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Review article

# Subclinical Hyperthyroidism: Clinical Consequences and Management

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## Abstract

### Background

Subclinical hyperthyroidism (Shyper) is a common clinical entity which represents a condition of mild thyroid over-activity. Whether or not Shyper should be treated remains a matter of debate, despite the body of evidence that demonstrates an association between this condition and significant adverse effects.

### Summary

After an overview of the etiology, differential diagnosis, epidemiology and natural history of Shyper, this review will focus on the clinical outcomes related to this condition, i.e., cardiovascular morbidity and mortality, bone health, mood and cognitive function. The treatment options of Shyper are essentially the same as overt hyperthyroidism. Notwithstanding the lack of appropriately designed prospective studies, we provide a practical framework to effectively manage Shyper.

### Conclusion

Treatment of Shyper should be considered after evaluating four critical parameters: age>65 years, the degree of TSH suppression (TSH <0.1mU/L), the presence of clinical thyroid abnormalities and underlying relevant co-morbidities.

**Keywords:** Subclinical hyperthyroidism; Treatment; Cardiovascular risk; Atrial fibrillation; Osteoporosis

## Introduction

Subclinical hyperthyroidism (SHyper) has been increasingly recognized due to availability of thyroid functioning tests, as a condition characterized by a low or undetectable concentration of serum thyrotropin (TSH) with normal free thyroxine (FT4) and free triiodothyronine (FT3) levels [1]. This entity has emerged due to the increase in sensitivity of TSH assays. Third-generation assays, which have a functional sensitivity of 0.01-0.02 are able to discriminate between complete and incomplete TSH suppression [2]. The pituitary gland is extremely sensitive to small changes in thyroid hormone levels. TSH and FT4 have a negative log-linear relationship such that small changes in FT4 levels results in large changes in TSH levels [3-5]. Although thyroid hormone levels are, by definition, within the normal range in SHyper, they are often near the upper limit of the reference range. In fact, in some individuals, serum thyroid hormones concentrations in the normal range are sufficiently high to suppress TSH and produce adverse tissue effects [2]. Actually, TSH is more sensitive than FT4 for assessing mild thyroid function excess. Moreover, interindividual differences in the thyroid-pituitary set point, which are genetically determined, may explain the different peripheral thyroid hormone effects in subjects with the same hormonal setting, thus the distinction between SHyper and hyperthyroidism is somewhat artificial [6-7].

## Review

### Etiology

SHyper may be caused by exogenous thyroid hormone therapy, given in patients with differentiated thyroid carcinoma or, less frequently, for benign nodular thyroid disease or as replacement therapy in patients treated for hypothyroidism (exogenous SHyper). SHyper may also result from autonomous thyroid function as occurs in Graves' disease, multinodular goiter or solitary autonomous nodules (endogenous SHyper) (Table 1).

| |
|---|
| Exogenous |
| Suppressive thyroid hormone therapy |
| Excessive thyroid hormone replacement therapy |
| Endogenous |
| Multinodular goiter |
| Solitary autonomous nodule |
| Graves' disease |

**Table 1.** Causes of Persistent Subclinical Hyperthyroidism.

Various forms of thyroiditis (subacute, painless or post partum) are a frequent cause of transient Shyper, easily misdiagnosed if someone don't think about it (Table 2). Very rarely, activating mutations of the TSH receptor gene may be the cause of hereditary non- autoimmune hyperthyroidism or SHyper [8-9]. Deleterious tissue effects remain the same regardless the cause of SHyper.

| |
|---|
| Various forms of thyroiditis (subacute, post-partum and silent thyroiditis) |
| Some forms of hCG-mediated hyperthyroidism in pregnancy |
| ( hyperemesis gravidarum, gestational transient thyrotoxicosis) |
| Treatment of overt hyperthyroidism with anti-thyroid drugs or radioiodine. |

**Table 2.** Causes of Transient Subclinical Hyperthyroidism.

### Differential Diagnosis

The diagnosis of SHyper should be made in presence of persistent low-undetectable serum TSH levels documented on repeated thyroid function tests with normal thyroid hormone levels together with suitable detailed medical history and careful physical examination. It is important to differentiate true SHyper from other causes of low TSH serum concentrations (Table 3). Although TSH distribution progressively shifts toward higher concentrations with age [10],TSH concentration may be subnormal in some healthy elderly individuals without hyperthyroidism due to decreased thyroid hormone clearance or an altered set-point of the hypothalamic-pituitary-thyroid axis with aging [2,11-13].

| |
|---|
| Non-thyroidal illness |
| High-dose glucocorticoid or dopamine therapy |
| Psychiatric diseases |
| Hypothalamic/pituitary diseases |
| Smokers |
| Elderly |
| Racial distribution of TSH concentrations (lower in some black individuals) |

**Table 3.** Causes of Low TSH levels Unrelated to Thyroid Hyperactivity.

Studies have found that TSH serum concentra¬tion is lower in smokers, both males and females, compared with non smokers [14-15]. Low TSH levels may be seen in severely ill hospitalized patients (euthyroid sick syndrome). In these patients the FT4 and FT3 levels are typically low and this laboratory pattern mimics central hypothyroidism. In addition, high-dose steroids or dopamine therapy, psychiatric diseases and hypothalamic/pituitary disorders may lower TSH levels. TSH suppression may also be transient and self- limited (Table 2). Gestational thyrotoxicosis, notably, occurs in 10-15% of pregnancies [16-17]. In these women, the high serum concentration of human chorionic gonadotropin (hCG) during early pregnancy (10-12 weeks) can lead to subclinical or mild overt hyperthyroidism that subside without treatment as the hCG levels falls by 14-20 weeks gestation. With the exception of pregnant women naturally, whenever the diagnosis is not straightforward, thyroid imaging may be judicious [18]. Radioiodine uptake (RAIU) either with $^{123}$Iodine or $^{99}$mTechnetium may disclose significant uptake or autonomic thyroid areas in Graves disease or toxic nodular goiter whereas poor visualization of thyroid and very low RAIU are consistent with the destructive process in subacute thyroiditis .Color flow Doppler sonography can reveal different intrathyroid vascularity patterns that may reflect underlying autoimmune process (Hashimoto's thyroiditis or Grave's disease ) or autonomous functioning nodules [19]. Measurement of thyroid autoantibodies (peroxydase, thyroglobulin and TSH receptor antibodies) may be advised in patients with suspected Graves' disease or Hashimoto's thyroiditis

### Epidemiology

The prevalence of SHyper is related to cause of the disease, age, sex, iodine intake, the sensitivity of the method used to measure TSH and the diagnostic criteria, as determined by the investigator. In the third US National Health and Nutrition Examination Survey (NHANES III), using a TSH cut-off of 0.1mU/L, the overall prevalence of SHyper was 0.7%. With a cut-off of 0.4 mU/L, the prevalence reached 3.2% and there

was a significant preponderance of females as well as blacks compared to whites and Hispanics [6]. The frequency of SHyper increases with age, especially in women [6,13]. Highest rates of SHyper are seen in patients on thyroid hormone therapy. In the Framingham Heart study, 3.9% of 2575 patients older than 60 years had a TSH < 0.1 mU/L, half of them were taking levothyroxine [13]. In the Colorado cross sectional study, SHyper (TSH<0.3mU/L) was found in 0.9% of 24,337 individuals not taking thyroid medication but was present in 20.7% of the 1525 subjects taking thyroid hormone preparations [20]. Among 339 community dwelling elderly people aged >65 years and using thyroid hormones, 41% had low TSH (<0.45mU/L) [21]. The prevalence of endogenous SHyper due to thyroid autonomy is inversely correlated with the population's iodine intake. The overall prevalence of SHyper in the adult population of an iodine deficient village of the Southern Italy was 6.4% which is much higher than that reported in iodine-sufficient areas, where this condition is rare [22]. In Jutland, an area of iodine deficiency in Denmark, 9.8% of 423 elderly subjects had SHyper, compared with 1% of 100 aged-matched subjects living in iodine-rich Iceland [23].

**Natural History**

Many patients with low serum TSH may recover spontaneously when re-tested. A large study from Israel indicates that low TSH levels (<0.35 mIU/L) returned to normal in over 50% of the patients during a 5-year follow-up period [24]. Conversely, some patients with SHyper may develop overt hyperthyroidism with time. The progression rate to overt hyperthyroidism varies among studies: In a retrospective study, Das G et al. reported that among 323 patients with Shyper, 31.6% reverted to euthyroidism, 56.7% remained subclinically hyperthyroid and only 11.3% progressed to overt hyperthyroidism during a mean follow up period of 32 months. Higher progression rates were observed in patients with TSH<0.1mIU/l (20.3%) than in those with TSH between 0.1-0.39mIU/l (6.8%) [25]. In a retrospective study of 96 patients with SHyper, the progression to overt hyperthyroidism reached 26% at 5 years [26]. In a retrospective analysis of a cohort of 75 patients, 45.3% developed overt hyperthyroidism with a highest incidence rate of 29.63 cases per 100 patient-year in subject with initial TSH values <0.1mIU/l [27]. The variations in incidence may be partly explained by disparities in diagnosis criteria, dietary iodine intake and thresholds for treatment intervention. The best predictor of outcome in patients with SHyper is the baseline TSH level. Most studies have shown a relationship between the degree of suppression of TSH level (<0.1 mIU/L) and the progression to overt hyperthyroidism [25, 27, 28]. In the only prospective study to date, Rosario showed that in elderly women with SHyper, a TSH below 0.2 mIU/L predicted overt hyperthyroidism during a median follow up time of 41 months [29]. In contrast to these studies, Schouten et al. found that the etiology of hyperthyroidism as determined by scintiscan was the only significant predictor of outcome, patients with autonomous nodules having the highest risk for progression [26]. Notably, Graves' disease is the most common cause of SHyper in young patients while nodular thyroid disease is the most common in the elderly. Although the etiology of SHyper is a significant variable in assessment of the progression to clinical disease, the relationship between diagnosis and outcome is still controversial. While some studies have reported that patients with autonomous solitary nodules or multinodular goiter are more likely to progress to overt hyperthyroidism than patients with Graves' disease [26, 30] others have reported no such association [27] or even an inverse association [28]. Though, the small proportion of patients with Graves' disease in these cohorts [26-28, 30] may explain the disparity of the results. In very old or debilitated subjects, the predictive value of a low TSH level may be poor [31]. A low TSH value in patients with a history of hyperthyroidism successfully treated with anti-thyroid drugs, predicts a relapse of the thyroid dysfunction [32, 33].

**Cardiovascular Risk in Subclinical Hyperthyroidism**

Some of the most characteristic symptoms and signs of hyperthyroidism result from the effects of thyroid hormones on the heart and cardiovascular system [34]. T3 has both genomic and non-genomic effects on the cardiac myocyte and systemic vasculature. Genomic mechanisms involve T3 binding to thyroid nuclear receptors, which regulate transcription of specific cardiac genes, as the myosin heavy chain genes, the sarcoplasmic reticulum $Ca^{2+}$-ATP-ase and its inhibitor, phospholamban [35]. Expression of these key structural and regulatory genes is responsible for the increased heart rate, contractility, and diastolic relaxation present in overt hyperthyroidism and to a lesser extent in SHyper. By extra-nuclear non-genomic mechanisms, T3 also directly modulates membranes' ion channels for sodium, potassium and calcium and targets a variety of intracellular signaling pathways in the heart and vascular smooth muscle cells. T3 enhances endothelial nitric oxide production leading to relaxation of vascular smooth cells and decrease of systemic vascular resistance, which thereby increases cardiac output.

**Risk of Atrial Fibrillation**

Both cross-sectional and longitudinal studies showed an increased risk of atrial fibrillation in patients with SHyper, particularly in elderly subjects older than 60 years. This observed association is a cause-effect relationship in view of the known regulatory effects of thyroid hormone on the cardiac pacemaker activity [35]. Thyroid hormone affects the action potential duration and repolarization currents in cardiac myocytes through both genomic and non- genomic mechanisms [36]. In a landmark prospective study on a Framingham study cohort, Sawin and colleagues reported a threefold increase of cumulative incidence of atrial fibrillation over 10 years in elderly subjects with low TSH (<0.1mU/L) compared to those with normal TSH (37) .In the more recent Cardiovascular Health Study [38], the risk of atrial fibrillation almost doubled over 13 years, in elderly patients with undetectable (<0.1mU/L) and detectable (0.1-0.44mU/L) TSH levels. In a retrospective study

of more than 23000 patients aged 65-70 years, of whom most had underlying cardiac disease, a similar frequency of atrial fibrillation was found in SHyper subjects with TSH<0.4 mU/L (13%,) and overt hyperthyroidism (14%), compared with 2% in subjects with normal TSH levels [39]. A subsequent population-based study of 5860 people aged ≥65 years showed a significantly higher prevalence of atrial fibrillation in subjects with SHyper compared with euthyroid subjects (9.5% vs. 4.7%) [40].

In summary, there is evidence that Shyper is a condition that increases the risk of cardiac arrhythmias and this risk increase with age, duration of SH and the degree of TSH suppression.

**Cardiovascular Morbidity and Mortality**

Results from prospective cohort studies and study-level meta-analyses have reached contradictory conclusions regarding the association between exogenous or endogenous SHyper and cardiovascular morbidity and mortality [41]. In a large population-based study among 17684 patients with exogenous SHyper (mean age: 61.6 years), individuals with TSH <0.03 mU/l were at in increased risk for cardiovascular morbidity and mortality after adjustment for age, sex, history of thyroid disease, cardiovascular disease and presence of diabetes, during a median follow-up of 4.5 years [42]. In the same population, patients with a lesser suppressed TSH (0.04-0.4 mU/l) did not have an increased cardiovascular risk, compared with euthyroid subjects (TSH>0.4mU/l). Bauer et al. did not find an association between low TSH levels (<0.5mU/l) and excess mortality in elderly women (>65 years old) using thyroid hormones for 15.8 years [43]. Unfortunately, both these studies failed to report the thyroid hormone levels. In contrast, in a cohort of subjects > 85 years, the cumulative all- cause mortality during 4-years follow-up was highest in patients with abnormally low thyrotopin levels ( <0.3mU/l) at baseline [44]. Recently, an independent association has been shown between low TSH levels and increased cardiovascular mortality during long-term follow-up in thyroid cancer patients on thyroxin suppressive therapy [45]. Similarly to exogenous disease, the association of endogenous SHyper with cardiovascular risk is controversial. In a cohort of 3121 cardiac patients with a mean age of 61 years, TSH levels < 0.3mU/l represented an independent predictor for cardiac death during a follow up of 32 months [46]. In another prospective study, 1751 Japanese-Brazilians living in Sao Paulo State, Brazil, aged ≥ 30 years were observed during 7.5 years. After 4 years of follow-up a significant association emerged between SHyper, defined as TSH level < 0.45mU/l with normal FT4 level and all-cause and cardiovascular mortality. This association persisted after adjusting for age, sex and multiple potential confounders [47].In addition, it seems that patients with Shyper have an increased risk of heart failure, and this is a major cause of cardiovascular mortality [48-50]. Conversely, other prospective cohort studies did not find an increase in total or cardiovascular mortality in patients with SHyper [38, 51-53] or even with overt hyperthyroidism [54]. Several meta-analyses have evaluated the impact of SHyper on total and cardiovascular mortality, producing conflicting results. Three study-level meta-analyses have failed to demonstrate any increase in circulatory or all-cause mortality in patients with SHyper [55-57]. By contrast, a meta-analysis based on seven cohorts including 290 individuals with subclinical hyperthyroidism, demonstrated a 41% increase in relative all- cause mortality versus euthyroid control subjects. Mathematical modeling suggested that absolute excess mortality might increase progressively over 10 years after diagnosis, especially beyond the age of 60, predominately in men than in women and in patients with co-morbidities [58]. In a recent study based on the individual data of 52674 subjects from 10 cohorts , SHyper defined as TSH level <0.45 mU/l with normal FT4 concentration, was associated with increased total mortality, cardiovascular mortality, and atrial fibrillation, irrespective of age, sex, or preexisting cardiovascular disease. The risk of cardiovascular mortality and atrial fibrillation was highest with TSH values <0.1mU/l [59]. In a recent prospective study, 5599 patients with heart failure were followed at a health maintenance organization (HMO) during a median time of 434 days for cardiac related hospitalizations and mortality. Both high (>4.5) and low TSH (<0.45) levels were associated with an increase in mortality rate [60]. Furthermore, several studies suggested that SHyper could increase the atherosclerotic risk: In 2128 subjects participating in the Study of Health in Pomerania [61], the prevalence of carotid artery plaques and stroke was higher in subjects with serum TSH levels <0.25 mU/l. This early accelerated atherosclerosis is possibly linked to heart failure and coronary events [62] The biological mechanisms that could link low serum TSH levels with atherosclerosis remains to be elucidated. Additionally, SHyper patients are potentially in a hypercoagulable state, which may have contributed to increased thrombembolic risk [63-65].

Overall, according to most of studies it appears that there is a small but significant increase risk in cardiovascular mortality in patients with Shyper. This excessive risk increase with age and the degree of TSH suppression.

**Bone and Mineral Metabolism in Subclinical Hyperthyroidism**

Thyroid hormones are known to exert direct effects on bone remodeling. Thyroid hormone excess results in net loss of bone and subsequently reduction in bone mineral density (BMD) [66]. It is well recognized that overt hyperthyroidism is associated with an increased risk of osteoporosis and fracture [67]. A decrease in BMD is well documented in post-menopausal women with SHyper, especially in cortical bone-rich sites, whereas there is little evidence of bone loss in premenopausal women or in men [68-70]. Most studies suggest an increases risk regarding the risk of bone fracture in SHyper. A cohort of 686 women aged ≥65 years were followed for approximate-

ly 4 years, the baseline TSH levels <0.1mU/l were associated with a four-fold increased risk of vertebral fractures and three-fold increased risk of hip fracture [70]. In another prospective study over 13-year follow-up period in elderly subjects (>65-year old), the incidence of hip fracture was higher in men with SHyper (TSH<0.45 mU/l) than in men with normal TSH. Such an increased risk was not found in women with SHyper [71]. Moreover, in a systematic review and meta-analysis of 7 prospective cohort studies intended to assess the association between subclinical thyroid dysfunction and fracture risk, the pooled estimates hazard ratios for the 7 cohorts were not statistically significant: 1.26 (CI, 0.96 to 1.65) for hip fractures and 1.16 (CI, 0.95 to 1.42) for nonspine fractures [72]. Hyperthyroidism-associated bone loss has been classically attributed to excess of thyroid hormones. In post-menopausal women with SHyper, thyroid hormone levels within the upper normal level range were associated with an increasing bone loss at the hip and an increased risk of non-vertebral fracture, while higher TSH levels showed a protective effect [73]. In a recent meta-analysis of individual data obtained from 13 prospective studies involving 70298 participants, those with Syper defined as TSH<0.45 mU/l (3.2%) appear to face an increase risk for hip and other fractures, regardless of age and gender [74]. Independently of thyroid hormones, TSH deficiency was suggested to increase bone turnover in patients with SHyper [75]. Moreover, studies of the effects of variation of thyroid function across the reference range on health outcomes showed that lower TSH/ higher thyroid hormone levels are associated with reduced bone mineral density and increased fracture risk [76]. This assumption is supported by the findings of a direct inhibiting effect of TSH on osteoblast and osteoclast precursors via TSH receptor [77] and by the modulating effect of recombinant human TSH on bone metabolism markers [78].

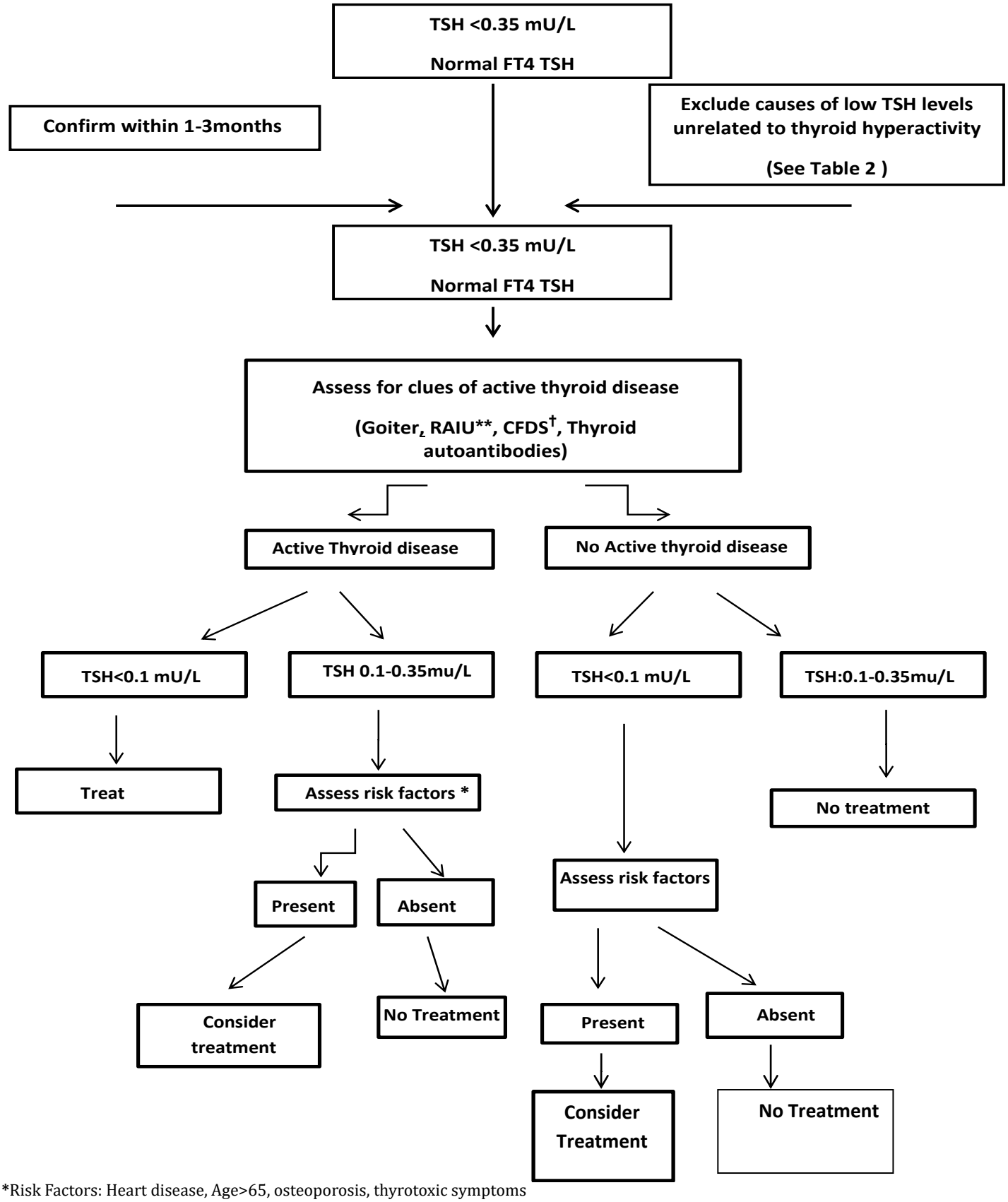
In summary, there is a faster decrease in BMD and increased risk of fracture in patients with Shyper. Restoring normal TSH levels seems to be logical to slow or reverse the bone loss [79]

## Quality of Life, Mood and Cognitive Function in Subclinical Hyperthyroidism

Patients with SHyper, particularly those younger than 50 years, were found to have high prevalence of physical and psychological symptoms of adrenergic over-activity i.e. palpitations, tremor, anxiety, heat intolerance, nervousness, reduced feeling of well-being, lower quality of life scores and inability to concentrate [80, 81]. The association between low serum TSH and cognitive impairment in the elderly is controversial. A recent systematic review included 23 studies examining the association between SHyper and cognition. Fourteen of these studies, including well-powered cross-sectional and longitudinal analyses showed a consistent association between SHyper and cognitive impairment or dementia [82]. In a prospective population study from Korea, 54 out of 313 patients who showed decline in cognitive function had lower TSH levels within the normal reference range compared with individuals whose cognitive function was stable or improved [83]. In contrast, cross-sectional studies of patients with endogenous S Hyper in China [84] and in women taking T4-suppressive therapy in the United States [85] failed to demonstrate an association of subclinical hyperthyroidism with cognitive function. There is no clear mechanistic explanation for these associations, nor any evidence to support treatment of the thyroid dysfunction for improving the decline in cognitive performance.

## Treatment

Treatment of SHyper is controversial, since no appropriately powered prospective, randomized, double-blind study has been performed to show clear benefit of therapy. Different recommendations and position papers have been published by various professional associations [86-89]. The recent guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists recommend treatment of SHyper in patients older than 65 years who have TSH levels <0.1mU/L[90]. This recommendation is based on the aforementioned studies showing an increased risk of atrial fibrillation and bone loss in patients with suppressed TSH and on findings of small uncontrolled studies showing improvements of several cardiac parameters following treatment [91,92]. In patients < 65 years who have TSH levels <0.1mU/L, treatment is also recommended in presence of comorbidities as heart disease, osteoporosis or symptoms of thyrotoxicosis [91, 93 -95]. There are insufficient data to recommend treatment in asymptomatic individuals ≤ 65 years of age or premenopausal women with TSH levels <0.1mU/L. When TSH level is merely below the lower limit of normal (0.1-0.5mU/L), treatment is generally only considered in individuals ≥ 65 years of age due to the increased risk of atrial fibrillation [38] or in patients with cardiac morbidity or symptoms of thyrotoxicosis, especially if abnormalities are obvious on thyroid imaging. However it has to be recognized that changes in cardiovascular system may occur during Shyper with TSH higher than 0.1 mU/L[96]. Approach to management of SHyper is depicted in Figure1. The treatment of SHyper is similar to that of overt hyperthyroidism. Radioactive iodine is the preferred form of treatment in patients with multi-nodular goiter or autonomous solitary adenoma, especially in older patients, since spontaneous remission is unlikely. In some patients with compressive large multi-nodular goiter, surgery is a valuable option. A 12-18 month course of low dose anti-thyroid drugs is a reasonable alternative in patients with Graves' disease and SHyper especially in younger patients demonstrating higher remission rates [97]. Long term, low dose anti thyroid drug therapy may be used in patients with multi-nodular goiter and SHyper who are reluctant to definitive treatment (radioactive iodine or thyroidectomy). Some elderly patients with persistent low TSH levels and no evidence of thyroid disease may be followed every 6-12 months without treatment, especially if thyroid hormone levels are below the average of the normal range.




*Risk Factors: Heart disease, Age>65, osteoporosis, thyrotoxic symptoms
** RAIU: radioactive iodine uptake; †CFDS: color flow Doppler sonography

**Figure 1.** Algorithm for Management of Subclinical Hyperthyroidism.

**Concluding Remarks and Recommendations**

The decision to treat Shyper should rest on the benefit expected for the patient of such treatment. Although definitive prospective, randomized, double-blind controlled studies proving the benefits of treatment of SHyper are warranted, benefit of such treatment has be demonstrated by studies ,in terms of reversal of atrial fibrillation , reduction of vascular resistance and increased bone mass [1]. In our practice we see many "high risk" patients with Shyper which are left unfortunately untreated for years. In our opinion, based on the available data demonstrating associations between SHyper and increased cardiovascular morbidity and mortality, stronger consideration for treatment should be appropriate, especially in elderly patients with cardiac morbidity or osteoporosis , in patients with symptoms of thyrotoxicosis, and those with undetectable TSH.

**Author Disclosure Statement**

The author declares he has no commercial association that might pose a conflict of interest.

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