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HYPOTHYROIDISM IN OLDER ADULTS

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ABSTRACT

Hypothyroidism is more common among elderly individuals due to the increasing incidence and prevalence of autoimmune thyroiditis that occurs with aging. Accurate diagnosis of this condition in the elderly may be challenging due to several factors including a relative paucity of referable symptoms, confounding findings that may be related to comorbid disorders, changes in thyroid hormone levels that may be related to nonthyroidal illness (NTI), and upward shifts in thyroid stimulating hormone (TSH) levels that may occur with normal aging. Effective treatment of hypothyroidism in the elderly relies on consideration of potential drug interactions and changes in the metabolic clearance of thyroid hormone that occur with aging. Specific attention should be paid to minimizing the risks of atrial arrhythmias and progressive bone loss that may be associated with iatrogenic thyrotoxicosis caused by over-treatment with excessive doses of levothyroxine (LT4). Subclinical hypothyroidism identified in the elderly does not appear to be associated with any changes in cognitive function or functional status. Studies that have sought to determine the risk of cardiovascular disease associated with subclinical hypothyroidism and the potential benefits of treatment targeted to normalize TSH levels in elderly individuals with subclinical hypothyroidism have reported conflicting results. Elderly patients presenting with untreated or undertreated severe hypothyroidism may be particularly susceptible to decompensation that may progress to a state of myxedema coma.

INTRODUCTION

Hypothyroidism increases in prevalence and incidence among the elderly (1). It is important for clinicians to appreciate certain aspects of hypothyroidism in older individuals. Its clinical manifestations may be less obvious in the setting of somatic complaints and other conditions related to aging. Thyroid function test interpretation may be altered due to the presence of nonthyroidal illness (NTI). Special considerations may apply in planning treatment due to changes in the metabolic clearance of thyroid hormone, drug interactions, and potential adverse reactions.

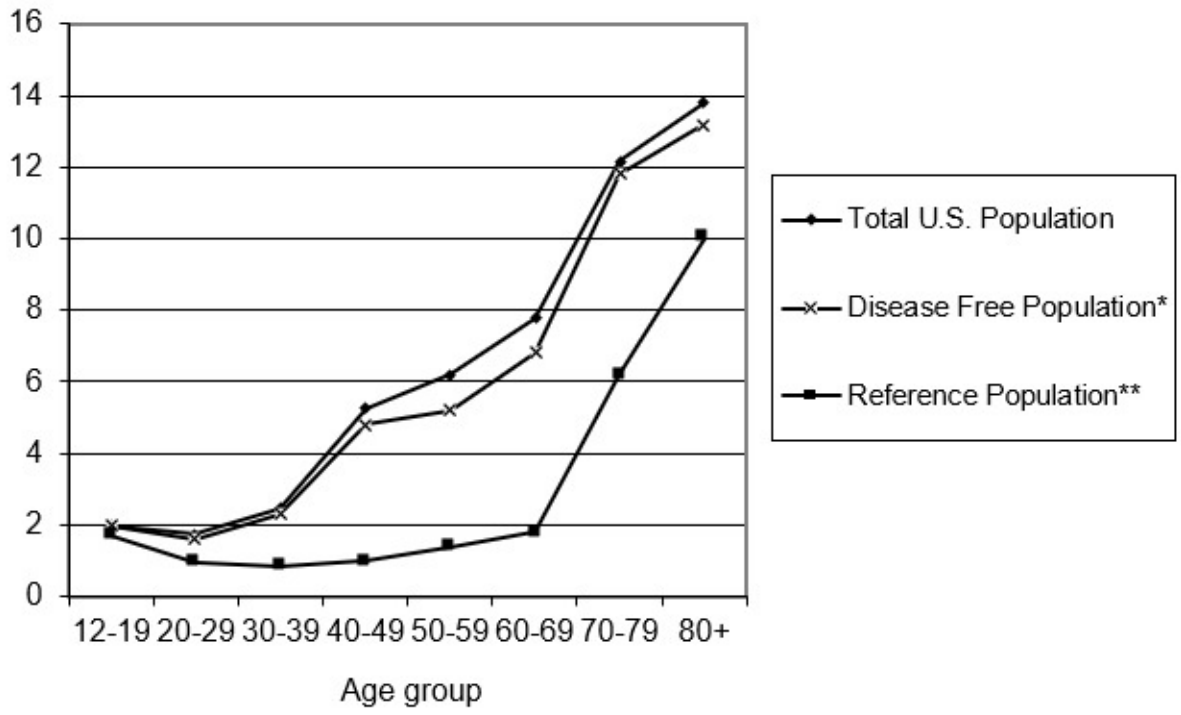

Figure 1. Percentage of Population with High Serum Thyroid Stimulating Hormone (TSH) Level (>4.5mU/L). Adapted from Hollowel et al. (2). * Excluding persons with reported histories of thyroid disease, goiter, or treatment with thyroid medications. ** Excluding persons with reported histories of thyroid disease, goiter, treatment with thyroid medications, conditions predisposing to thyroid function test abnormalities, or positive antithyroid antibodies (3).

PREVALENCE

Hypothyroidism is more common in older persons than younger individuals, especially among women, principally due to the rising incidence and prevalence of autoimmune thyroiditis. Furthermore, the incidence of hypothyroidism steadily increases with advancing age (Figure 1). Estimates of the prevalence of hypothyroidism among the elderly have varied depending on the populations studied and the criteria used to define the condition. An older survey employing the calculated free thyroxine index found that 2.3% of elderly inpatients met criteria for hypothyroidism (3). More recent community surveys of populations of healthy adults have found that 7%-14% of elderly subjects have serum thyroid stimulating hormone (TSH) levels above the upper limits of reference ranges (4),(5),(6),(7),(8). Comparable prevalences of hypothyroidism have been found in community dwelling and hospitalized older persons. A screening study that evaluated more than 25,000 individuals attending a health fair in Colorado revealed that 10% of men and 16% of women aged 65-74 had TSH levels that were above the upper limit of the reference range (5 mU/L), while 16% of men and 21% of women aged 75 and older had increased TSH levels (9). The Third National Health and Nutrition Examination Survey (NHANES III) reported that a significantly greater number of women aged 50-59 and 60-69 met criteria for subclinical and clinical hypothyroidism compared to men in the same age ranges. This survey also reported a higher prevalence of increased TSH levels and anti-thyroid antibody titers among whites and Mexican Americans compared to blacks (2). A study evaluating geriatric patients under medical care demonstrated that 15% of the women and 17% of the men had previously undiagnosed hypothyroidism (10). Similar studies

evaluating skilled nursing facility and nursing home residents demonstrated that 7%-12% had evidence of previously undiagnosed hypothyroidism at the time of admission (11),(12). A treatment survey of an unselected population of older adults revealed that 10% of the women and 2% of the men studied were taking a prescribed form of thyroid hormone (13). Among this population, 12% of the women and 29% of the men were reportedly taking thyroid hormone preparations for inappropriate reasons. A cross-sectional analysis looking at participants ≥ 65 years old in the Atherosclerosis Risk in Communities study (N=5,392) found an overall hypothyroid prevalence of 23.78% with untreated overt and subclinical hypothyroidism having prevalences of 0.82% and 6.06%, respectively (14). An Iranian cross-sectional analysis looking at adults ≥ 60 years old (N=363) randomly selected from the Birjand longitudinal aging study found a crude prevalence of 22.31% for total hypothyroidism, 3.86% for overt hypothyroidism, and 18.46% for subclinical hypothyroidism (15). Another study using the PolSenior 2 data found that amongst 5,987 community-dwelling Polish Caucasian seniors ≥ 60 years old the prevalence of hypothyroidism was 13.9% with 21.9% of these hypothyroid individuals being untreated (16). A 2017 United Kingdom study looking to estimate the prevalence of hypothyroidism in the general population as well as by decade of life for the year of 2016 found an overall prevalence of hypothyroidism of 3.6% in the general population with an estimated prevalence of hypothyroidism of ~10.4% in individuals > 70 years old (17).

Future estimates of the prevalence of hypothyroidism among the elderly based on current definitions may need to factor in growing evidence that normal TSH distribution curves appear to be shifted towards higher value ranges in older individuals (18). Age-specific analysis of TSH levels and anti-thyroid antibody titers measured as part of the most recent NHANES study demonstrated that 12% of subjects aged 80 and older without any evidence of underlying autoimmune thyroiditis had TSH levels greater than 4.5 mIU/L (19). In this analysis, the upper 95% confidence limit for TSH in euthyroid individuals over age 80 was 7.5 mIU/L (19). The prevalence of subclinical hypothyroidism is determined by the upper limit of normality defined for TSH. Because serum TSH concentrations increase with age, the true prevalence of subclinical hypothyroidism in older age is likely not as high as described in many studies.

Dietary iodine content appears to have an impact on the prevalence of hypothyroidism in the elderly. A survey of Chinese adults living in a region of low iodine intake revealed that only 1.0% of elderly subjects studied met criteria for hypothyroidism, while a study of Eastern European nursing home residents revealed that subjects living in regions of abundant iodine intake had six-fold higher rates of hypothyroidism than subjects living in regions of low iodine intake (20),(21). Additional data supporting the notion that excess iodine intake appears to be a risk factor promoting the development of hypothyroidism in the elderly are the results of a 2024 Chinese study looking to quantify the prevalence of overt and subclinical hypothyroidism in an elderly Chinese population chronically exposed to excess iodine intake. This study found that high urinary iodine content, a marker of excess iodine intake, was a risk factor for development of hypothyroidism in adults ≥ 70 years old (22). On the other hand, the possible protective nature of iodine deficiency in preventing the development hypothyroidism in the elderly is further supported by a 2009 Danish study comparing patients aged 75-80 years old from two different areas of Denmark, one area where residents were known to be mildly iodine deficient (Randers) and the other area where residents were known to be iodine sufficient (Skagen). This study discovered statistically significant higher rates of hypothyroidism in elderly residents from Skagen (13%) compared to those of Randers (6%), respectively (23). Taken together, the results of the above studies suggest that mild iodine deficiency may have a protective effect against the development of hypothyroidism, whereas iodine excess and possibly iodine sufficiency may predispose the elderly to developing hypothyroidism.

Secondary and/or tertiary hypothyroidism, collectively referred to as central hypothyroidism lacks a sex predilection and is rare accounting for approximately 0.1% of hypothyroid cases with a prevalence ranging from 1:16,000 to 1:100,000 in the general population (24),(25),(26),(27),(28). While epidemiological data regarding the incidence and prevalence of central hypothyroidism in the elderly and changes in these parameters with aging is lacking, one study looking to classify the etiology of hypothyroidism in adults > 55 years-old found that amongst 655 patients with hypothyroidism, central hypothyroidism accounted for ~2.3% of all hypothyroidism cases amongst this age group (29). Additionally, use of immune checkpoint inhibitor (ICI) therapy to treat various malignancies is likely contributing to an increasing incidence of central hypothyroidism. This is due to the increased incidence of hypophysitis associated with ICI therapy (30), In fact one study looking at 285 patients ages 16-94 years-old prior to receiving ICI therapy, of whom 218 had no baseline TFT abnormalities, found that 11/218 (5.0%) went on to develop central hypothyroidism following treatment with ICI therapy (31).

ETIOLOGY

Autoimmune thyroiditis is the most common cause of hypothyroidism among the elderly, as it is in younger persons (32),(33),(34). A survey of endocrinology clinic patients revealed that 57% of patients aged 55 and older presenting with primary hypothyroidism carried a diagnosis of autoimmune thyroiditis, while 32% carried a diagnosis of postsurgical hypothyroidism and 12% had a diagnosis of post-radioiodine hypothyroidism (29). Only 2% of the patients in this referral population presented with documented evidence of secondary hypothyroidism.

Other endocrinologic conditions associated with the development of hypothyroidism include type 1 and type 2 diabetes mellitus (35), polycystic ovarian syndrome (36), and auto-immune polyglandular syndrome types 2 and 3 (37),(38). Furthermore, certain aneuploidies, such as Turner syndrome (39),(40),(41),(42) and Down syndrome (43) are associated with development of hypothyroidism.

The incidence of post-ablative hypothyroidism has been noted to be higher in patients aged 55 and older (44). Older studies found the annual incidence of post-ablative hypothyroidism in the elderly to be ~8%, with 12% of these patients presenting with evidence of thyroid failure in the first year after undergoing treatment with radioactive iodine. Hypothyroidism appears to be less common after radioiodine ablation treatment in patients with hyperfunctioning multinodular and uninodular goiters (45),(46). Newer studies indicate that anywhere from 19-66% of elderly patients treated with radioactive iodine therapy go on to develop hypothyroidism within the first 60 months after radioactive iodine treatment (47),(48),(49). Thus, thyroid function should be continually monitored in all patients treated with radioactive iodine therapy.

The incidence of postsurgical hypothyroidism following subtotal thyroidectomy for treatment of hyperthyroidism has been estimated to be 16-27%, with 19% of patients presenting with evidence of thyroid failure in the first year after surgery (50). More recent studies show iatrogenic hypothyroidism incidence rates following hemithyroidectomy in patients ≥ 62 years old being as high as 42%, with older age being a risk factor strongly associated with development of post-surgical hypothyroidism (51),(52),(53).

External beam radiation therapy (EBRT) for treatment of head and neck malignancies has been associated with a high incidence of primary hypothyroidism. Up to 28% of patients treated with this modality eventually develop primary hypothyroidism at a median time of 15 months after completion of radiotherapy (54). In fact, according to the 2016 American Cancer Society Head and Neck Cancer Survivorship Care Guideline the prevalence of post-EBRT induced hypothyroidism is ~20% at 5 years and 27-59% at 10 years depending on the type of radiation patients receive (55). Along similar lines, a 2023 systematic review reported a post-EBRT induced hypothyroidism median estimated

incidence of 36%, ranging from 3-79% (56). When it comes to the influence of age on chances of developing post-EBRT hypothyroidism, a 2009 study found that amongst patients > 65 years old treated with EBRT the 5-year incidence of developing hypothyroidism was 20% whereas the 10-year incidence was 59% (57). These findings suggest that the risk of developing overt hypothyroidism following EBRT increases with age.

Certain diseases are treated more often in older patients with medications that can induce thyroid dysfunction (e.g., amiodarone, tyrosine kinase inhibitors, or immune checkpoint inhibitors) (see Figures 2 and 3).

Drug effect	Compound	Condition/Test Results
Disruption of hypothalamic–pituitary control	• Retinoid bexarotene • Mitotane • Immune checkpoint Inhibitors (when causing hypophysitis)	Central Hypothyroidism (↓ TSH production)
	• Others: Glucocorticoids, dopamine agonists, somatostatin analogs, metformin	• Suppress TSH and normal free thyroxine (FT4), because of decreased TSH release
Affecting thyroid hormone synthesis or release	• Iodolactones and iodoaldehydes, iodinated contrast agents, high iodine content medications	• Primary hypothyroidism (Wolff–Chaikoff effect) or thyrotoxicosis (Jod–Basedow phenomenon) if preexisting autonomy
	• Amiodarone (see also Hyperthyroidism)	
	• Lithium	• ↓ thyroid hormone release: Lithium causes goiter (50%) & hypothyroidism (17%)
Enhance thyroid autoimmunity	• Immune checkpoint Inhibitors (e.g. CTL-4, PD-1)	• Painless thyroiditis (50% exhibit positive anti-thyroid antibodies): Transient thyrotoxicosis followed by persistent and/or irreversible hypothyroidism
	• Interleukin-2 and interferon alpha	• Thyroid dysfunction (15-50%); varying degrees of hypothyroidism often preceded by thyrotoxicosis due to thyroiditis, often positive anti-thyroid antibodies
	• Alemtuzumab (for multiple sclerosis)	• Thyroid dysfunction in 41%; Graves' disease in 71% of affected
	• After active antiretroviral therapy for HIV infection	• Graves' disease
Destructive thyroiditis	• Amiodarone (see also Hyperthyroidism)	
	• Multikinase inhibitors (Sunitinib)	• Thyroiditis with hypothyroidism (14-25%) transient or permanent

Figure 2. Effects of drugs on the thyroid gland (I). Thyroid hormone control, synthesis, release, transport, and metabolism may be interfered by a wide variety of medications, and many of these are used preferentially by elderly patients. The tables summarize the main therapeutic agents that can affect the thyroid gland (58), Burch HB. Drug Effects on the Thyroid. N Engl J Med. 2019;381(8):749-761.

Drug effect	Compounds	Condition/Test Results
Affecting protein binding of thyroid hormone	• Oral estrogens, selective estrogen-receptor modulators, methadone, heroin, mitotane, and fluorouracil	• ↑ thyroxine-binding-globulin (TBG): Elevated total T4 and T3 but normal free thyroxine (FT4) and TSH
	• Androgens, glucocorticoids, niacin	• ↓ TBG: Decreased total T4 and T3 with normal FT4 and TSH
	• Phenytoin* and carbamazepine*, salsalate* and some nonsteroidal anti-inflammatory drugs, high-dose furosemide, heparin preparations†	• Drug-induced displacement of thyroid hormone from binding proteins: (1) All exhibit normal TSH. (2) *Low FT4 trend, †High FT4 trend
Affecting thyroid hormone activation, metabolism, and excretion	• Amiodarone, glucocorticoids (dexamethasone), propranolol (high doses), iodinated contrast agents, propylthiouracil	• ↓ conversion of T4 to T3
	• Drugs inducing glucuronidation (antiepileptic agents, rifampin and others) and tyrosine kinase inhibitors (sorafenib)	• ↑ thyroid hormone metabolism; FT4 dose increase may be needed
Affecting absorption of thyroid hormone preparations	Bile acid sequestrants, proton-pump-inhibitors, ferrous sulfate, calcium carbonate, aluminum hydroxide, sucralfate, raloxifene	See treatment of hypothyroidism
Causing abnormal thyroid tests in euthyroid patients	• Biotin	The direction & degree of interference depend on the assay platform: Frequently, a falsely ↓ TSH, and ↑ FT4 level, with spuriously positive results of TSH-receptor antibodies
	• Amiodarone, heparin, phenytoin, carbamazepine, and salsalate	• See above and hyperthyroidism

Figure 3. Effects of drugs on the thyroid gland (II) (58), Burch HB. Drug Effects on the Thyroid. N Engl J Med. 2019;381(8):749-761.

ICI therapy for the treatment of various malignancies is another common cause of hypothyroidism that requires special attention in the elderly. Painless thyroiditis with 50% positive anti-thyroid antibodies and transient thyrotoxicosis followed by persistent and/or irreversible hypothyroidism has been shown on ICI therapy. This is because ICI use in the elderly is more likely to occur for the following reasons: 1) the likelihood of developing cancer increases with age (59), 2) ICI therapy is already approved for the treatment of numerous malignancies either as first line therapy or for treatment refractory disease with new disease specific indications for ICI treatment continually being obtained (60),(61), and 3) rates of ICI therapy use are increasing (62). Hence, cancer patients receiving ICI therapy are more likely to be elderly. With respect to thyroid function, this matters because according to a 2017 systematic review and meta-analysis that looked at 38 randomized controlled trials with a total 7,551 participants with solid tumors treated with various ICI regimens the incidences of developing hypothyroidism in patients treated with either anti-CTLA-4 monotherapy (ipilimumab), anti-PD-1 monotherapy (nivolumab or pembrolizumab), anti-PD-L1 therapy monotherapy (atezolizumab), or combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab plus nivolumab) were 3.8%, 7%, 3.9%, and 13.2%, respectively (30). Furthermore, this study showed that the odds of developing ICI-induced hypothyroidism were highest among patients treated with combination ICI therapy (ipilimumab and nivolumab) followed by anti-PD-1 monotherapy when comparing each of these treatment regimens to ipilimumab monotherapy with odds ratios of 3.81 (CI 2.10-6.91) and 1.89 (CI 1.17-3.05), respectively (30). While this study focused on the association between the type of ICI therapy that patients received and subsequent risk of developing hypothyroidism, it did

not comment on the influence of age on the development of ICI-induced hypothyroidism making it difficult to comment on the relationship between age and likelihood of developing ICI-induced hypothyroidism. However, a 2022 study comparing the incidence of various immune related adverse events in 217 patients, 125 of whom were ≥ 65 years old, treated with at least one dose of either anti-PD-1 or anti-PD-L1 therapy found that there was no significant association between older age and development of ICI-induced thyroid dysfunction, suggesting that older age alone does not predispose patients treated with either anti-PD-1 or anti-PD-L1 therapy to developing ICI-induced hypothyroidism (63).

Unlike primary hypothyroidism, where the issue is at the level of the thyroid gland resulting in an inability to make enough thyroid hormone and TSH levels rise in a compensatory fashion, in central hypothyroidism, the issue is in the pituitary or hypothalamus. There can be alterations in the thyroid hormone feedback setpoint, or either quantitative and/or qualitative changes in TSH or thyotropin releasing hormone (TRH) molecules resulting in impaired stimulation of the thyroid follicular cells and reduced thyroid hormone production (24),(26),(28),(64).

Central hypothyroidism can be congenital or acquired, but when it comes to the elderly it is typically acquired. Acquired central hypothyroidism in adults can be isolated or combined with other hypothalamic and/or pituitary hormonal deficiencies (27). Causes of isolated central hypothyroidism in adults include certain medications such as antipsychotics, antidepressants, glucocorticoids, dopamine or dopamine agonists, somatostatin, growth hormone replacement, ICIs, bexarotene, and mitotane versus being idiopathic in etiology (27),(28),(64). Combined central hypothyroidism in adults can be due to hypothalamic and/or pituitary tumors (functional or non-functional and/or primary vs metastatic tumors), autoimmune diseases (lymphocytic or postpartum hypophysitis), vascular diseases (pituitary apoplexy, post-partum necrosis, carotid aneurysm, or subarachnoid hemorrhage), head trauma, infiltrative diseases (sarcoidosis, hemochromatosis, histiocytosis X, or eosinophilic granulomas), infections (tuberculosis, syphilis, viral or fungal infections), or be iatrogenic secondary to neurosurgery, radiation, or medications (ICIs) (26),(27),(65),(64).

CLINICAL FEATURES

Symptoms

Elderly patients developing hypothyroidism may present with classic symptoms, but complaints are generally even less specific than those reported by younger patients presenting with evidence of thyroid hormone deficiency (66),(67),(68),(69),(70). In part this may be due to patients and physicians ascribing nonspecific complaints to other comorbid disorders common among the elderly, or to the effects of aging itself (71),(72),(73),(74). A study that compared the frequency of 24 symptoms of hypothyroidism reported by elderly and nonelderly patients found that complaints of fatigue and weakness were reported by more than 50% of elderly patients, but that significantly fewer complaints were reported by the elderly compared to a nonelderly group (75),(76). Elderly patients less often complained of cold intolerance, weight gain, paresthesias, and muscle cramps. Evaluation of a questionnaire administered to patients newly diagnosed with hypothyroidism ascribed to autoimmune thyroiditis showed that while all 13 referable symptoms were more prevalent in subjects younger than 60 years of age, the only referable symptoms that were more prevalent in older subjects were fatigue, dyspnea, and wheezing (77). Other neurological symptoms that have been reported to occur more commonly in older patients include hypogeusia and dysgeusia, impaired hearing, and ataxia. Additionally, acute depression of mental state can be precipitated by infections, trauma, hypothermia, or administration of sedatives and narcotics in elderly hypothyroid patients.

Signs

Physical findings evident in hypothyroid elderly individuals may include bradycardia, diastolic hypertension, pallor, dry skin, coarse hair, hoarseness, dysarthria, delayed relaxation of deep tendon reflexes, which is specific if present, and mental status changes (78). The severity of specific findings may be exacerbated by comorbid cardiovascular, neuropsychiatric, dermatologic, or rheumatologic conditions that are more common among the elderly (79). In some cases, it may be necessary to evaluate responses to thyroid hormone replacement to determine the extent to which certain findings represent manifestations of thyroid hormone deficiency.

Morphologic changes in the size and appearance of the thyroid do not appear to increase with aging (80). Elderly patients with autoimmune thyroiditis are more likely to present with the atrophic form of the disorder without goiter (81). Neuropsychological testing of elderly patients with hypothyroidism has demonstrated that they score lower on Mini-Mental Status Tests and on 5 of 14 specific indices of visual-spatial function, memory, word fluency, attention, and psychomotor function (82). That being said, there is conflicting evidence to suggest that hypothyroidism itself predisposes elderly patients to developing cognitive impairment and/or dementia (83),(84),(85),(86).

Analysis of laboratory test results has demonstrated that 54% of patients (22/41) diagnosed with hypothyroidism have increased serum creatinine levels that may be correlated with advancing age (87). A 1999 study looking at 24 patients with acquired hypothyroidism following total thyroidectomy for treatment of thyroid cancer showed that serum creatinine levels rose while these patients were overtly hypothyroid but then normalized with treatment of the hypothyroidism (88). An individual participant data meta-analysis consisting of 72,856 patients from 16 different cohorts that sought to identify whether or not there was a relationship between thyroid hormone dysfunction and renal dysfunction found that relative to euthyroid patients (n=66,542), patients with overt (n=704) and subclinical (n=3,356) hypothyroidism were not more likely to develop accelerating decline in renal function (89). Taken together, these results suggest that reversible increases in serum creatinine can be seen in inadequately treated hypothyroid patients and that hypothyroidism itself is not a risk factor for the development and/or worsening of chronic kidney disease.

Pericardial effusion is one of the few radiographic findings associated with hypothyroidism, with an incidence ranging from 3-37% (90),(91),(92),(93). Additional, radiographic findings associated with hypothyroidism include low attenuation of the thyroid on unenhanced CT scan as well as anterior pituitary hyperplasia as seen on MRI in the setting of acute onset hypothyroidism (94),(95).

Morbidity

Severe medical complications of hypothyroidism are more common in affected elderly persons. Most patients presenting with myxedema coma are elderly women (76),(96),(97),(98). Elderly patients with unrecognized hypothyroidism may be at greater risk for the development of perioperative and intraoperative complications. One study that compared patients with unrecognized hypothyroidism with controls matched for age, sex, and operative procedure identified higher rates of intraoperative hypotension, heart failure, and postoperative gastrointestinal and neuropsychiatric complications in hypothyroid patients (99). Furthermore, hypothyroidism in the perioperative setting has been shown to be a risk factor for more difficult intubation, prolonged intubation duration, hyponatremia, and simultaneous bleeding and clotting (100). A prospective study that screened hospitalized patients aged 60 and older for thyroid dysfunction reported that unrecognized overt hypothyroidism in this population may be associated with significantly higher mortality (101). Along these lines, additional studies have shown an association between diagnoses of overt and subclinical hypothyroidism in elderly patients with increased mortality (102),(103),(104).

AGE-RELATED CHANGES IN THYROID FUNCTION

With increasing age, the hypothalamic-pituitary-thyroid (HPT) axis is affected in multiple ways (Figure 4). At the systemic level, reduced clearance of thyroxine (T4) and triiodothyronine (T3) that occurs with aging, results in longer half-lives of these hormones and a compensatory decrease in the production of new thyroid hormone (70),(105),(106),(107),(108). It is also possible that the thyroid gland itself may become less responsive to TSH stimulation, further resulting in reduced production of T4 and T3 (70). The exact mechanism by which the thyroid loses responsiveness to TSH is unclear, but one hypothesis is that the aging process itself results in decreased thyroid volume secondary to atrophy and fibrosis (109),(110). If this is the case, this potentially means less functional thyroid tissue is available to make thyroid hormone, thus leading to lower thyroid hormone levels that may or may not be sufficient to maintain euthyroidism.

Biochemically, studies have shown that the effects of aging on thyroid hormone levels can manifest as free T4 (FT4) levels that can either remain stable, decrease, or even increase with age (2),(105),(111),(112),(113),(114). Although in most cross-sectional and longitudinal studies, FT4 has not been shown to change significantly in the healthy elderly (69). One explanation behind why FT4 levels may decrease with age is the hypothesis that there is an age-related decline in iodine uptake by the thyroid (115). On the other hand, T3 levels tend to decrease with age, although within the normal range, in carefully selected healthy populations (see below). In the longitudinal Cardiovascular Health Study All Stars (113) total T3 dropped by 13% in 13 years, while TSH rose by a similar amount (13%) in healthy, community-dwelling people (n= 843) with an average age of 85.3 years-old. Furthermore, serum T3 concentrations decrease slightly, together with TSH, in centenarians and in very old people (69) suggesting that it is a physiological marker of aging, disease, and frailty. The mechanism underlying these findings is speculated as being an age-related decline in 5'-deiodinase activity, thus allowing for slower metabolism and maintenance of T4 levels at the expense of T3 levels (70),(111),(113).

Looking more proximally at the HPT axis, TSH levels tend to increase with age regardless of the presence of concurrently normal FT4 levels. This finding has been confirmed even when looking at older adults without any history of thyroidal illness and with concurrently negative antithyroid antibody levels (19),(105),(112),(113). While the exact mechanism behind this age-related increase in TSH is not known, proposed age-related mechanisms for this change include increased production of TSH molecules with reduced biologic activity due to alterations in thyrotroph post-translational processing of TSH (70),(112), decreased sensitivity of thyrotrophs to negative feedback from circulating thyroid hormone (116), and/or development of TSH resistance by the thyroid gland (70).

In terms of the relationship between thyroid autoimmunity and aging, multiple studies have shown that antithyroid antibodies increase with age, especially in women, making chronic autoimmune thyroiditis one of if not the most common cause of hypothyroidism in the elderly (19),(111),(117),(118).

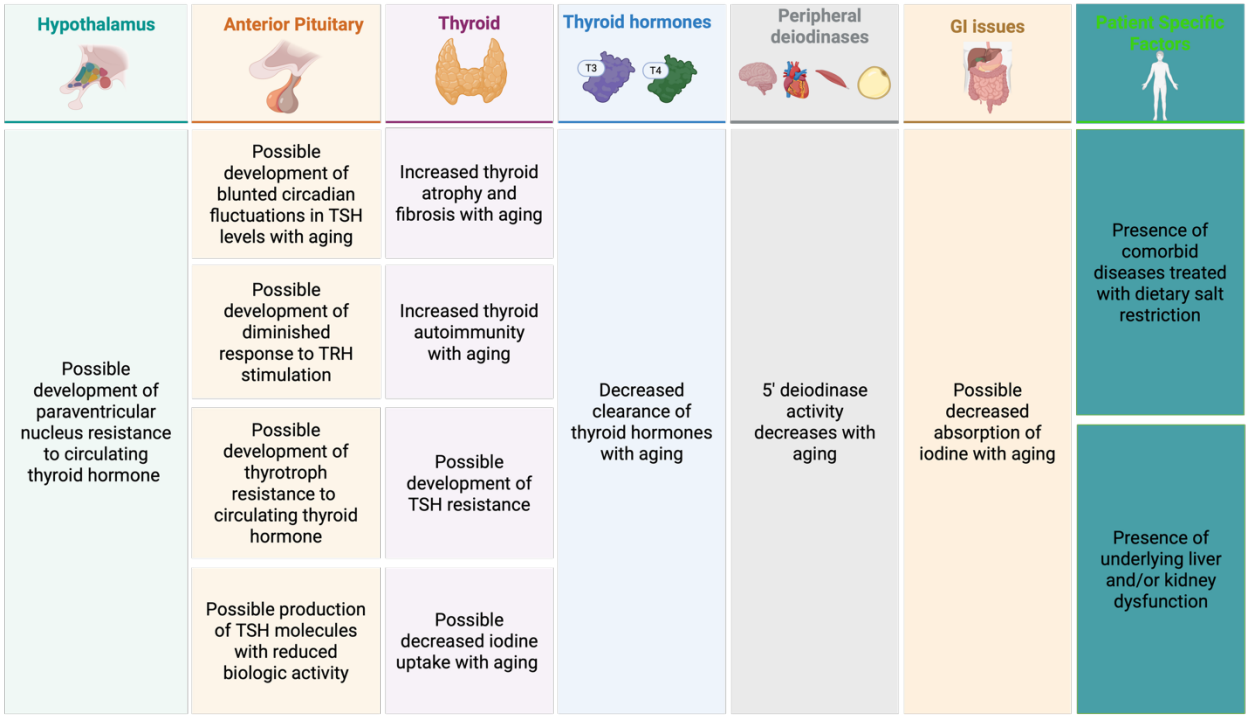

Figure 4. Changes in the Thyroid Axis with Age. TSH= thyroid stimulating hormone, TRH= thyrotropin releasing hormone. Created with BioRender.com.

Additional factors complicating the relationship between thyroid hormone levels and aging include the presence of comorbid diseases including hypertension, heart failure, liver failure, and kidney failure, all of which are more prevalent amongst the elderly. In fact, thyroid hormone metabolism relies in part on the liver and kidneys (58), so if either of these organ systems are impaired it can further affect clearance of thyroid hormone. Furthermore, all the comorbidities listed above tend to be treated with dietary salt restriction. As iodized salt is one of the major sources of dietary iodine in the U.S., elderly patients with these comorbidities who follow a low salt diet may be at increased risk for developing iodine deficiency (115),(119). It is also possible that elderly patients experience an age-related decrease in gastrointestinal iodine absorption (115). This combination of decreased iodine intake and absorption with age can in turn predispose elderly patients to iodine deficiency. If iodine deficiency is severe enough, regardless of age, it can result in the development of hypothyroidism (120). This is opposed to the effects of mild iodine deficiency in the elderly, which appear to be protective against the development of hypothyroidism when compared to elderly patients with sufficient iodine intake (23).

A number of studies have sought to determine whether the biochemical diagnosis of thyroid disorders in the elderly may be confounded by age-related changes in thyroid function (121). An early study of thyroid function profiles in women aged 60 and older reported higher serum thyroxine (T4) and TSH levels, and decreased triiodothyronine (T3) and reverse triiodothyronine (rT3) levels in comparison to reference ranges (122). Similar findings were confirmed in a contemporaneous study comparing thyroid function profiles in elderly men and women to those of younger persons, and in a more recent study comparing thyroid function profiles in women aged 70 and older to those in their middle-aged offspring (123),(124). In contrast, when other investigators stratified elderly patients by health status (i.e. healthy elderly adults, nursing home residents, or hospitalized elderly adults), they found that lower serum T3 levels and higher rT3 levels were only detected in

institutionalized elderly adults (125). Consequently, previously observed patterns of age-related changes may have reflected effects of non-thyroid illness (NTI). Two studies that evaluated thyroid hormone profiles in healthy adults have clarified this issue. One study that measured T3 and free T3 levels in healthy adults aged 65 and older determined that while levels of these hormones were lower than in younger adults, they fell well within the limits of reference ranges (108). Another study of thyroid hormone profiles in a range of healthy adults who were not taking prescribed medications determined that there were no significant differences in T4, free T4, T3, free T3, or rT3 levels between groups stratified by age (126). These findings thus argue against the existence of a "low T3" syndrome associated with normal aging (See figure 5).

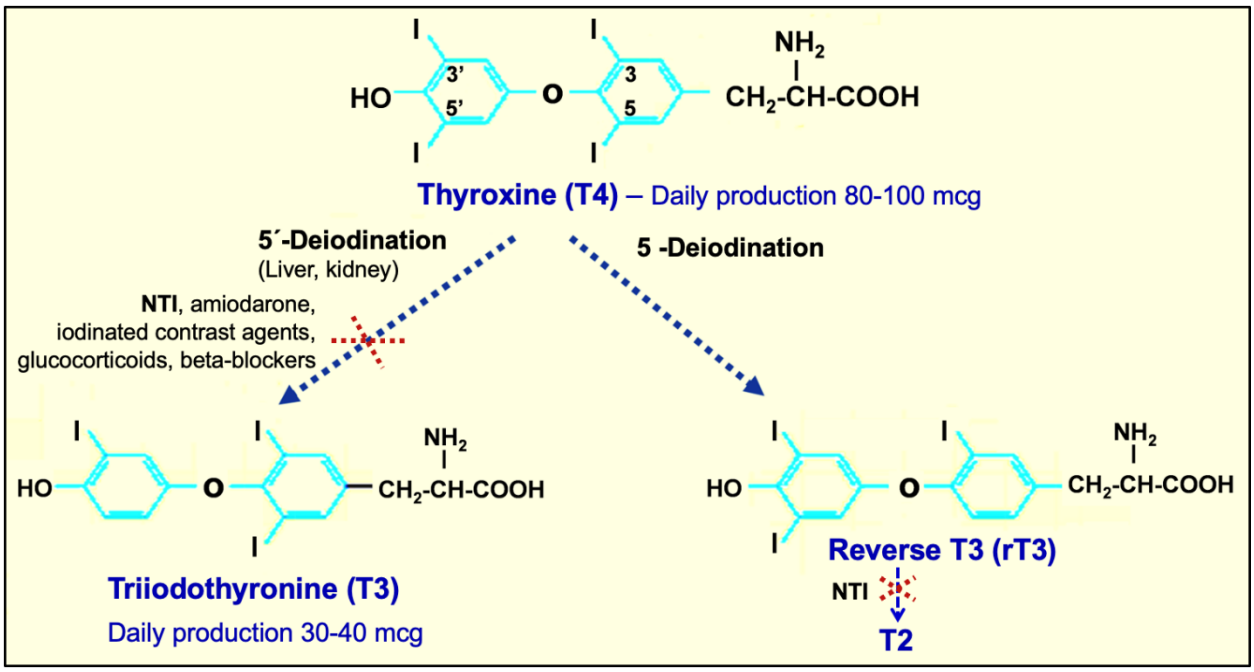

Figure 5. Changes in deiodination due to diseases and drugs. In healthy young adults, the daily production is 80-100 mcg for T4 and 30-40 mcg for T3 which is mostly converted (80%) by extrathyroidal 5'-deiodination of T4 in the liver and kidney. The daily production of biologically inactive rT3 is similar to that of T3 and results almost entirely from extrathyroidal 5-deiodination of T4. The 5'-deiodination of T4 decreases, resulting in low T3 levels, in patients with various non-thyroidal Illnesses (NTI) and elderly-specific disorders, in situations of caloric deprivation, and with administration of amiodarone and high doses of beta-blockers. Also, in NTI, 5'-deiodination from rT3 to T2 decreases, resulting in high levels of rT3. Concurrently, patients with NTI may exhibit low TSH (0.05 to 0.3 mU/L) of probable central origin, likely due to the negative effects of pro-inflammatory cytokines. The aforementioned is more common in the elderly making the diagnosis of thyroid dysfunction more challenging in this population. *NTI: Non-thyroidal illnesses.*

Most circulating T4 (99.95%) and T3 (99.5%) are transported by thyroxine binding globulin (TBG), and a lower proportion by transthyretin (TTR). It is well known that peripheral thyroid hormone transport does not change with aging in healthy older subjects because, although TBG decreases, transthyretin (TTR) increases.

Studies of hypothalamic-pituitary function in the elderly have shown blunted circadian fluctuations in TSH levels and decreases in mean 24-hour TSH secretion and TSH pulse amplitude especially during the night. Diminished TSH responses to TRH stimulation may also be detected in elderly males

(127),(128),(129). The cause of this phenomenon is unclear. There are no histological or immunoreactive differences in the thyrotroph cells of elderly patients (130). Measurement of serum deiodinase levels in a range of healthy adults has demonstrated a significant inverse correlation of 3',3'-diiodothyronine, 3',5'-diiodothyronine, and 3,5-diiodothyronine levels with increasing age (131). One study showed that the decline in deiodinase activity noted with increasing age was paralleled by a decline in selenium levels. At the time of that study, it was thought that selenium supplementation may effectively increase selenium levels, deiodinase activity, and T3/T4 ratios in elderly patients (132). However, results of studies looking at selenium supplementation and thyroid function have been mixed. One meta-analysis showed no benefit in patients with hypothyroidism secondary to Hashimoto's thyroiditis treated with selenium (133). Another meta-analysis showed that selenium supplementation in patients with Hashimoto's thyroiditis from selenium deficient areas resulted in a lower TSH level in patient's not receiving levothyroxine (LT4) and in lower anti-TPO antibody levels regardless of treatment with LT4 (134).

THYROID FUNCTION TESTS

Accurate diagnosis of primary hypothyroidism in the elderly relies primarily, as it does in all patients, on the measurement of a sensitive serum TSH level. Although data from the NHANES III study has established that median TSH levels appear to increase with advancing age, the normal upper limit of an established reference range may still be used as a cutoff to confirm the diagnosis of primary hypothyroidism in most elderly patients. While a blood spot TSH level has been shown to be an adequate screening test for the detection of overt primary hypothyroidism in the elderly, it may not be sensitive enough to detect cases of subclinical hypothyroidism characterized by elevated serum TSH levels with normal T4 and FT4 levels (135). One study has determined that there may be a negative correlation between age and the degree to which TSH levels are elevated in elderly patients presenting with primary hypothyroidism (136).

In cases of suspected secondary or tertiary hypothyroidism (central hypothyroidism) that may result from disruption of the anatomy or function of the hypothalamic-pituitary axis, the TSH level may not be relied upon as an accurate index of thyroid function. In this setting the FT4 level may serve as more reliable measure of thyroid hormone production (137).

The interpretation of thyroid function test profiles in hospitalized or institutionalized patients must be tempered by an understanding of how NTI may produce changes in TSH and thyroid hormone levels (138) (Figure 5). In fact, in admitted patients, clinical guidelines (139) usually recommend measuring TSH only if there is high suspicion of thyroid dysfunction, because it may be abnormal in NTI and it is altered by some medications (Figure 2 and 3). The direction and extent of changes observed may depend on the severity of an underlying illness and the point in the course of recovery at which thyroid function tests are measured (140). Longitudinal studies have demonstrated that early on in the course of severe illnesses or protracted procedures, TSH levels in euthyroid patients may decline to levels that fall below the lower limits of normal reference ranges (141). This change may be paralleled by a decline in T4 and T3 levels that may be particularly pronounced in elderly patients with a corresponding increase in reverse T3 levels (142). One study demonstrated that 59% of elderly patients known to be euthyroid had documented low T3 levels measured during a course of hospitalization, whereas another demonstrated that changes in T3 levels detected in elderly hospitalized patients were more closely correlated with the severity of each underlying illness than with advanced age itself (143),(144). Studies have demonstrated a correlation between declining T4 and T3 levels and increasing mortality rates in critical care patients (145),(146). Free T4 levels measured by equilibrium dialysis or ultrafiltration methods, if they are within reference ranges, may help to distinguish hypothyroidism from the effects of altered thyroid

hormone binding that may occur in critically ill patients (147).

Current data indicates that the normal or low TSH levels found in the presence of low T4 and T3 levels in the setting of NTI likely reflect the combined effects of central hypothyroidism and reduced peripheral generation of T3, effectively representing a deficiency of thyroid hormone. Whether nonthyroidal illness syndrome (NTIS) should be treated with administration of thyroid hormone preparations remains controversial. Some observers argue in favor of thyroid hormone replacement, while others weigh against it, without conclusive data to support either viewpoint (148),(149),(150),(151). Despite this uncertainty, the American Thyroid Association recommends against the treatment of NTIS with any form of thyroid hormone supplementation given the lack of evidence showing a clear benefit while at the same time raising concern for potential harm with treatment of NTIS (25).

If a patient survives to recover from NTIS, TSH levels may transiently rise above the upper limits of reference ranges (152). If thyroid function tests are checked when a transiently increased TSH level precedes increases in low T4 and/or T3 levels, the profile that emerges may appear to be consistent with primary hypothyroidism (153). This could lead to unnecessary treatment with thyroid hormone, which would probably be inconsequential in the short term, but could eventually cause iatrogenic thyrotoxicosis. Thus, TFTs checked during and/or around the time of acute illness need to be interpreted with caution. That being said, TSH levels greater than 20-25 µU/mL (which are equivalent to 20-25 mIU/L) are more suggestive of a diagnosis of primary hypothyroidism rather than recovering NTIS (154). In cases where changes in TSH and thyroid hormone levels may be plausibly ascribed to NTI, the patient's thyroid function tests should be reassessed approximately four weeks later to see if the observed changes seen during the acute illness are resolving (155). One study that tracked thyroid function test profiles in hospitalized elderly female patients showed that while 14% of the subjects had increased TSH levels and decreased T4 and T3 levels on initial assessment, only 2% were proven to have evidence of underlying primary hypothyroidism during follow up (156).

Measurement of anti-thyroid antibody levels may help to confirm a suspected diagnosis of autoimmune thyroiditis as the underlying cause of primary hypothyroidism, but it should be noted that the absence of anti-thyroid antibody positivity does not exclude a diagnosis of autoimmune thyroiditis (157),(158),(159). The presence or absence of elevated anti-thyroid antibodies may not be an absolute indicator of the likelihood of eventual development of primary hypothyroidism in elderly individuals. One study that measured TSH and anti-microsomal antibody levels in healthy elderly adults showed that positive titers were detected in only 67% of subjects with TSH levels > 10.0 mIU/L and 18% of subjects with normal TSH levels (160). A similar study that measured anti-thyroid antibody levels in nursing home residents detected positive titers in only 64% of the women and 32% of the men presenting with increased TSH levels (161). Comparative measurements of anti-thyroglobulin, anti-microsomal, and anti-thyroid peroxidase antibodies have demonstrated that while there may be a similar prevalence of positive anti-microsomal and anti-thyroid peroxidase titers among elderly adults, mean values of anti-thyroid peroxidase antibody levels tend to be much more commonly elevated in this population (162). Although positive antithyroid antibodies are more common in women than in men and increase with age, positivity is less prevalent in centenarians and very old people in good health (111). Nonetheless anti-thyroid antibody measurements in the elderly may help to predict the likelihood of progression from subclinical to overt hypothyroidism (163). Interestingly, while both anti-thyroid peroxidase and anti-thyroglobulin antibodies predispose to the development of hypothyroidism, they may also confer protective effects in breast cancer (164).

The TFT pattern consistent with a diagnosis of central hypothyroidism is that in which the FT4 is low with

either a concurrently low or normal TSH level. That being said, accurate diagnosis of central hypothyroidism can be challenging. This is for a multitude of reasons including 1) the variability and lack of specificity of hypothyroid symptoms regardless of the etiology combined with the fact that patients with central hypothyroidism tend to have milder hypothyroid symptoms compared to their primary hypothyroidism counterparts and can concurrently have symptoms of other pituitary hormone deficiencies that either overlap with or mask those of hypothyroidism (27),(64), 2) the emphasis on using isolated TSH or TSH with reflex FT4 testing to diagnose hypothyroidism, which is an effective strategy for diagnosing primary but not central hypothyroidism since TSH can be inappropriately normal despite having a concurrently low FT4 (27), 3) the clinical context of testing matters as checking TFTs when patients are on certain medications, acutely ill, pregnant, recovering from thyrotoxicosis of any etiology, transitioning from being hyperthyroid to hypothyroid following a bout of thyroiditis, or have primary hypothyroidism and have stopped their LT4 for any reason can give TFT patterns that mimic that of central hypothyroidism (26),(27), 4) the TFT pattern of central hypothyroidism can be confused with that of subclinical hyperthyroidism if the FT4 is low normal to normal with a concurrently low TSH (27), 5) the presence of quantitative or qualitative TBG abnormalities can affect thyroid hormone binding to TBG resulting in low total T4 (TT4) levels and a low FT4 index which can be confused as being consistent with a diagnosis of central hypothyroidism (26),(27), 6) the possibility of having TSH molecules with reduced bioactivity which can lead to normal to even slightly elevated TSH levels with concurrently low FT4 levels thus casting doubt on a diagnosis of central hypothyroidism (27), 7) the presence of heterophilic antibodies can interfere with the TSH assay, artificially raising TSH levels and thus casting doubt on a diagnosis of central hypothyroidism (64), 8) use of labelled analogue methods to measure FT4 can give artificially low FT4 measurements leading to incorrect diagnosis of central hypothyroidism (64), 9) the presence of certain genetic mutations like MCT8 mutations seen in Allan-Herndon-Dudley syndrome, 10) THRA mutations leading to thyroid hormone resistance alpha syndrome, and/or TSHβ mutations with conserved bioactivity but lost immunoreactive of circulating TSH molecules can all give TFT patterns consistent with that of central hypothyroidism when in reality patients afflicted with these conditions do not have central hypothyroidism (26). Hence, to accurately diagnosis central hypothyroidism, one must have a high clinical suspicion for it based on information obtained from the patient's history and physical exam such that TSH and FT4 are checked simultaneously, ideally see that the central hypothyroidism TFT pattern is persistent over time on the span of weeks if not months, and rule out those possible diagnostic confounders listed above.

Abnormalities in other routine laboratory test parameters may suggest possible undetected hypothyroidism. Hyponatremia caused by decreased free water excretion may complicate moderate and severe cases of primary hypothyroidism (165). Hyperlipidemia characterized by a variety of lipid profile abnormalities including either isolated or mixed hypercholesterolemia and/or hypertriglyceridemia has been reported in hypothyroid patients (166),(167),(168). In fact, one study found that amongst 1,509 patients referred for dyslipidemia evaluation, 4.2% were found to have hypothyroidism, which was twice the incidence of hypothyroidism seen in the general population (168). Cases of primary hypothyroidism that are severe enough to precipitate myopathy may present with increased creatine phosphokinase levels (169). Anemia can manifest in various ways in the hypothyroid patient. Most commonly, the anemia seen with hypothyroidism is a normochromic normocytic hypoproliferative anemia (170). Hypochromic microcytic anemia independent of an underlying hemoglobinopathy or iron deficiency, and macrocytic anemia can also be seen in hypothyroid patients (170),(171),(172),(173). Interestingly, there appears to be an association between the presence of Hashimoto's thyroiditis and development of atrophic gastritis and pernicious anemia, which is an alternative reason for hypothyroid

patients to develop either microcytic or macrocytic anemias (174). In the absence of underlying vitamin B12 or folate deficiency or use of medications that impair DNA synthesis, hypothyroidism by itself can cause macrocytosis (170). One way to differentiate between the macrocytosis caused by hypothyroidism and that caused by vitamin B12 and/or folate deficiency or that caused by drugs that impair DNA synthesis is that the macrocytosis seen with hypothyroidism should not be megaloblastic, so hypersegmented neutrophils should not be present, whereas the macrocytosis seen in vitamin B12 or folate deficiency or that caused by drugs that impair DNA synthesis should be megaloblastic (170). Increased prevalence of hyperuricemia thought to be due to decreased renal plasma flow and impaired glomerular filtration has also been reported in hypothyroid patients (175). Homocysteine and lipoprotein (a) levels may be increased in patients with primary hypothyroidism, potentially contributing to an increased risk of atherosclerotic disease (176).

TREATMENT

Initial treatment of hypothyroidism in elderly patients should typically start with sodium levothyroxine (thyroxine) administered in lower doses than those usually prescribed for healthy younger patients with starting doses as low as 12.5 to 50 mcg daily (70),(76),(177). According to the 2014 Guidelines for the treatment of Hypothyroidism from the ATA, LT4 should consistently be taken either 60 minutes before breakfast or at bedtime at least three hours after an evening meal to maximize absorption (25). Despite this being the official recommendation by the ATA, studies looking at taking LT4 with breakfast (178), 30 minutes before breakfast vs 60 minutes before the main meal of the day vs at least two hours after dinner (179), or 60 minutes before breakfast vs 60 minutes after the last meal of the day (180) have all shown similar treatment efficacy rates. Anecdotally, the results of these findings likely explain why many practitioners instruct their patients to take LT4 30-60 minutes before breakfast or at night, particularly in elderly men, if they awaken to use to use the restroom.

T4 is available as levothyroxine sodium (LT4) tablets and, in some countries, is also marketed as soft gelatin capsules with T4 pre-dissolved in glycerol and as liquid formulations with T4 pre-dissolved in ethanol or glycerol. Most patients receive LT4 tablets, either brand-name or generic. T4 in capsules or liquid may have therapeutic advantages over LT4 in tablets in some circumstances, although the evidence supporting the use of these preparations is weak in clinical studies (181). The three afore-mentioned formulations are bioequivalent in healthy individuals; however, the active ingredient in the liquid formulation achieves systemic circulation more rapidly, as it bypasses the disintegration and dissolution phases required for absorption (182). The liquid formulation has demonstrated efficacy in limited cohorts of patients presenting with active H. pylori infection (183), atrophic gastritis (184), or those undergoing treatment with proton pump inhibitors (185) or antacid medications (186). Other study (187) involving 50,000 patients treated with T4 demonstrated a significant decrease in the frequency of TSH measurements following the transition from tablet to liquid formulation; this outcome was ascribed to concurrent use of medications known to interfere with LT4 absorption. Moreover, the liquid formulation has been shown to reduce sensitivity to food interference compared to tablet forms (181), (188). TSH concentrations were comparable whether liquid T4 was administered with breakfast or 30 minutes prior (189). Additionally, liquid formulations have been recommended for patients undergoing sleeve gastrectomy (188). A recent meta-analysis indicated that patients treated with LT4 tablets who presented with suboptimal TSH levels reached target TSH concentrations following a switch to an equivalent dose of the liquid formulation (190). In contrast, another meta-analysis reported no significant differences among patients without malabsorption (191).

It can be concluded that capsule or liquid formulations (181), (188) while potentially advantageous in the context of specific comorbidities and concomitant medications, still present uncertainties and unresolved

questions. Evidence suggests that these newer formulations may mitigate the requirements for taking tablets with respect to concomitant intake with food, beverages, and certain medications. Additionally, these formulations may be advantageous for patients experiencing fluctuating gastrointestinal conditions or those taking medications that affect absorption, as they can decrease the frequency of required visits for thyroxine dose adjustments.

Once cardiovascular tolerance of a starting dose has been assessed, most experts recommend gradually increasing daily doses by 12.5-25 mcg every six to eight weeks until adequate replacement is confirmed by repeat TSH measurement (76). The degree to which this general strategy has been adopted in practice was confirmed by a recent survey of members of the American Thyroid Association (192). A recent trial demonstrated that older patients without any underlying cardiovascular disease could be safely started on full replacement doses of thyroxine (1.6 mcg/kg) without any adverse effects (193). Given that older patients tend to require less thyroid hormone replacement to achieve euthyroidism compared to their younger counterparts and that there are no formal weight-based dosing recommendations for starting LT4 in the elderly, questions regarding whether weight based LT4 dosing using the 1.6 mcg/kg starting dose is the best initial dosing strategy in this patient population. A study looking at 185 adults ≥ 65 years old who participated in the Baltimore Longitudinal Study of Aging found that elderly patients needed ~1/3rd less thyroid hormone replacement compared to younger population to achieve euthyroidism irrespective of whether LT4 was being dosed using actual body weight (1.09 mcg/kg) or ideal body weight (1.35 mcg/kg) suggesting that elderly patients who qualify for full dose levothyroxine replacement therapy at the time diagnosis of hypothyroidism need less than the 1.6 mcg/kg that is typically needed by their younger counterparts (194). While a great deal of interest has arisen regarding the potential benefits of adding doses of liothyronine (T3) to thyroxine to approximate physiologic thyroid hormone secretion, a number of randomized trials have shown that this mode of treatment does not have any significant impact on identified symptoms, mood, cognitive function, or quality of life (195),(196),(197),(198),(199),(200),(201),(202),(203).

Serial measurements of TSH levels six to eight weeks after each change in thyroxine dosage should be used to monitor thyroid hormone replacement therapy. In a comparison trial based on a reference standard of measured TSH response to TRH administration, basal TSH levels proved to be more sensitive to fine alterations in thyroxine doses than basal free T4 or free T3 levels. Most experts recommend targeting a normal TSH range in elderly patients (204),(205). However, a recent trial comparing a standard TSH target (0.4 to 4.0 mIU/L) to a high TSH target (4.01 to 8.0 mIU/L) in 48 adults ≥ 80 years old with established hypothyroidism on LT4 saw that at 24 weeks into treatment the higher TSH target group did not experience any adverse impact with respect to patient reported outcomes, cardiovascular risk factors, or bone resorption markers compared to the standard TSH group (206). These results call into question the notion of targeting a TSH within the population-defined normal range for elderly hypothyroid patients. Physiologically this makes sense given the fact that TSH levels tend to increase with age. Hence, it is not surprising to see that both the ATA and ETA hypothyroidism guidelines recommended raising the target serum TSH in patients >70 years old and >70-75 years old on LT4, respectively with the ATA calling for a TSH target of 4-6 mIU/L and the ETA calling for a TSH target of 1-5 mIU/L. (25),(207). Figure 6 illustrates a proposed treatment algorithm for the management of primary hypothyroidism in the elderly that relies heavily upon knowing the acuity with which the hypothyroidism developed and knowing whether the patient has concurrent coronary heart disease when deciding on what LT4 dose to start an elderly patient on.

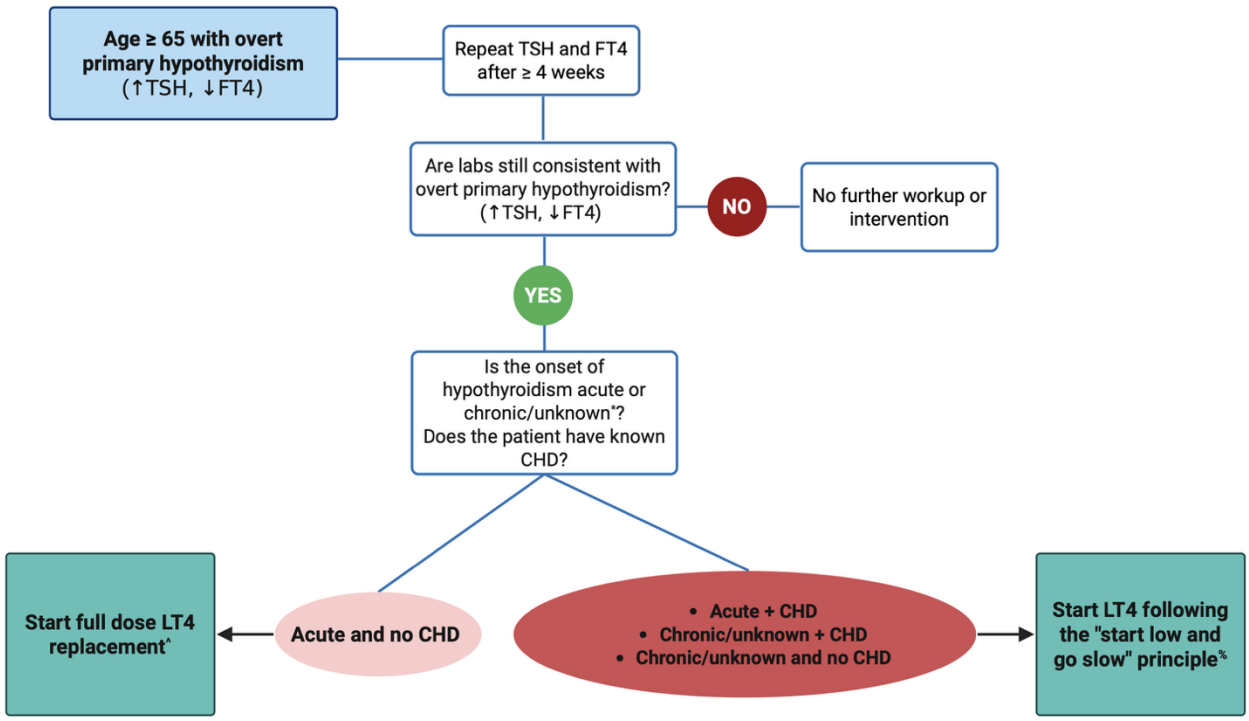

Figure 6. Management of Primary Hypothyroidism in the Elderly. * Acute means < 2 months in duration, chronic means ≥ 2 months in duration. ^ Full replacement LT4 dose in the elderly is ~1.09 mcg/kg actual body weight/day. Titrate LT4 dose in 6–8-week intervals as needed for target TSH of < 6 mIU/L (age < 80) or < 7 mIU/L (age ≥ 80). % Start LT4 at 25-50 mcg daily and increase the dose every 6-8 weeks. The goal is to get the patient to the maximally tolerated LT4 dose that does not precipitate angina while simultaneously achieving the desired TSH target. Target TSH is <6 mIU/L (age < 80) or <7 mIU/L (age ≥80). TSH = thyroid stimulate hormone, FT4= free T4, LT4 = levothyroxine, CHD = coronary heart disease.

Surveys amongst practitioners caring for elderly hypothyroid patients across the US suggest that age does play a role in what TSH value they target for their patients. In fact, while 39% of ATA members recommended targeting a TSH range of 0.5-2.0 mIU/L when treating younger patients, a comparable number reported that they were generally more liberal in their approach to elderly patients, targeting TSH ranges of 1.0-4.0 mIU/L. Along similar lines, a national survey of primary care physicians and endocrinologists showed that 53% of physicians factor age into their decision making process when determining the TSH target for their patients with hypothyroidism on LT4. When this same group of physicians was presented with clinical scenarios regarding treatment of hypothyroidism in patients differing in age and sex, they preferentially targeted a higher TSH level in octogenarians. Taken together, these results imply a tendency by practitioners to avoid overtreatment with LT4 in the elderly (208). Treatment with thyroxine in overt hypothyroidism has been shown to improve signs and symptoms associated with hypothyroidism, improve cardiac and cognitive function, and reduce orocecal transit time from an average of 135 minutes in a hypothyroid state to 75-95 minutes with adequate replacement (209),(210),(211).

While thyroid hormone supplementation to a level that completely corrects the hormonal deficiency may be an optimal goal, some patients with ischemic heart disease may not be able to tolerate full replacement doses of LT4 (212),(213),(214),(215). One study of patients with known coronary artery disease and primary hypothyroidism reported that precipitation of angina symptoms limited titration of LT4 in two-thirds of cases, while precipitation of hypothyroid symptoms

limited titration of antianginal agents in one-third of cases. Even with the addition of propranolol at maximally tolerated doses, 46% of the patients surveyed rated control of their angina and hypothyroid symptoms as fair to poor (216).

Thyroxine dose requirements in elderly patients may be related to several factors including declining metabolic clearance, progression of underlying thyroid failure, declining body mass, and interactions with other medications prescribed for the treatment of co-morbid conditions (217),(218). On average, elderly patients with primary hypothyroidism receive initial daily doses that are 20 mcg lower and maintenance daily doses that are 40 mcg lower than those prescribed for younger and middle-aged patients (219),(220),(221). One study suggested that lean body mass may be a better predictor of daily replacement doses than age or weight alone (222). Another reported that most of the age-dependent differences in LT4 requirements noted might be attributed to the effects of chronic disease, since substantially lower average daily replacement doses were reported by elderly patients treated for other chronic medical disorders (223). A study that tracked changes in elderly patients' LT4 requirements over time based on the etiology of their primary hypothyroidism reported that daily replacement doses increased in patients who initially presented with autoimmune thyroiditis or postsurgical hypothyroidism, decreased in patients who initially presented with post-ablative hypothyroidism, and did not change in patients who initially presented with subclinical hypothyroidism or drug-induced hypothyroidism (224).

In situations where cognitive or functional impairment may make it difficult for patients to comply with daily administration of LT4, alternative dosing schedules may be considered. A study that compared daily administration of LT4 to twice weekly administration of comparable cumulative daily doses in elderly women showed that both regimens produced similar peak and trough free T4, T3, and TSH levels (225). Trials and case reports/series of regimens based on once weekly administration of cumulative daily doses of LT4 have demonstrated similar results without any evidence of precipitation of thyrotoxicosis (226),(227),(228).

A number of medications used to treat other comorbid conditions in the elderly may interfere with absorption and metabolism of LT4 (229). Simultaneous ingestion of 1,200 mg of calcium carbonate with LT4 therapy is known to decrease thyroxine absorption and raise TSH levels and ingestion of 2,000 mg of calcium carbonate has been shown to interfere with the peak and total incremental absorption of a concomitantly administered treatment dose of LT4 (230),(231). Ferrous sulfate, sucralfate, aluminum hydroxide, cholestyramine, colestipol, and raloxifene have also been reported to impair absorption of LT4 (232),(233),(234). In postmenopausal women with primary hypothyroidism, treatment with estrogen replacement therapy may lead to increased LT4 dose requirements as a consequence of increased production of thyroid binding globulin (TBG) (235). Women with hormonally-responsive breast cancer who receive fluoxymesterone may require substantially lower doses of LT4 during courses of treatment, as exposure to this androgenic steroid may decrease effective TBG production (236). Long-term administration of phenytoin, carbamazepine, phenobarbital, or rifampin in the setting of treated primary hypothyroidism typically increases metabolism of thyroxine, increasing the dose of LT4 required to provide optimal replacement (237),(238),(239) . A retrospective cohort study among 538,137 veterans ≥ 65 years old from 2004-2017 that sought to discover how common concurrent use of LT4 with medications known to interfere with thyroid hormone metabolism discovered that 31.4% of elderly patients were on at least one medication that interfered with thyroid hormone metabolism, thus illustrating that concurrent use of medications affecting thyroid hormone metabolism amongst the elderly is frequent (240).

Overtreatment with excessive doses of LT4 in the elderly is common, occurring in 9.6%-50% of elderly patients treated with LT4, and may also be associated with significant morbidity in this population

(241),(242),(243). Palpitations, anxiety, tremulousness, irritability, insomnia, heat intolerance, hyperdefecation, and weight loss may be precipitated or exacerbated by iatrogenic thyrotoxicosis. In elderly patients, exposure to excessive amounts of thyroid hormone may be associated with increased risks of atrial fibrillation, other tachyarrhythmias, progressive declines in bone mineral density, increased risk of fractures, and increased incidence of cognitive disorders (244),(245),(246). A prospective study of the incidence of atrial arrhythmias in patients aged 60 and older determined that over the course of a 10-year period, the relative risk of development of new-onset atrial fibrillation in subjects with initial TSH levels < 0.1 mIU/L was 3.1 when compared to subjects with normal TSH levels (247). Further analysis revealed that suppressed TSH levels identified in 77% of these subjects were attributable to iatrogenic thyrotoxicosis resulting from overtreatment. A study that tracked bone mineral density changes in women treated with LT4 documented greater mean rates of decline in the lumbar spines of those with suppressed TSH levels (248). A recent cohort study that tracked TSH and free T4 and T3 levels in healthy aging adults in tandem with inventories of medication use reported that half of the cases of prevalent and incident thyrotoxicosis identified could be attributed to over-treatment with LT4 (242).

Like primary hypothyroidism, the mainstay of treatment for central hypothyroidism is LT4. Whereas the TSH level is the primary biochemical marker used to assess the adequacy of LT4 dosing in primary hypothyroidism, in central hypothyroidism the FT4 level is relied on instead. This is due to the underlying pathophysiology of central hypothyroidism, as inadequate stimulation of the thyroid by TSH, either from a hypothalamic or pituitary problem, results in low FT4 levels, thus making FT4 rather than TSH a better marker of thyroid status in these patients. However, TSH should not be completely ignored. Per multiple sources, TSH values ≥ 0.5 mU/L are suggestive of inadequate thyroid hormone repletion regardless of the concurrent FT4 level (24),(64), whereas the European Thyroid Association suggests that TSH values > 1.0 mU/L with concurrent FT4 levels below or near the lower limit of normal indicate inadequate LT4 repletion in patients with central hypothyroidism (26).

Given the possibility of concurrent central adrenal insufficiency in patients with central hypothyroidism, patients with central hypothyroidism should be screened for adrenal insufficiency and treated with glucocorticoid replacement therapy if they have a positive screen prior to initiation of LT4 (24),(26),(27). Following assessment of an individual's hypothalamic-pituitary-adrenal axis and initiation of glucocorticoid replacement therapy if it is needed, LT4 should be initiated with the goal of targeting a FT4 level in the upper half of the reference range (25),(26),(27),(28),(139),(249). The reasons for targeting a FT4 level in the upper half of the reference range in patients with central hypothyroidism are multifactorial and are based on studies showing that FT4 levels below the upper half of the reference range amongst this patient population were associated with higher body mass index, higher total cholesterol levels, higher LDL cholesterol levels, lower FT3 levels, and lower body temperature (250),(251). Additionally, because patients with primary hypothyroidism require a higher FT4 level to normalize their TSH level compared to euthyroid controls, this finding implies that the goal FT4 level in patients with central hypothyroidism should be in the upper half of the reference range (252).

The European Thyroid Association in its 2018 guidelines on the diagnosis and management of central hypothyroidism recommends targeting a LT4 dose of 1-1.2 mcg/kg body weight/day in adults ≥ 60 years old with central hypothyroidism and specifies that if needed LT4 can be started at a lower dose and gradually up-titrated to reach this target dose (26). Others recommend starting elderly patients with central hypothyroidism on 25-50 mcg/day and gradually up-titrating the dose until a FT4 level in the upper half of the reference range is achieved (27),(64). While, the ATA agrees with targeting a FT4 level in the upper half of the reference range in patients with central hypothyroidism, they do make an exception for

elderly patients or patients with comorbidities who are at higher risk of developing side effects of thyroid hormone excess (25). Similar to primary hypothyroidism, use of combination LT4 and liothyronine is not routinely recommended for the treatment of central hypothyroidism (25),(27). Overtreatment of central hypothyroidism should be considered when the FT4 level is near or above the upper limit of normal in the context of the patient having signs and/or symptoms of thyrotoxicosis and/or an elevated T3 level (26),(27).

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism, which is characterized by an increased TSH level with concomitant free thyroid hormone levels that fall within normal limits, is very common among elderly men and women. The estimated prevalence of this condition among adults has varied from 3-15% (253),(254). In fact, the tendency of TSH to increase with age combined with the use of a standardized TSH reference range across the population is likely contributing to overdiagnosis and treatment of subclinical hypothyroidism amongst the elderly (19),(105). A study evaluating a community of healthy elderly adults in the southwest of France reported that 4.2% of subjects presented with increased TSH levels and normal free T4 levels (255). Within this group, subclinical hypothyroidism was linked with an increased prevalence of symptoms of depression. A study that evaluated thyroid function profiles in a bi-ethnic urban community reported that subclinical hypothyroidism was more commonly identified in females and non-Hispanic white subjects than Hispanic subjects (256). Stratified analysis of the impact of subclinical hypothyroidism in this population revealed no significant alterations in health status measures in subjects with TSH levels ranging between 4.7-10.0 mIU/L. A study that inventoried clinical findings of hypothyroidism in a population of geriatric clinic patients reported that while 15.4% of the men and 14.6% of the women screened met criteria for subclinical hypothyroidism, the incidence of symptoms and signs consistent with thyroid hormone deficiency detected in these subjects was similar to that reported for euthyroid subjects (257). An array of studies that have tracked changes in thyroid function in cohorts of aging subjects in the United States, Australia, the Netherlands, Spain, the United Kingdom, and China have reported that the development of hypothyroidism in elderly patients does not appear to be associated with any change in cognitive function, increased levels of depression, or diminished ability to perform activities of daily living (85),(258),(65),(259),(260),(261),(262). A study that measured an array of anthropometric, biochemical, and neuropsychiatric parameters in Korean subjects aged 65 years and older showed that subclinical hypothyroidism did not appear to be associated with any discernible metabolic or neuropsychiatric derangements (263). A study that evaluated subgroups of subjects enrolled in the Health, Aging, and Body Composition study found that those determined to have mild subclinical hypothyroidism (defined by a TSH level of 4.5-7.0 mIU/L with normal thyroid hormone levels) demonstrated better mobility, cardiorespiratory fitness, and walking ease than subjects who were euthyroid or determined to have moderate subclinical hypothyroidism (defined by a TSH level of 7.0-20.0 with normal thyroid hormone levels) (264). An analysis of subgroups in this cohort study identified increased odds of prevalent metabolic syndrome among subjects with TSH levels > 10 (265). The possible beneficial effects of mild TSH elevation may not only be limited to enhanced physical performance amongst the elderly, but have also been associated with increased longevity as demonstrated by multiple studies (116),(266),(267),(268),(269). A multi-cohort individual participant data analysis consisting of 74,565 participants from 23 different cohorts with study specific median baseline ages ranging from 57 to 93 years old looking at the association between thyroid dysfunction with cognitive function showed no association between subclinical hypothyroidism with worsening cognitive function, accelerated cognitive decline, and the presence of incident dementia. Rather, data from this study suggested subclinical hypothyroidism was associated with improved cognitive function, specifically within the domains of executive function and memory. Hence,

the authors of this study recommend against screening for subclinical thyroid dysfunction in older adults experiencing cognitive decline (270).

A study that evaluated postmenopausal women at risk for development of osteoporosis reported that subclinical hypothyroidism was not associated with decreased bone mineral density or an increased risk of vertebral or non-vertebral fracture (271). A meta-analysis looking at the risk of hip, non-spine, and spine fractures in addition to fractures of any kind in patients with mild (TSH 4.5-6.9 mIU/L), moderate (TSH 7.0-9.9 mIU/L), and severe (TSH ≥ 10 mIU/L) subclinical hypothyroidism showed that there was no increased risk of any fractures regardless of the severity of subclinical hypothyroidism (272). Another study seeking to determine if there was any relationship between subclinical hypothyroidism and femoral osteopenia or osteoporosis in adults ≥ 50 years-old found no association between the two over a four-year window (273).

Several longitudinal studies have tracked the natural history of untreated subclinical hypothyroidism in elderly persons. A study of nursing home residents confirmed that over time TSH levels declined to normal ranges in 51% of subjects with initial TSH levels that were lower than 6.8 mIU/L (274). Serial TSH levels were persistently elevated in the remainder of these subjects and in all subjects with initial TSH levels greater than 6.8 mIU/L. A similar study that stratified subjects on the basis of anti-thyroid antibody levels reported that 80% of elderly adults with mild hypothyroidism with initial measured anti-microsomal antibody titers greater than 1:1,600 eventually progressed to develop overt hypothyroidism requiring treatment with thyroxine replacement therapy (162). A study that tracked 505 subjects diagnosed with mild hypothyroidism over time showed that positive anti-thyroid peroxidase antibodies and higher total cholesterol levels measured at baseline were associated with increased odds of eventual progression to overt hypothyroidism (275). One study showed that progression from subclinical to overt hypothyroidism was faster in women with anti-thyroid antibody positivity (4.3% per year) when compared to those without (2.6% per year) (276). Two studies showed that when elderly patients diagnosed with subclinical hypothyroidism were tracked over a span of 4-4.2 years, 44-54% demonstrated normalization of TSH levels consistent with reversion to a euthyroid state (277),(278). Findings that were associated with reversion included lower baseline TSH levels, homogenous echotexture of thyroid tissue on ultrasound imaging, and an absence of detectable anti-thyroid peroxidase antibodies. A more recent study showed that subclinical hypothyroidism was transient with normalization of TSH on repeat testing in 61% of individuals greater than or equal to 80 years old (279), leading to the recommendation that subclinical hypothyroidism only be diagnosed in patients with persistently elevated TSH levels at least one month after the initially elevated TSH level was detected (280).

Questions have been raised about the possible association of subclinical hypothyroidism with an increased risk of cardiovascular disease in the elderly. One study that confirmed the presence of subclinical hypothyroidism in 10.8% of subjects drawn from a cohort of postmenopausal women reported a greater age-adjusted prevalence of coronary and aortic atherosclerosis in mildly hypothyroid women (281). Even stronger associations between subclinical hypothyroidism and atherosclerotic disease were noted among postmenopausal women with elevated anti-thyroid antibody levels. Another study that evaluated the prevalence of peripheral vascular disease among nursing home residents reported that 78% of subjects with mild hypothyroidism presented with reproducible claudication, whereas symptomatic peripheral vascular disease was only identified in 17% of euthyroid subjects (282). A study that evaluated thyroid function in patients enrolled in a study of pre-existing heart failure reported that subclinical hypothyroidism presenting with TSH levels ≥ 7 mIU/L was associated with an increased risk of a need for the use of ventricular assist devices, heart transplantation, and death (283).

Population-based studies that have tracked thyroid function in elderly subjects have reported differing results regarding risks of cardiovascular disease. A study that examined community-dwelling subjects aged 70-79 years enrolled in the Health, Aging, and Body Composition study found that subclinical hypothyroidism was associated with an increased incidence of congestive heart failure (284). A study that examined subjects aged 65 years and older enrolled in the Cardiovascular Health study found that subclinical hypothyroidism was not associated with an increased incidence of coronary artery disease, cerebrovascular disease, cardiovascular mortality, or all-cause mortality (285). Analysis of subgroup data tracked over the course of 12 years and echocardiographic parameters tracked over the course of 5 years demonstrated that subjects with TSH levels ≥ 10.0 mIU/L had a higher incidence of heart failure events, a greater increase in left ventricular mass, and appreciable changes in measurements reflecting changes in diastolic function compared to euthyroid subjects (286). Two meta-analyses that analyzed data from a range of prospective cohort studies incorporating measurements of thyroid function identified a modest increase in the risk of coronary artery disease and associated mortality in subjects determined to have evidence of subclinical hypothyroidism (287),(288). When adjusted for age and sex, a diagnosis of subclinical hypothyroidism was associated with increased CHD events and increased CHD mortality when TSH levels were ≥ 10.0 mIU/L and ≥ 7.0 mIU/L, respectively (288). Along similar lines, a meta-analysis looking at 55 cohort studies identified an increased risk of ischemic heart disease events and cardiovascular mortality in patients with subclinical hypothyroidism when TSH levels were ≥ 10.0 mIU/L (289). More recent analyses of subgroups tracked in cohort studies have reported that persistent subclinical hypothyroidism does not appear to be associated with an increased risk of all-cause mortality, cardiovascular mortality, coronary artery disease, myocardial infarction, or congestive heart failure (290),(291),(292). That being said, an individual participant data analysis of 24,742 individuals from six prospective cohorts where the median age was 70 years old, revealed that severe subclinical hypothyroidism (TSH ≥ 10.0 mIU/L) was associated with an increased risk of heart failure events (293). With respect to the relationship between strokes and subclinical hypothyroidism, an individual participant data analysis looking at 37,842 individuals from 12 prospective cohorts saw that there was no association between subclinical hypothyroidism, regardless of severity, and the risk of stroke events. That same study also looked at data from 47,244 individuals from 17 prospective cohorts and found that moderate subclinical hypothyroidism (TSH 7.0-9.9 mIU/L) was associated with an increased risk of fatal stroke whereas severe subclinical hypothyroidism (TSH ≥ 10.0 mIU/L) was not associated with an increased risk of fatal stroke, with the lack of statistical significance in the latter group being attributed to the small sample size and lack of power (294). An analysis of NHANES III data has identified increased mortality in subjects diagnosed with concurrent subclinical hypothyroidism and congestive heart failure, and a retrospective cohort study from Israel involving 17,440 patients with subclinical thyroid disease showed that TSH levels > 6.35 mIU/L were associated with increased mortality (104),(295).

Treatment

Knowing that TSH elevations in the elderly can be physiologic with varying degrees of TSH elevation being unique to individuals, combined with the facts that such TSH elevations may be transient if checked in the setting of acute illness, that sustained isolated TSH elevations in the elderly may be advantageous, and that there is mixed data to suggest that treatment of subclinical hypothyroidism in the elderly is beneficial, it is easy to see why this topic is fraught with confusion. If the decision is made to treat then additional questions, such as what TSH and FT4 levels to target arise. Not to mention, one of the major concerns in treating subclinical hypothyroidism in the elderly is the risk of iatrogenic harm from overtreatment, which occurs in ~13-28% of elderly patients treated with LT4 (243),(296),(297).

Overtreatment with LT4 is of particular clinical concern in the elderly given it associations with increased risk of developing atrial fibrillation (247), osteoporotic fractures (298),(299), dementia (300),(301),(302), and depression (303),(304) all of which elderly patients are already more prone to developing at baseline. Furthermore, empiric initiation of LT4 for subclinical hypothyroidism in the elderly increases healthcare expenses, the risk of polypharmacy, and likely overmedicalizes this patient population, who may not have an actual thyroid problem, by necessitating additional laboratory testing, doctor's visits, and prescriptions (280). Despite the risks associated with LT4 overtreatment, LT4 remains one of the most prescribed medications in the US and abroad (305),(306), and one of if not the most common reasons for prescribing LT4 for adults in the US is for the treatment of subclinical hypothyroidism (307). In contrast to what the high prescribing rates of LT4 in the US suggest, prescribing LT4 to the elderly should not be taken lightly given all the potential risks associated with doing so. Lastly, once prescribed, many barriers to thyroid hormone deprescribing exist in the elderly, particularly at the patient, physician, and systems levels, which in turn favor elderly patients' remaining on it indefinitely once started (308).

As the diagnosis of subclinical hypothyroidism relies on the detection of an isolated elevated TSH level that is greater than the 97.5th percentile with a concurrently normal FT4 using standardized population-based assays that do not consider the expected changes in TSH levels that result from aging, overdiagnosis of subclinical hypothyroidism in the elderly becomes more prevalent. Increased detection of this supposed problem can then precipitate increased treatment to correct the problem. To prevent overdiagnosis and treatment of subclinical hypothyroidism in the elderly, many experts have called for the use of age-specific TSH reference ranges to reduce the rates of diagnosis and treatment of subclinical hypothyroidism (280),(309),(310),(311),(312),(313). Despite the strong push for the use of age-specific TSH reference ranges, widespread implementation of them has yet to become the norm in the US.

While use of age-specific TSH reference ranges would decrease the number of elderly patients being diagnosed with subclinical hypothyroidism, there would still be elderly patients who meet criteria for having this condition. In these patients, consideration of treatment of subclinical hypothyroidism remains a prominent issue of debate and it is often predicated on the notion that restoration of normal thyroid hormone levels might help to relieve symptoms that could be exacerbated by a deficiency of thyroid hormone.

The Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism (TRUST) trial was specifically designed to address this question (314). It randomized 737 subjects ≥ 65 years of age with persistent subclinical hypothyroidism to double-blinded placebo-controlled administration of doses of LT4 adjusted to normalize TSH levels. Assessment based on a thyroid-related quality-of-life questionnaire after one year of treatment showed no difference in hypothyroid symptom scores or tiredness scores. An analysis that combined data from 146 TRUST trial subjects ≥ 80 years of age with data from 145 subjects enrolled in the Institute for Evidence-Based Medicine in Old Age 80-plus trial who were evaluated with a similar protocol also showed no improvement in hypothyroid symptoms or fatigue; however, a majority of those with elevated TSH levels had values below 7 mIU/L (279). Additional sub-studies using the TRUST trial data have shown that treatment with twelve months of LT4 compared to placebo in elderly patients with subclinical hypothyroidism showed no significant difference between the two groups when they were further divided by a hypothyroid symptom score of > 30 or ≤ 30 as well as a tiredness score > 40 or ≤ 40 (315). Furthermore, LT4 therapy in elderly patients with subclinical hypothyroidism did not lead to a significant difference in the Pittsburg Fatigability Scale (PFS) physical and mental scores nor a significant difference in the 15-item geriatric depression scale (GDS-15) questionnaire (316),(317). All in all, these findings suggest that LT4 therapy in older patients with subclinical hypothyroidism does not improve physical nor psychiatric complaints or symptoms. Hence, it is

reasonable to conclude that prescribing of LT4 to elderly patients with subclinical hypothyroidism for these reasons should be avoided.

Given that increased cardiovascular disease risk is one of the major concerns in patients with subclinical hypothyroidism (113), researchers have sought out to determine if there are any cardiovascular benefits to treatment of subclinical hypothyroidism with LT4. One study looking at the effects of LT4 vs placebo on cardiac function in elderly patients with mild subclinical hypothyroidism (mean baseline TSH < 7 mIU/L) showed a significant decrease in pulmonary artery systolic pressure in the LT4 group, whereas no significant difference was seen between the treatment and placebo groups when looking at other measures of cardiac function including left ventricular ejection fraction (LVEF), the ratio between mitral peak flow velocity of early filling (E) to early diastolic mitral annular velocity, the ratio of doppler-derived transmitral flow pattern, and E deceleration time (318). Another study looking at elderly patients with subclinical hypothyroidism and recent acute myocardial infarction showed that administration of LT4 for 52 weeks did not result in a significant difference in LVEF, left ventricular mass, or median infarct size (319). Additionally, a nested trial incorporated in the TRUST trial showed that normalization of TSH levels with LT4 for a span of one year did not have any impact on carotid intima media thickness or carotid atherosclerosis (320). With respect to cardiovascular disease outcome measures, treatment with LT4 compared to placebo in elderly patients with subclinical hypothyroidism did not show any significant difference in the number of fatal and non-fatal cardiovascular events, all-cause mortality, proportion with new onset atrial fibrillation, and proportion with new onset heart failure (314),(321). Taken together these findings suggest that empiric LT4 therapy in elderly patients with subclinical hypothyroidism may not improve common measures of cardiac function nor reduce adverse cardiovascular disease outcomes.

When it comes to answering the question of whether treatment of subclinical hypothyroidism corrects other laboratory abnormalities associated with this condition the data is mixed. Partial or complete reversibility of hypercholesterolemia has been shown to accompany LT4 treatment of subclinical hypothyroidism in the majority of small interventional trials addressing this issue (322). Lowering of lipoprotein (a) levels has been shown in some, but not all studies (323). Hyperhomocysteinemia in patients with mild hypothyroidism has not been shown to be reversed with LT4 therapy.

Whether LT4 therapy in elderly patients with subclinical hypothyroidism improves bone strength is an area that has also been investigated. Studies looking to see if there is any reduction in fracture rates and improvement in bone strength as measured by bone mineral density of the lumbar spine, total hip, and femoral neck as well as lumbar spine trabecular bone score in elderly patients with subclinical hypothyroidism receiving LT4 vs placebo have shown no improvement in any of the above metrics following one year of LT4 treatment (314),(324). Therefore, there is no data to support the notion that treatment with LT4 in elderly patients with subclinical hypothyroidism will improve bone health.

When it comes to the management of subclinical hypothyroidism in general let alone in the elderly, consensus is lacking (207),(325),(139). One of the most recent reviews on the subject suggests avoiding initiation of LT4 in elderly patients when their TSH is between 4.5-6.9 mIU/L and starting LT4 in any elderly patient whose TSH is between 10.0-19.9 mIU/L. For those elderly patients with TSH levels between 7.0-9.9 mIU/L a more nuanced approach is needed when deciding whether to initiate treatment that considers the patient's age as well as underlying cardiovascular comorbidities (326). Figure 7 illustrates a proposed algorithm for the management of subclinical hypothyroidism in the elderly. This algorithm focuses on ensuring that TSH is persistently elevated prior to starting LT4, checking markers that have been associated with progression to overt hypothyroidism in

elderly patients with TSH levels between 4.5 and 6.9 mIU/L (specifically anti-TPO antibody and total cholesterol levels), avoiding treatment with LT4 therapy in most elderly patients with subclinical hypothyroidism unless their TSH is ≥ 10-20 mIU/L, and targeting a TSH level ≤ 6.0 mIU/L if LT4 treatment is initiated.

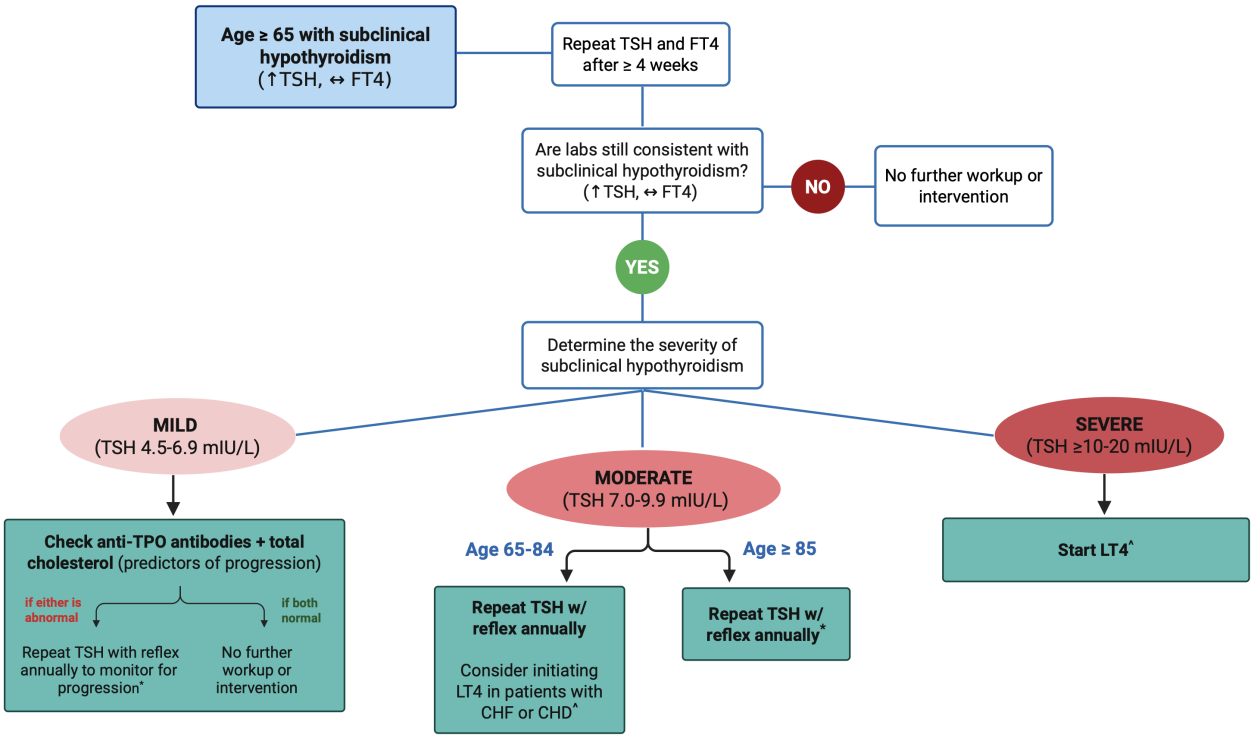

Figure 7. Management of Subclinical Hypothyroidism in the Elderly. * Do not initiate LT4 unless TSH increases ≥10 mIU/mL or there is development of overt primary hypothyroidism (↑TSH, ↓FT4). ^ If decision to start LT4 is made, do so following the "start low and go slow" principle, meaning start LT4 at 25-50 mcg daily and increase the dose every 6-8 weeks. The goal is to get the patient to the maximally tolerated LT4 dose that does not precipitate angina while simultaneously achieving the desired TSH target. Target TSH is <6 mIU/L (age < 80) or <7 mIU/L (age ≥80). TSH = thyroid stimulating hormone, FT4= free T4, LT4 = levothyroxine, CHF = congestive heart failure, CHD = coronary heart disease.

MYXEDEMA COMA

Patients with severe hypothyroidism may present in a state of pronounced multisystem failure termed myxedema coma (327),(328). Elderly patients with untreated or undertreated primary hypothyroidism and comorbid disorders may be particularly susceptible to decompensation that leads to onset and progression of this life-threatening condition (329),(330). In fact, myxedema coma occurs almost exclusively in patients ≥ 60 years old and > 90% of cases of myxedema coma occur in women (331),(332). In addition to coma, there may be hypothermia, bradycardia, hypotension, congestive heart failure, ileus, and hypoventilation with hypercapnia and respiratory acidosis. In situations where historical information may be unobtainable, physical examination may reveal evidence of prior thyroid surgery, laryngeal surgery, or head and neck external beam radiation therapy. Radiographic studies may reveal pericardial effusions, which may also be reflected in low voltage waves on electrocardiograms. Although such pericardial fluid collections may be large, they are usually not hemodynamically significant. Laboratory evaluation confirming severe hypothyroidism may also reveal

evidence of hyponatremia, hypoglycemia, and/or adrenal insufficiency.

Myxedema coma is an endocrine emergency with a mortality rate that may approach 40% (333),(334). In addition to older age, factors that may be associated with an increased risk of mortality include comorbid cardiovascular disease and treatment with high-dose LT4 replacement therapy (335). Generally recommended supportive measures include critical care-level monitoring of vital signs, careful external rewarming with heating blankets, correction of fluid and electrolyte imbalances, avoidance of hypnotics and sedatives, empiric treatment of suspected underlying infections, and mechanical ventilatory support as indicated (336). Given the theoretical risk of concomitant adrenal insufficiency due to polyglandular autoimmune syndromes or hypothalamic-pituitary compromise, many experts recommend empiric treatment with stress-dose glucocorticoids until definitive testing to exclude a concurrent diagnosis of adrenal insufficiency can be performed. This is because thyroid hormone is known to accelerate the metabolism of glucocorticoids (27),(58),(337),(338). Hence treatment with thyroid hormone alone in patients with myxedema coma can precipitate adrenal crisis if the patient has concomitant adrenal insufficiency (339),(340).

Recommendations regarding the dose and composition of thyroid hormone preparations that should be administered to treat myxedema coma differ (331),(341),(342),(343),(344). Most experts concur that intravenous LT4 should be used to circumvent impaired gastrointestinal absorption. Some have recommended initial LT4 loading doses, while others have advocated co-administration of liothyronine (T3). Treatment of critically ill hypothyroid patients with high-dose LT4 has been associated with a significant increase in cardiac index due to increased heart rate and stroke volume with decreased systemic vascular resistance (345). Although the onset of action of liothyronine is more rapid than LT4, supraphysiologic T3 levels measured after treatment have been correlated with increased mortality in older patients presenting with myxedema coma (329),(346). Of note the 2014 ATA hypothyroidism guidelines provide recommendations on dosing of IV LT4 and T3 for the treatment of myxedema coma and specify that older age should be a consideration for giving lower doses of these agents (25). Therefore, a judicious approach may involve administration of a loading dose of 200-300 mcg of intravenous LT4 followed by administration of 50 mcg daily. Depending on the estimated risk of underlying cardiovascular disease, a loading dose of 5-25 mcg of T3 may be administered concomitantly followed by doses of 2.5-5 mcg every eight hours until clinical improvement is evident. Intravenous hydrocortisone may be administered in stress doses of 50-100 mg every 8 hours while testing for underlying adrenal insufficiency is performed. IV LT4 and T3 should be continued until the patient clinically improves, at which point a transition to oral LT4 should be made (25),(347).

SCREENING AND CASE-FINDING RECOMMENDATIONS

Professional organizations and task forces have issued a range of recommendations concerning the advisability and timing of biochemical screening for hypothyroidism in adult populations (Table 1) (139),(348),(349),(350),(351),(352),(353),(354),(355),(356),(357).

Table 1. Screening Recommendations for Hypothyroidism in Adults			
Guideline	**Methods used to analyze evidence**	**Organization**	**Year of publication**
American Thyroid Association guidelines for the detection of thyroid dysfunction	Narrative literature review Expert opinion	American Thyroid Association	2000
Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association	Narrative literature review Expert opinion	American Association of Clinical Endocrinologists and the American Thyroid Association	2012
Consensus Statement: Subclinical Thyroid Dysfunction: A Joint Statement on Management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society	Narrative literature review Expert opinion	American Association of Clinical Endocrinologists, the American Thyroid Association, the Endocrine Society	2005
Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism	Narrative literature review Expert opinion	Royal College of Physicians of London Society for Endocrinology	1996
Laboratory medicine practice guideline for the diagnosis and monitoring of thyroid disease testing	Narrative literature review Expert opinion	American Association of Clinical Chemists American Association of Clinical Endocrinologists American Thyroid Association Endocrine Society National Academy Clinical Biochemistry	1990, in progress
Periodic health examinations: summary of AAFP policy recommendations & age charts	Based on systematic review performed by US Preventive Services Task Force Expert opinion	American Academy of Family Physicians	1996, 2001
Screening for thyroid disease	Systematic review Meta-analysis of observational trials	American College of Physicians - American Society of Internal Medicine	1997
Screening for thyroid disease	Systematic review	US Preventive Services Task Force	1996

Screening for Thyroid Dysfunction: U.S. Preventive Services Task Force Recommendation Statement	Systematic review	US Preventive Services Task Force	2015
Clinical practice guidelines for the management of hypothyroidism	Systematic Review	Taks Force on Hypothyroidism of the Latin American Thyroid Society Study Group	2017
AACE clinical practice guidelines for the evaluation and treatment of hyperthyroidism and hypothyroidism	Narrative literature review Expert opinion	American Association of Clinical Endocrinologists American College of Endocrinology	1996
Treatment guidelines for patients with hyperthyroidism and hypothyroidism	Narrative literature review Expert opinion	American Thyroid Association	1995, 1999
Screening for thyroid disorders and thyroid cancer in asymptomatic adults	Systematic review	Canadian Task Force on Preventive Health Care	1994, 1999
Recommendation on screening adults for asymptomatic thyroid dysfunction in primary care CMAJ 2019).	Systematic review	Canadian Task Force on Preventive Health Care	2019

In 2002, a panel of invited experts representing the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society at a consensus development conference found a paucity of evidence regarding the morbidity and impact of subclinical thyroid disease, as well as the potential complications of instituting therapy. Consequently, this panel concluded that there was insufficient evidence to support routine population-based screening of asymptomatic adults. However, the panel did conclude that the weight of available evidence supported the adoption of aggressive case-finding strategies in patients at high risk for the development of hypothyroidism. Specific groups identified as being at increased risk for thyroid dysfunction include women aged 60 years and older and patients with histories of atrial fibrillation, thyroid surgery, radioactive iodine treatment, external beam radiation therapy, or family members with confirmed thyroid disease (323). Despite being independently published in 2004, the conclusions and recommendations reached by this panel were not entirely in line with the views of the overseeing bodies resulting in a joint consensus statement in 2005 from the ATA, AACE, and the Endocrine Society that favored both routine screening of the general adult population and pregnant women for subclinical thyroid dysfunction as well treatment of most patients with subclinical hypothyroidism (353).

A guideline issued by the American College of Physicians states that it is reasonable to check TSH levels in women aged 50 years and older presenting with symptoms that may be consistent with thyroid dysfunction, given the high prevalence of undiagnosed thyroid disorders among that population (358),(359),(360).

The Policy Recommendations for the Periodic Health Exam published by the American Academy of Family Physicians (AAFP) take a more neutral stance, recommending against routine screening in patients less than 60 years old without any specific provisions (361). In 2012 and 2021, the AAFP released publications reviewing hypothyroidism that introduce the concept of targeted screening for hypothyroidism in select groups at increased risk for development of this condition. The risk factors they specify that would

prompt targeted screening include a history of any of the following: Down syndrome, Turner syndrome, the presence of other autoimmune diseases especially autoimmune endocrinopathies, the presence of a goiter, a family history of thyroid disease, prior subtotal thyroidectomy and/or radioiodine treatment, prior head and neck radiation therapy, and treatment with medications that are known to affect thyroid function (362),(363). Figure 8 shows a proposed algorithm for screening for hypothyroidism in the elderly using the risk factors associated with hypothyroidism as described by the AAFP as the major determinants in deciding whether to screen.

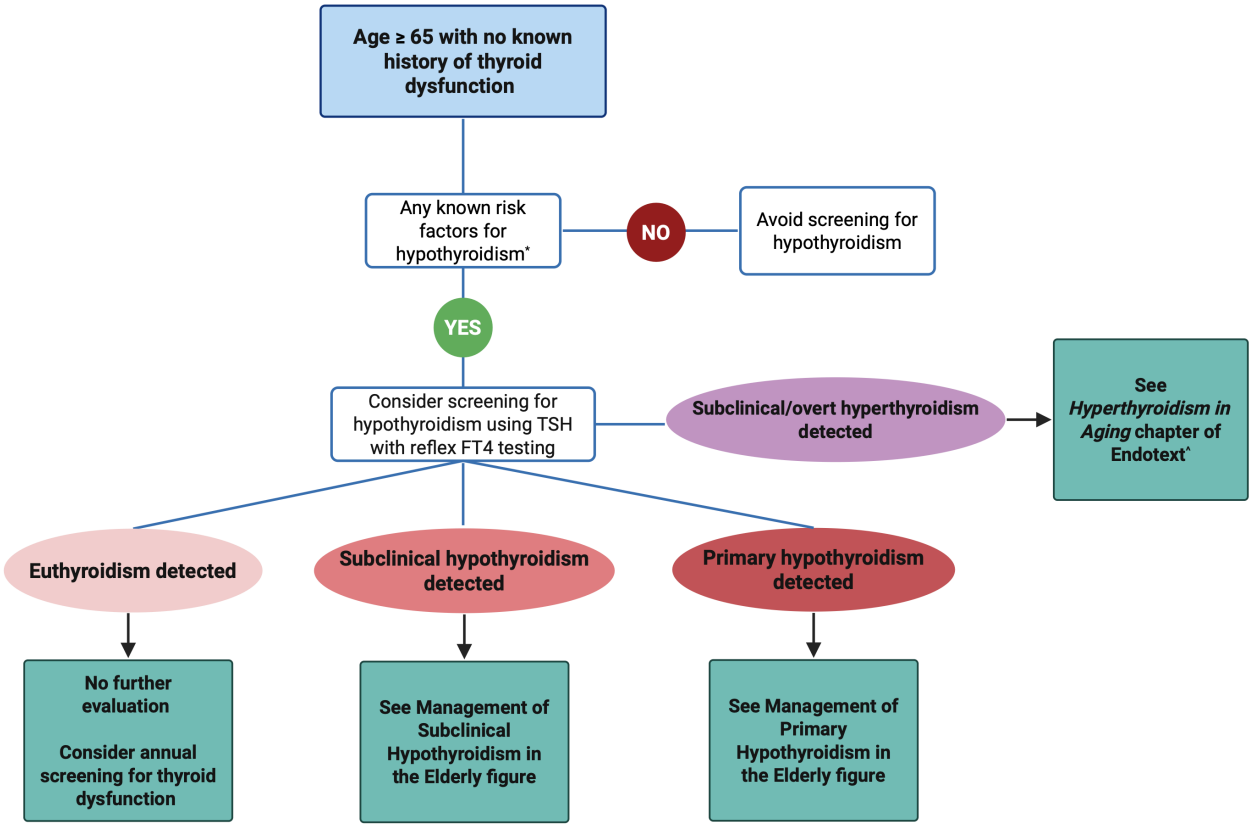

Figure 8. When to Screen for Hypothyroidism in the Elderly. * Risk factors for hypothyroidism include but are not limited to any of the following: history of Down Syndrome, Turner Syndrome, comorbid autoimmune diseases (especially autoimmune endocrinopathies), subtotal thyroidectomy, radioiodine treatment, head and neck radiation therapy, treatment with medications known to affect thyroid function (especially immunotherapy), family history of thyroid disease, and/or presence of a goiter on exam. ^ Samuels MH. Hyperthyroidism in Aging. In: Feingold KR, Ahmed SF, Anawalt B, et al, eds. *Endotext*. 2000. TSH = thyroid stimulating hormone, FT4= free T4.

The United States Preventive Services Task Force and the Canadian Task Force on the Periodic Health Examination have both concluded that there is not enough evidence regarding the impact of diagnosis and treatment of detectable thyroid disease to rule for or against routine screening of asymptomatic adults (355),(360),(364),(365). In 2019, the Canadian Task Force on Preventative Health Care issued updated recommendations about screening adults for asymptomatic thyroid dysfunction. In these guidelines they strongly recommend against screening for thyroid dysfunction in asymptomatic nonpregnant adults (357). Utility analysis based on decision modeling has demonstrated that routine periodic screening for subclinical hypothyroidism may become more cost-effective with increasing age (366).

Studies focusing on actual screening of identified populations of elderly adults have reported mixed results. One study reported that selection of candidates based on body mass index, symptoms consistent with thyroid dysfunction, or a family history of thyroid disease failed to identify the majority of elderly patients eventually confirmed to have elevated or suppressed TSH levels (367). Another study that evaluated elderly patients presenting with suspected dementia revealed that hypothyroidism was the second most common undiagnosed disorder contributing to cognitive impairment (368). A similar study reported that measurement of TSH levels identified hypothyroidism in 3.6% of elderly adults presenting for evaluation of mental status changes (369). However, a more recent study conducted in the Netherlands that screened asymptomatic outpatients who were at least 85 years old for hypothyroidism and followed these patients for three years showed that there was no association between an elevated TSH level and physical disability, depression, and cognitive impairment. Furthermore, this study found that elevated TSH amongst the participants was associated with lower mortality (260). Taken together, these studies suggest there are no specific signs or symptoms that reliably predict an underlying diagnosis of hypothyroidism in the elderly. While some may view that as a reason to empirically screen elderly patients for hypothyroidism, no society has gone as far to recommend that at this time.

Screening studies involving hospitalized patients reported that 2.3% of geriatric inpatients and 11.2% of patients admitted for elective cardiac surgery had thyroid function profiles consistent with hypothyroidism (370). These findings are not surprising considering the substantial prevalence of hypothyroidism among elderly patients in general. An analysis of profiles of TSH and thyroid hormone levels tracked in subjects enrolled in the Birmingham Elderly Thyroid Study reported high stability of euthyroid and subclinical hypothyroid indices over a 5 year interval, indicating that repeat testing may not be warranted in this population (371). Other studies focusing on the natural progression of subclinical hypothyroidism in the elderly did not find the same degree of stability in TFTs measurements in patients with subclinical hypothyroidism over time. In fact, these studies found a significant association between the ability to predict progression or reversion to overt hypothyroidism or euthyroidism, respectively using variables such as age, sex, degree of initial TSH elevation, initial free T4 level, anti-TPO antibody status, thyroid ultrasound findings, and timing of repeat thyroid axis assessment (277),(372). Given this lack of stability in TFTs overtime amongst elderly patients with subclinical hypothyroidism, some experts recommend obtaining at least three assessments of thyroid axis status, the second being at least three months after the first, and the third being at least one year after the second, to confirm a diagnosis of persistent subclinical hypothyroidism before initiating treatment (372).

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