]. Its contribution to diagnosis has been confirmed in a study where scintiscan was the most sensitive tool to detect AFTN [39]. Moreover, a recent meta-analysis has shown that about half of the patients with AFTN discovered in a scintigraphy had a TSH value within normal references (40).

Thyrotoxicosis due to diverse forms of destructive thyroiditis exhibit RAIU near 0% similarly to iodine-induced thyroiditis where the radioiodine uptake may remain low for 1–2 months after exposure. In this case the measurement of 24-h urinary iodine excretion may help to confirm suspected excessive iodine intake [1]. On the contrary, Graves' disease patients will display a moderate or frankly elevated uptake with a homogenous scintigraphic image. Autonomous adenomas will show the typical image of the single hot nodule and TMNG multiple hot areas, although very often a characteristic speckled or heterogenous pattern will be observed [1] (Fig. 1).

Thyroid scintigraphy can be performed with ^{131}I; however an alternative to ^{131}I scintiscan is a ^{123}I or a ^{99m}Tc—(sodium pertechnetate) scintigraphy. The advantage of using these two radioisotopes is a lower total body radiation exposure than with ^{131}I. However ^{123}I is expensive and not always available, while ^{99m}Tc, that is trapped by the thyroid but not organified, can yield some false-positive (about 5%) hot nodules that are not truly autonomous [41].

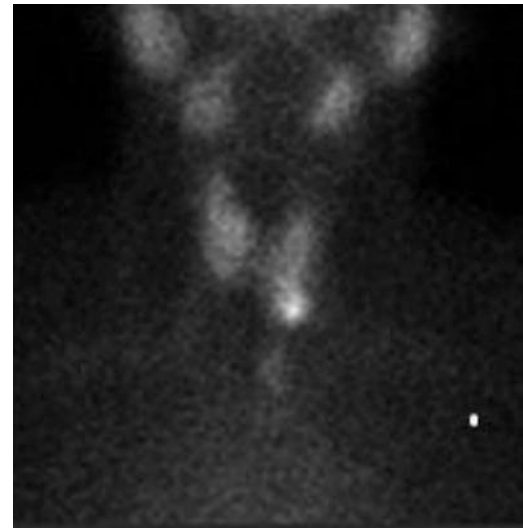

Fig. 1 Thyroid scintigraphy with 5 mCi ^{99m}Tc showing a multinodular goiter with increased uptake in lower left lobe in a patient with Shyper due to a TMNG

Another imaging test worth considering for the diagnosis of Shyper is Doppler ultrasound. Color Doppler flow of the inferior thyroid artery may be useful in the differential diagnosis of thyrotoxicosis in cases where nuclear imaging is contraindicated. Such is the situation with pregnancy and lactation, recent intake of iodine-rich food, and injection of iodine-based contrast media (coronary angiography, computed tomography, etc.) or when TRAb are not available. Diffusely increased thyroid blood flow is pathognomonic of untreated Graves' disease. Peak systolic velocity of the inferior thyroid artery was reported significantly higher (>40 cm/s) in Graves' disease patients when compared to patients with destructive thyroiditis [42]. However, in a recent study assessment of the peak systolic value at the superior rather than at the inferior thyroid artery was proposed as an easier way to differentiate between these two entities [43].

Although the likelihood of malignancy in a toxic nodule is very low [44], the presence of malignant nodules in Shyper patients is always of concern. The only indication to perform a fine needle aspiration in patients with TMNG is within the hypofunctioning thyroid nodules in a thyroid scan, particularly in those with suspicious ultrasound findings [15].

Computed tomography (CT) or magnetic resonance imaging (MRI) can also be indicated for diagnosis of patients with Shyper and large goiters. An objective measure of thyroid size evaluated by diagnostic imaging of intrathoracic (often referred to as substernal) goiter in patients with compressive symptoms can be achieved by these imaging tests. Furthermore, either CT or MRI can detect extrathyroidal extension and/or regional lymphadenopathy suggestive of thyroid malignancy and provide valuable information regarding the dimensions of the trachea and surgery strategies [45, 46].

Assessment of Clinical Significance

Due to the detrimental impact of Shyper on the cardiovascular system, several cardiac tests such as ECG, Holter ECG, and Doppler echocardiography have been recommended for symptomatic patients, the elderly, or those with cardiovascular risks or previous cardiovascular disease. Furthermore, bone mineral density should also be assessed in postmenopausal women, in elderly patients, and in patients with underlying bone risk factors [1].

Clinical Significance

The clinical consequences of overt hyperthyroidism on the general health, particularly on the cardiovascular and skeletal system, are well established, but the clinical significance of Shyper remains unclear. However, more recently a growing body of high-quality evidence has associated Shyper with an increased risk of coronary heart disease (CHD), atrial fibrillation (AF), bone fractures, and lower life expectancy. Less consistently, Shyper has been associated with a decreased quality of life, cognitive impairment, dementia, insulin resistance, and hypercoagulability (Table 2).

Quality of Life, Cognitive Impairment, and Dementia

The literature on the association of Shyper with quality of life, cognitive impairment, and dementia is large, heterogeneous, and controversial. Patients with Shyper are usually asymptomatic, but some few small studies have associated Shyper with clinical manifestations of thyrotoxicosis, particularly when applying specific clinical indexes to rate signs and symptoms of thyrotoxicosis [47, 48]. In fact, a larger prospective cohort study on hyperthyroidism in France showed that most patients with Shyper had signs or symptoms of thyrotoxicosis [49], but in another large community-based study in women, no impact of Shyper on well-being or quality of life was found [50].

In the last years, there have been an increasing number of studies exploring an association of Shyper with cognitive impairment and dementia with conflicting findings. The first data suggesting an association between Shyper and dementia or Alzheimer's disease was derived from the Rotterdam Study. In a sample of 1843 participants aged ≥55 years, subjects with reduced TSH levels at baseline had a more than threefold increased risk of dementia and Alzheimer's disease after adjustment for age and sex over 2-year follow-up [51]. More recently, a cross-sectional population-based study from Brazil with 1119 elderly ≥65 years also described an association of Shyper with any type of dementia and vascular dementia in men, but not in women [52]. In another prospective population-based study from Korea [53] with 313 participants (mean age 72.5 ± 6.9 years), a lower normal serum TSH level (but not FT4 level) was independently associated with the risk of cognitive impairment and dementia during 5-year follow-up. In an Australian prospective population-based study, comprising 3401 community-dwelling men aged 70–89 years, there was no association between TSH quartiles and incident dementia over 5.9-year follow-up. However, men who developed dementia had higher baseline FT4 levels compared with men who did not receive this diagnosis, and the association persisted significant even when the analysis was restricted to euthyroid men [54].

Conversely, in a larger retrospective cohort from Scotland including 2004 patients with Shyper, no relationship with TSH concentration was found, suggesting no causal relationships between Shyper and dementia [55]. Moreover,

Table 2 Summary of evidences on the clinical relevance of subclinical hyperthyroidism

	Shyper grade 1 (TSH 0.1–0.39 mIU/L)	Shyper grade 2 (TSH < 0.1 mIU/L)
Quality of life	Insufficient	Insufficient
Cognitive dysfunction and dementia	Moderate (elderly)	Moderate (elderly)
Metabolic consequences	Insufficient	Insufficient
Osteoporosis	Insufficient	Strong (postmenopausal women)
Fractures	Insufficient	Strong
Atrial fibrillation	Strong (≥60 year)	Strong (≥60 year)
Heart failure	Insufficient	Strong
Coronary heart disease and mortality	Insufficient	Strong
Stroke	Insufficient	Insufficient
Thromboembolism	Insufficient	Insufficient

in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) with 5182 participants with a mean age of 75.2 years and a follow-up of 42 months, there were no differences on the self-reported functional capacity between participants with Shyper compared to those in euthyroidism [56]. In the same population, another study also found no consistent association of Shyper with altered cognitive performance on the individual cognitive tests [57]. In another prospective cohort study from Spain with 307 inhabitants aged 85 years at baseline, Shyper patients were not significantly associated with poor physical or cognitive function at baseline when compared to euthyroid subjects [58]. A negative finding was also found in a prospective cohort of the Longitudinal Aging Study Amsterdam comprising 1219 individuals aged ≥65 years. In this study, Shyper was not related to impairment in any of the tested domains of cognitive function nor to more depressive symptoms at baseline compared to euthyroid subjects [59].

Finally, in two recent reviews [60, 61] including several well-designed and well-powered studies, Shyper was significantly associated with cognitive impairment or dementia in elderly people.

In summary, at the current time, there is no definitive evidence on the association of Shyper with low quality of life, but there is moderate-quality evidence on the association of Shyper with cognitive impairment and dementia in older people. Nevertheless, there is still a need of larger, powered, and well-designed studies as to allow analysis according to TSH levels and age groups (Table 2).

Metabolic Consequences

Thyroid hormones have important effects on lipid metabolism that are clearly observed in overt hyperthyroidism [62]. With regard to the lipoprotein profile of Shyper patients, normal levels of total LDL and HDL cholesterol, triglycerides, Lp(a), apoA1, and apoB have all been reported [63]. On the other hand, in a population screening study of patients over 60 years, with persistently low TSH with normal free T4, a reduction in total cholesterol was detected [64]. Furthermore, in TMNG patients with Shyper, total serum HDL, LDL cholesterol, and triglycerides were lower when compared to a control group [65].

Similarly to what has been described in overt hyperthyroidism [66], subclinical thyrotoxicosis has also been associated with insulin resistance [67–69], although in some but not all studies [70]. The heterogenous nature of this condition can partly explain this controversy. Shyper may have a larger impact on glucose metabolism due to its chronicity and higher T3 levels when compared to exogenous administration of T4 [69].

Osteoporosis and Fractures

Thyroid hormones strongly affect the skeletal development and bone structure and strength by acting in all phases of the bone remodeling cycle, stimulating both bone formation and reabsorption [71]. Thus, either thyroid hormone excess or deficiency can have detrimental effects in the bone. In fact, overt hyperthyroidism has been consistently associated with bone mineral density (BMD) loss, osteoporosis, and fractures, but whether Shyper is associated with the same risks remains controversial [72].

In the last three decades, data derived from several small studies on the association of Shyper with loss of BMD, osteoporosis, and fractures are conflicting. However, most of these studies agree on an association between Shyper and a reduction in BMD and osteoporosis in postmenopausal women [3, 71]. Two meta-analyses found that a long-term suppressive L-thyroxine treatment is associated with a significant BMD loss in postmenopausal women, but not in premenopausal women [73, 74]. In fact, a recent review [3] found no evidence of an association between Shyper and deleterious bone consequences in men or in premenopausal women.

In the last years, Shyper has been related to an increased risk of osteoporotic fractures, but results derived from prospective studies are also conflicting. In the Cardiovascular Health Study (CHS), a prospective cohort of 3567 US community-dwelling ≥65 years, men (but not women) with Shyper had a more than fourfold increased incidence of hip fractures compared to euthyroid individuals in 13-year follow-up [75]. Interestingly, a subsequent study with an expansion of the same study population to 4936 participants found no association between Shyper and incident hip fracture in either sex. These results were strengthened by the findings in a subset of 1317 participants with dual-energy X-ray absorptiometry scans in whom Shyper was not related to loss of BMD at the lumbar spine, total hip, or femoral neck sites [76].

In another population-based prospective cohort study from Israel comprising 14,325 participants ≥65 years and a mean follow-up of 102 ± 3 months, low-normal TSH levels were associated with a higher risk of hip fractures in euthyroid women, but not men [77]. In a larger population-based cohort study from Denmark, a first and single low TSH in a patient without known thyroid disease was associated with an increased risk of hip fracture over a median follow-up of 7.5 years, which remained significant in women but not in men after adjusting for confounders. In addition, in this study the risk increased exponentially by the length of time during which TSH remained low, and the risk of fractures increased significantly with each SD unit of TSH decrease in euthyroid patients [78]. By contrast, in a large retrospective cohort study from Scotland, Shyper was associated with a higher risk of osteoporotic fracture, but there was no dose-response effect according to TSH level, suggesting no causal effect [55].

Despite controversies among prospective cohort studies, three recent meta-analyses of prospective studies have demonstrated an increased fracture risk in Shyper. In a first meta-analysis with 50,245 participants, it was reported that Shyper might be associated with an increased risk of hip and nonspine fractures, particularly for adults with a TSH ≤ 0.1 mIU/L [79]. In a second meta-analysis, individual participant data were obtained from 13 prospective cohorts comprising 70,298 participants. Compared to euthyroid participants, the HR for Shyper was 1.36 for hip fracture (95% CI, 1.13–1.64), 1.28 for any fracture (95% CI, 1.06–1.53), 1.16 for nonspine fracture (95% CI, 0.95–1.41), and 1.51 for spine fracture (95% CI, 0.93–2.45). Lower TSH (≤0.10 mIU/L) was associated with higher fracture rates [80]. Finally, the third meta-analysis included 314,146 participants from five population-based cohort studies including both endogenous and exogenous subclinical thyroid dysfunction. The relative risk (RR) for subclinical hyperthyroidism vs. euthyroid subjects was 1.25 (95% CI 1.11–1.41) in a multivariable-adjusted model, and a subgroup analysis indicated that the risk of fracture was higher in the endogenous group than the exogenous group [81].

These data show that there is high-quality evidence on the association of Shyper with an increased risk of BMD loss and osteoporosis in postmenopausal women, as with an increased risk of osteoporotic fractures in elderly, particularly for those with grade 2 Shyper (TSH ≤ 0.1 mIU/L) (Table 2).

Atrial Fibrillation

The association between Shyper and the increased risk of atrial fibrillation (AF) has been considered the most consistent evidence to recommend treatment of Shyper in elderly people with both Shyper grade 1 and Shyper grade 2 [1, 2], based on data derived from prospective studies and meta-analysis.

In a prospective cohort of the Framingham Heart Study with 2007 subjects ≥60 years, a low serum TSH (≤0.1 mIU/L) at baseline was associated with a threefold higher risk of AF in a 10-year follow-up period, while for those with slightly low TSH (0.1–0.4 mIU/L) values, no significant difference was found [82]. In the context of the CHS, which consisted of 3233 individuals aged 65 years or older, participants with Shyper had nearly twice the risk of developing AF in a 13-year follow-up period. The risks (HR) were similar for both Shyper grade 2 [1.98 (95% CI, 1.29–3.03), $p < 0.001$] and Shyper grade 1 [1.85 (95% CI, 1.14–3.00), $p = 0.007$] [83].

Compared to euthyroid subjects, in a large population-based cohort study from Denmark, comprising 586,460 individuals, the risk [incidence rate ratio—IRR (95% CI)] of AF increased with decreasing levels of TSH, from individuals with high-normal thyroid function [TSH 0.2–0.4 mIU/L, 1.12 (1.03–1.21)] to those with mild Shyper [TSH 0.1–0.2 mIU/L; 1.16 (0.99–1.36)] and more severe Shyper [TSH < 0.1 mIU/L, 1.41 (1.25–1.59)] in a median follow-up of 5.5 years [84]. Finally, in a recent individual participant data meta-analysis with 8711 participants from 5 cohorts, during a mean follow-up of 8.8 years, in age- and sex-adjusted analyses, the overall HR (95% CI) for participants with Shyper compared with euthyroidism was 1.68 (1.16–2.43; 17.1 vs. 12.5/1000 person-years). The risks were increased for both Shyper grade 1 [1.63 (1.10–2.41)] and Shyper grade 2 [2.54 (1.08–5.9) [16].

Taken together, these data suggest that the risk of AF in individuals with Shyper aged 60 years or more is higher for both grade 1 and grade 2 Shyper. In addition, these findings also suggest a dose-response relationship between low TSH levels and an increased risk of AF and justify recommendations for treating all patients >60 years with grade 1 and grade 2 Shyper [1, 2] (Table 2).

Heart Failure

Thyroid hormones have marked effects on the heart and cardiovascular system through genomic and non-genomic actions. It is well known that in overt hyperthyroidism thyroid hormone excess can lead to a hyperdynamic state, systolic and diastolic dysfunction, cardiac hypertrophy, low ventricular performance, increased pulmonary arterial pressure, and heart failure (HF) that can be reversible after euthyroidism with treatment [85]. Moreover, in some studies, but not in all, Shyper has been associated with similar abnormalities, such as with increased resting heart rate, supraventricular arrhythmias, increased left ventricular mass, impairment of systolic and diastolic functions, and hemodynamic abnormalities, which could be reversible after restoring the euthyroid state [48].

More recently, some population-based prospective studies have assessed the association between Shyper and HF. Rodondi et al. [86] studied 3044 individuals ≥65 years initially free of HF in the CHS. Compared to euthyroidism, Shyper was associated with larger left atrial size, impaired E/A ratio, and increased heart rate, although no increased risk of HF was found during the 12-year follow-up. Nanchen et al. [87] studied the incidence rate of HF hospitalization according to baseline thyroid function in 5316 patients aged 70–82 years with known cardiovascular in the context of PROSPER study. Over 3.2-year follow-up, the rate of HF was higher for Shyper compared with euthyroidism [HR = 2.93 (95% CI, 1.37–6.24, $P = 0.005$)].

Gencer et al. [88] performed a pooled analysis of individual participant data from 6 prospective cohorts which consisted of 25,390 individuals. Among 648 (2.6%) Shyper participants, in an age- and sex-adjusted analyses, risk [HR (95% CI)] of HF events was significantly increased for TSH levels ≤0.10 mIU/L [1.94 (1.01–3.72)], but not for TSH of 0.10–0.44 mIU/L [1.31 (0.88–1.95)], compared to euthyroidism. However, in a study including 758 patients hospitalized for systolic HF, Shyper was not associated with increased age-adjusted mortality risk after a median follow-up of 3 years [89], and no clinical trial has assessed yet whether treating Shyper improved HF outcome.

In conclusion, Shyper is consistently associated with an increased risk of HF in older people, particularly for those with Shyper grade 2 (Table 2).

Coronary Heart Disease and Mortality

The association between Shyper and CHD has been investigated in several prospective population-based cohort studies with variable results. Some studies have reported significant findings [90], while others have found no association between Shyper and cardiovascular risk [83]. Similarly, data from study-level meta-analyses on the topic are also conflicting. In a meta-analyses including 3385 individuals from 5 higher-quality prospective studies, Ochs et al. [91] found that Shyper was associated with only a modest increased relative risk [RR (95% CI)] for CHD [1.21 (0.88–1.68)], cardiovascular mortality [1.19 (0.81–1.76)], and total mortality [1.12 (0.89–1.42)]. By contrast, based on 7 cohorts including 290 participants with Shyper, Haentjens et al. [92] estimated that the pooled HR (95% CI) for all-cause mortality was 1.41 (1.12–1.79), being the excess mortality increased beyond the age of 60, especially in aging men.

Several factors have been implicated to justify these controversial findings, including different population characteristics (such as ethnia, age, gender), different Shyper and CHD definitions, different inclusion and exclusion criteria, and different confounder adjustments among studies. However, most recently, a well-designed, powered, and robust study based on individual participant data (IPD) analysis from large cohort studies might have reconciled these conflicting results, by having uniformed inclusion and exclusion criteria, CHD definition, and TSH cutoff levels used for Shyper definition for all participants, therefore providing pooled survival estimates less prone to bias [16].

In such IPD analysis, individual data on 52,674 (2188 with Shyper) were pooled from 10 cohorts. In age-and sex-adjusted analyses, Shyper was significantly associated with an increased risk [HR (95% CI)] of CHD events [1.21 (CI, 0.99–1.46)], CHD mortality [1.29 (1.02–1.62)], and total mortality [1.24 (1.06–1.46)]. Risks remained significant even after further adjustment for cardiovascular risk factors and did not differ significantly by age, sex, or preexisting cardiovascular disease. However, CHD mortality risks were higher in participants with Shyper grade 2 compared to those with Shyper grade 1 [16].

In summary, despite controversy among prospective studies and meta-analyses, there is now strong evidence suggesting a significant association between Shyper and fatal and nonfatal CHD, particularly for TSH levels <0.1 mIU/L. However, clinicians should take these data with caution, since there are no randomized controlled studies on the benefits of treating Shyper regarding these outcomes [93] (Table 2).

Stroke

Stroke is one of the most important causes of mortality and morbidity globally, and some of its risk factors such as hypertension and cardiac arrhythmia, particularly AF, are associated with Shyper. In fact, the link between Shyper and AF has been consistently evidenced among prospective studies [82, 83] and meta-analysis [16]; nevertheless, the association between Shyper and stroke still remains unclear. There are a few available studies with heterogeneous qual-

ity and results on the topic. In a small case-control Swedish study including 153 patients with acute ischemic stroke, unknown Shyper was significantly associated with the cardio-embolic (based on the presence of AF) compared to non-embolic group (13% vs. 3%, $p = 0.048$) [94]. In another small study with a total of 165 consecutively recruited patients admitted for ischemic stroke, patients with Shyper had a significant increased risk of functional disability 3 months after stroke compared with those in euthyroidism [odds ratio, 2.63 (95% CI, 1.02–6.82)], adjusted for age, sex, and smoking status [95]. In a population-based prospective study including 609 subjects ≥50 years from general practice in Denmark, the incidence of stroke in median of 5 years of follow-up was substantially greater among Shyper subjects compared to euthyroid [HR 3.39 (95% CI, 1.15–10.00, p = 0.027)] after adjusting for sex, age, and atrial fibrillation [96].

Conversely, in a more consistent cohort study comprising 563,700 (mean age, 48.6 ± 18.2 years) subjects without prior thyroid disease from primary care in Denmark, the incidence rate ratios [1.02 (95% CI, 0.93–1.12)] of fatal stroke were not significantly associated with Shyper during a median follow-up of 5.5 years [97]. Most significantly, in a recent systematic review and meta-analysis with 6029 participants from 4 studies, no evidence supporting an increased risk for stroke associated with Shyper compared to euthyroidism was found [HR = 1.17 (95% CI, 0.54–2.56)] [98].

In conclusion, data about the association of Shyper with an increased risk of stroke are insufficient, and new larger prospective cohort studies are needed to clarify this uncertainty (Table 2).

Venous Thromboembolism

Thyroid hormone exerts important influence on the coagulation fibrinolytic system, and overt hyperthyroidism has been related to a hypercoagulable state and an increased thromboembolic risk [99], although there are few data on Shyper.

In a systematic review including only moderate-quality case-control and cohorts studies (no high-quality study was found), Shyper was significantly associated with subclinical laboratory findings suggesting a hypercoagulable and hypofibrinolytic state with a rise in factors VIII and IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1 that could induce a prothrombotic state and a higher venous thromboembolism (VTE) risk [100]. However, in a most recent prospective multicenter cohort of 561 elderly participants, in a mean follow-up of 20.8 months, the VTE incidence rate was 0.00 (95% CI, 0.00–0.58) in Shyper compared with euthyroid participants, without increased levels of thrombophilic biomarkers, suggesting that Shyper could be associated with a lower VTE risk [101]. In addition, in a larger prospective study comprising 11,962 subjects aged 25–89 years, low TSH levels were associated with only a modest and nonsignificant higher risk [HR = 1.55 (95% CI, 0.87–2.77)] of VTE during 8.2 years of follow-up, suggesting that only a minor proportion of the VTE risk in the population can be attributed to Shyper [102].

In summary, despite some evidence suggesting an association between Shyper and subclinical laboratory abnormalities on the coagulation and fibrinolytic state, there is no consistent evidence suggesting that Shyper enhances the risk of clinical outcomes associated to an hypercoagulable and hypofibrinolytic state. Further prospective cohorts might be needed to provide a more definitive information on the clinical significance of the association between Shyper and a hypercoagulability state (Table 2).

Case Finding

Screening for Shyper is not currently recommended [103]. However, as mentioned above Shyper is associated with atrial fibrillation, congestive heart failure, and osteoporosis in older persons and postmenopausal women. Therefore, aggressive case finding is advocated in these two sets of populations in particular [104]. Moreover, although the definition of Shyper is biochemical and not clinical, palpitations, weakness, heat-related signs, and disturbed sleep have been reported in patients even with mild degree of

hyperthyroidism [49]. Therefore, Shyper has to be discarded also in the presence of these signs or symptoms.

Treatment

Indications of Treatment

In the last two decades there have been continuous and exciting debates whether Shyper should be treated or not [105, 106]. Despite a growing body of robust evidence that Shyper (particularly grade 2) is associated with a higher risk of progression to overt disease; with cognitive impairment, dementia, AF, HF, and fractures in older people; with osteoporosis in postmenopausal women; and with CHD event and mortality, there are several arguments against treatment. Among them are the low rate of progression to overt hyperthyroidism, the risks associated with the treatment, and the lack of appropriately large-scale randomized trials able to detect the benefit of treating on the outcomes [93, 105]. Thus, making a decision to treat or not a patient with Shyper relies mainly in the potential risks of not treating and in on our best clinical judgment.

However, some features seem to be consensual. In a hypothyroid patient with exogenous subclinical thyrotoxicosis due to excessive dose of levothyroxine, titrating the dose to obtain the target TSH levels according to age is recommended. In patients under treatment with suppressive levothyroxine therapy for persistent or recurrent differentiated thyroid carcinoma, the use of beta-blockers should be considered, particularly for those with symptoms of adrenergic hyperactivity, age > 60 years, or with cardiovascular risk or previous cardiovascular disease. Postmenopausal women with persistent Shyper, particularly those without estrogen replacement therapy, should be monitored with bone densitometry, determination of calcium and vitamin D to assess the need for specific treatment with bone resorption inhibitors, and vitamin D and calcium supplementation. In elderly people (>60 years), with persistent Shyper and a defined thyroid disease (physiological adaptive low TSH with aging should be excluded), treatment should be considered for grade 1 or 2 Shyper. This recommendation is based on the association of Shyper with a higher risk of AF in elderly people even for those with low but not suppressed TSH levels [16].

A good suggested policy on how to manage Shyper patients in the clinical practice could be reached applying a stepwise approach in five steps [107]:

Step 1: Establish the diagnosis of persistent Shyper.

It is necessary to exclude T3 toxicosis. Non-thyroidal causes of low TSH should also be excluded. Repeat thyroid function tests over a period of 3 to 6 months to exclude transitory causes.

Step 2: Define the etiology.

The most common causes of subclinical thyrotoxicosis are exogenous. Endogenous Shyper has the same etiology of overt hyperthyroidism. Color-flow Doppler thyroid ultrasound, radionuclide thyroid scanning, TRAb determinations, and a detailed medical history will be useful to establish the etiology of most cases.

Step 3: Assessment of clinical significance.

A careful and detailed medical history may be useful in the identification of thyrotoxicosis symptoms in apparently asymptomatic patients. Patients should be evaluated regarding the potential harmful effects associated with Shyper, particularly on the cardiovascular system and skeleton. Previous cardiovascular disease and cardiovascular risk factors should be routinely investigated. According to clinical judgment, evaluate the need for ECG, ECG Holter, Doppler echocardiogram, and bone densitometry.

Step 4: Stratify patients according to the risks.

Stratify patients according to the severity of Shyper (Grade 1 or Grade 2) and the age of the patients. Grade 2 Shyper has been associated with a higher risk of progression to overt hyperthyroidism and incident coronary heart disease and mortality. Age > 60 years is associated to a significant risk of AF, HF, and fractures.

Step 5: Make a decision.

Each clinical situation should be individually analyzed considering the potential clinical conse-

quences of not treating, and the risks associated with the treatment, having in mind data from the previous steps and recommendations from recent society guidelines [1, 2]. Both ATA and ETA guidelines [1, 2] agree on the concept that the indication of treatment of Shyper highly depends on the age, degree of TSH suppression, and comorbidities present in each individual. Treatment is either "recommended" or "should be considered" accordingly (Table 3).

Treatment Modalities

Patients with Shyper are treated with antithyroid medications, radioiodine (RAI) or ^{131}I, or surgery, depending on the clinical circumstances and patient preference. Treatment modalities vary according to the etiology of Shyper, and there are no control trials comparing the efficacy among them. Furthermore symptomatic treatment includes cardioselective β-blocking agents with the aim of improving symptoms, heart rate, and supraventricular arrhythmias [108, 109].

In patients with Graves' disease, RAI therapy, antithyroid medication, and thyroidectomy are all acceptable modes of treatment. A treatment option can be chosen by the patients following comprehensive discussion with their physician. However in certain scenarios such as young Graves' disease patients with Shyper, long-term and low-dose (5–0.10 mg/day of methimazole) antithyroid drug therapy is the first choice since the remission rate is high [110]. Similarly, in patients older than 65 years with Graves' disease and grade 1 Shyper, antithyroid drugs may be used as an initial line of therapy [1], while for those elderly Graves' disease patients with grade 2 Shyper or for patients with cardiovascular disease, both antithyroid drugs or RAI can be considered as the first choice with the aim of a rapid remission of the disease [1].

Table 3 Treatment of Shyper according to age and degree of TSH suppression

Age (years)	Grade 1 Shyper (TSH 0.1–0.39 mIU/L)	Grade 2 Shyper (TSH < 0.1 mIU/L)
>65	Consider treatment	Treatment is recommended in all patients
<65	Consider treatment if symptomatic or with cardiovascular or bone fracture risk	Treatment is recommended in symptomatic patients or with cardiovascular or bone fracture risk

On the other hand, ^{131}I therapy and surgery are offered primarily to patients with TMNG or TA [111] especially in elderly patients. Although, pretreatment with antithyroid medication has been advocated to avoid exacerbation of hyperthyroidism due to RAI, its use remains controversial [112] considering that 10–15% increase in RAI activity will be needed after pretreatment with antithyroid drugs to maintain efficacy [112]. During the first week after RAI, the use of antithyroid medication may decrease complications such as atrial fibrillation; however, it may also decrease the efficacy of the RAI treatment [112]. In those elderly patients in whom neither surgery nor RAI are feasible, long-term antithyroid drugs can also be used [113].

In case of compressive symptoms, concomitant hyperparathyroidism or suspicion of thyroid malignancy, total or partial thyroidectomy is the best option. Iodine is primarily used now in conjunction with antithyroid drugs to prepare patients with Graves' disease for surgical thyroidectomy. Conversely, its use is not really needed in case of AFTN surgery since it may exacerbate thyrotoxicosis. In case of a solitary autonomous nodule, lobectomy and isthmus resection is sufficient [2]. In the presence of a patient with a large goiter with contraindication for surgery due to advanced age or comorbidities, other treatment modalities may be considered.

Low doses of recombinant human TSH before RAI have been advocated in the management of multinodular goiter to increase iodine uptake [114]. Its use however may be associated to transient exacerbation of hyperthyroidism.

With regard to possible adverse effects of all these treatments, they are the same as when administered for overt hyperthyroidism [2, 115]. However, since the proposed doses of antithyroid drugs in Shyper are low and the adverse effects with methimazole in particular are dose-related,

patients receiving this drug may not be at increased risk. With regard to the use of RAI in Graves' disease in patients with mild and active eye disease or smokers, steroid prophylaxis is recommended to avoid Graves' orbitopathy progression [116]. Another unfrequent consequence of RAI is the induction of Graves' disease in patients with TMNG. This situation has been associated to pre-existing thyroid autoimmunity in these patients despite undetectable TRAb levels [117].

In patients who are treated surgically, complications include permanent vocal cord paralysis and hypoparathyroidism, although with surgeons with high level of experience, these adverse events should be relatively low [118].

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