HYPOTHYROIDISM IN OLDER ADULTS

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Update July 9, 2020

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 a number of 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, and upward shifts in 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. Mild 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 mild hypothyroidism and the potential benefits of treatment targeted to normalize thyroid hormone levels in elderly individuals with mild 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. 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. Special considerations may apply in planning treatment due to changes in the metabolic clearance of thyroid hormone, drug interactions, and potential adverse reactions.

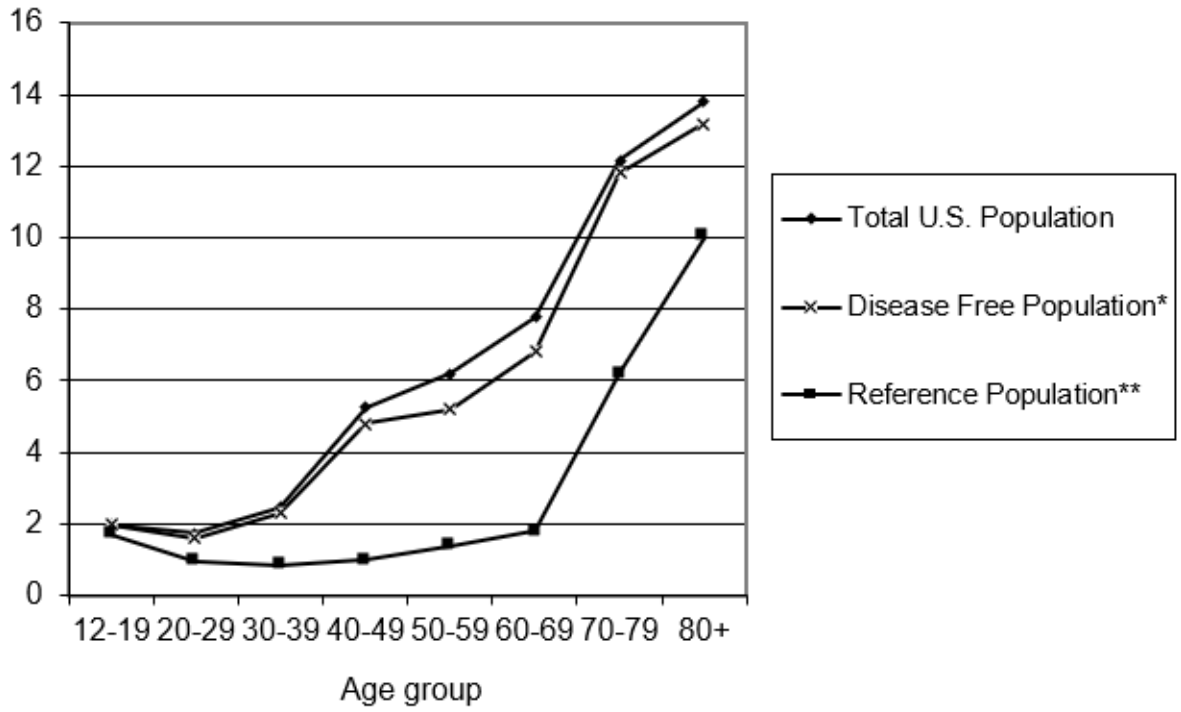

Figure 1. Percentage of Population with High Serum TSH Level (>4.5mU/L). Adapted from Hollowel et al. (1). *Excluding persons with reported histories of thyroid disease, goiter, or treatment with thyroid medications. ** Excluding persons with reported histories of thyroid disease, goiter, treatment with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

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 (2). 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 limit of reference ranges (3–7). Comparable prevalence's 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 age 65-74 had TSH levels that were increased above the upper limit of the reference range, while 16% of men and 21% of women age 75 and older had increased TSH levels (8). 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 (1). A study evaluating geriatric patients under medical care demonstrated that 15% of the women and 17% of the men had previously undiagnosed hypothyroidism (9). 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 (10,11). 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 (12). Among this population, 12% of the women and 29% of the men were reportedly taking thyroid hormone preparations for inappropriate reasons.

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. 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 (13). In this analysis, the upper 95% confidence limit for TSH in euthyroid individuals over age 80 was 7.5 mIU/L (13).

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 (14,15). These findings suggest that iodine deficiency may have a protective effect against the development of hypothyroidism in the elderly.

ETIOLOGY

Autoimmune thyroiditis is the most common cause of hypothyroidism among the elderly, as it is in younger persons (16–18). 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 (19). Only 2% of the patients in this referral population presented with documented evidence of secondary hypothyroidism. The incidence of post-ablative hypothyroidism has been noted to be higher in patients aged 55 and older (20). The annual incidence of post-ablative hypothyroidism in this population is estimated to be 8%, with 12% of patients presenting with evidence of thyroid failure in the first year after undergoing treatment with radioactive iodine (21,22). 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 (23). External beam radiation therapy 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 (24). The risk of developing thyroid failure in this setting increases with advancing age.

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 (25–27). 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 (28). 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 (29). 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 (30). Other neurological symptoms that have been reported to occur more commonly in older patients include hypogeusia and dysgeusia, impaired hearing, and ataxia.

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, and mental status changes (31). The severity of specific findings may be exacerbated by comorbid cardiovascular, neuropsychiatric, dermatologic, or rheumatologic conditions that are more common among the elderly (32). 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 (33). Elderly patients with autoimmune thyroiditis are more likely to present with the atrophic form of the disorder without goiter (34). 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 (35). Analysis of laboratory test results has demonstrated that 54% of patients diagnosed with hypothyroidism have increased serum creatinine levels that may be correlated with advancing age (36). Pericardial effusion is one of the few radiographic findings associated with hypothyroidism, but the true incidence of this complication appears to be lower than previously estimated (37).

Morbidity

Severe medical complications of hypothyroidism are more common in affected elderly persons. The majority of patients presenting with myxedema coma are elderly. 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 (38). 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 (39).

AGE-RELATED CHANGES IN THYROID FUNCTION

A number of studies have sought to determine whether biochemical diagnosis of thyroid disorders in the elderly may be confounded by age-related

changes in thyroid function (40). 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 (41). 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 (42,43). 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 the institutionalized elderly adults (44). Consequently, previously observed patterns of age-related changes may have actually reflected effects of nonthyroidal illness. 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 (45). 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 (46). These findings thus argue against the existence of a “low T3” syndrome associated with normal aging.

Studies of hypothalamic-pituitary function in the elderly have shown that blunted circadian fluctuations in TSH levels and diminished TSH responses to TRH stimulation may be detected in elderly males (47–49). The cause of this phenomenon is unclear. There are no histological or immunoreactive differences in the thyrotroph cells of elderly patients (50). 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 (51). One study showed that the decline in deiodinase activity noted with increasing age was paralleled by a decline in selenium levels. Furthermore, selenium supplementation may effectively increase selenium levels, deiodinase activity, and T3/T4 ratios in elderly patients (52).

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 or free T4 levels (53). 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 (54).

In cases of suspected secondary 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 free T4 level may serve as more reliable measure of thyroid hormone production.

The interpretation of thyroid function test profiles in hospitalized or institutionalized patients must be tempered by an understanding of how nonthyroidal illnesses may produce changes in TSH and thyroid

hormone levels (55). 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 (56). 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 (57). This change may be paralleled by a decline in T4 and T3 levels that may be particularly pronounced in elderly patients. 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 (58,59). Studies have demonstrated a correlation between declining T4 levels and increasing mortality rates in critical care patients (60). 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 (61).

Current data indicates that the normal or low TSH levels found in the presence of low T4 and T3 levels in the setting of nonthyroidal illness likely reflect the combined effects of central hypothyroidism and reduced peripheral generation of T3, effectively representing a deficiency of thyroid hormone. Whether this condition 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 (62,63).

If a patient survives to recover from nonthyroidal illness, TSH levels may transiently rise above the upper limits of reference ranges (64). 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 (65). This could lead to unnecessary treatment with thyroid hormone, which would probably be inconsequential. In cases where changes in TSH and thyroid hormone levels may be plausibly ascribed to nonthyroidal illness, the patient's thyroid function tests should be reassessed one to two weeks later to see if observed changes are resolving. 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 (66).

Measurement of anti-thyroid antibody levels may help to confirm a suspected diagnosis of autoimmune thyroiditis as the underlying cause of primary hypothyroidism. However, 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 (67). 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 (68). 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 (69). Nonetheless anti-thyroid antibody measurements in the elderly may help to predict the likelihood of progression from subclinical to overt hypothyroidism (70).

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 (71). Hyperlipidemia characterized by hypercholesterolemia is commonly evident (72). Cases of primary hypothyroidism that are severe enough to precipitate myopathy may present with increased creatine phosphokinase levels (73). A hypochromic microcytic anemia that is not associated with any detectable hemoglobinopathy or iron deficiency state may be evident in up to 15% of cases of moderate primary hypothyroidism (74). Homocysteine and lipoprotein (a) levels may be increased in patients with primary hypothyroidism, potentially contributing to an increased risk of atherosclerotic disease (75).

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 (e.g. 0.25 to 0.5 mcg/kg/day). Once cardiovascular tolerance of a starting dose has been assessed, most experts recommend gradually increasing daily doses by 12.5-25 mcg every four to six weeks until adequate replacement is confirmed by repeat TSH measurement. 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 (76). 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 (77). 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 (78–81).

Serial measurements of TSH levels four to six 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 (82). 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. Treatment with thyroxine has been shown to increase cognitive testing performance and reduce oro-cecal transit time from an average of 135 minutes in a hypothyroid state to 75-95 minutes with adequate replacement (83,84).

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 thyroxine (85,86). One study of patients with known coronary artery disease and primary hypothyroidism reported that precipitation of angina symptoms limited titration of thyroxine 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 (87).

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 (88,89). 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 (90–92). One study suggested that lean body mass may be a better predictor of daily replacement doses than age or weight alone (93). Another reported that most of the age-dependent differences in thyroxine 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 (94). A study that tracked changes in elderly patients' thyroxine 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 (95).

In situations where cognitive or functional impairment may make it difficult for patients to comply with daily administration of thyroxine, alternative dosing schedules may be considered. A study that compared daily administration of thyroxine 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 (96). Trials of regimens based on once weekly administration of cumulative daily doses of thyroxine have demonstrated similar results without any evidence of precipitation of thyrotoxicosis (97).

A number of medications used to treat other comorbid conditions in the elderly may interfere with absorption and metabolism of thyroxine (98). 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 thyroxine (99). Ferrous sulfate, sucralfate, aluminum hydroxide, cholestyramine, colestipol, and raloxifene have also been reported to impair absorption of thyroxine (100,101). In postmenopausal women with primary hypothyroidism, treatment with estrogen replacement therapy may lead to increased thyroxine dose requirements as a consequence of increased production of thyroid binding globulin (TBG) (102). Women with hormonally-responsive breast cancer who receive fluoxymesterone may require substantially lower doses of thyroxine during courses of treatment, as exposure to this androgenic steroid may decrease effective TBG production (103). 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 thyroxine required to provide optimal replacement (104–106).

Overtreatment with excessive doses of thyroxine may be associated with significant morbidity in the elderly. 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, and progressive declines in bone mineral density (107). 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 (108). 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 thyroxine documented greater mean rates of decline in the lumbar spines of those with suppressed TSH levels (109). 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 levothyroxine (110).

MILD HYPOTHYROIDISM (SUBCLINICAL HYPOTHYROIDISM)

Mild or 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 has varied from 4-15%. A study evaluating a community of healthy elderly adults in the southwest of France reported that 4.2% of subjects presenting with increased TSH levels had normal free T4 levels (111). Within this group, mild 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 mild hypothyroidism was more commonly identified in females and non-Hispanic white subjects than Hispanic subjects (112). Stratified analysis of the impact of mild 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 mild hypothyroidism, the incidence of symptoms and signs consistent with thyroid hormone deficiency detected in these subjects was similar to that reported for euthyroid subjects (113). 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 (114–120). 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 (121). 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) (122). An analysis of subgroups in this cohort study identified increased odds of prevalent metabolic syndrome among subjects with TSH levels > 10 (123). 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 (124).

Several longitudinal studies have tracked the natural history of untreated mild 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 (125). 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 (69). 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 (126). 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 (127,128). 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.

Questions have been raised about the possible association of mild hypothyroidism with an increased risk of cardiovascular disease in the elderly. One study that confirmed the presence of mild 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 (129). Even stronger associations between mild 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 (130). 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 $\geq$ 7 mIU/L was associated with an increased risk of a need for the use of ventricular assist devices, heart transplantation, and death (131).

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 (132). 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 (133). 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 $\geq$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 (134). 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 (135,136). 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 (137–139). 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 (140,141).

Consideration of treatment of mild hypothyroidism in the elderly 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 Adult with Subclinical Hypothyroidism (TRUST) trial was specifically designed to address this question (142). It randomized 737 subjects ≥ 65 years of age with persistent subclinical hypothyroidism to double-blinded placebo-controlled administration of doses of thyroxine 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 (143). The attendant risks of iatrogenic thyrotoxicosis in elderly individuals must be taken into account when weighing the potential risks and benefits of thyroid hormone replacement (144).

Partial or complete reversibility of hypercholesterolemia has been shown to accompany thyroxine treatment of mild hypothyroidism in the majority of small interventional trials addressing this issue (145). Lowering of lipoprotein (a) levels has been shown in some, but not all studies (146). Hyperhomocysteinemia in patients with mild hypothyroidism has not been shown to be reversed with thyroxine therapy. A nested trial incorporated in the TRUST trial showed that normalization of TSH levels with levothyroxine for a span of one year did not have any impact on carotid intima media thickness or carotid atherosclerosis (147).

MYXEDEMA COMA

Patients with severe hypothyroidism may present in a state of pronounced multisystem failure termed myxedema coma (148,149). 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 (150,151). 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% (152). 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 thyroxine replacement therapy (153). 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. 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 stimulatory testing can be performed.

Recommendations regarding the dose and composition of thyroid hormone preparations that should be administered to treat myxedema coma differ. Most experts concur that intravenous thyroxine should be used to circumvent impaired gastrointestinal absorption. Some have recommended initial thyroxine loading doses, while others have advocated co-administration of liothyronine (T3). Treatment of critically ill hypothyroid patients with high-dose thyroxine has been associated with a significant increase in cardiac index due to increased heart rate and stroke volume with decreased systemic vascular resistance (154). Although the onset of action of liothyronine is more rapid than thyroxine, supraphysiologic T3 levels measured after treatment have been correlated with increased mortality in older patients presenting with myxedema coma (155). A judicious approach may involve administration of a loading dose of 200-300 mcg of intravenous thyroxine followed by administration of 50 mcg daily. Depending on the estimated risk of underlying cardiovascular disease, a loading dose of 5-25 mcg of liothyronine 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.

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) (156–160).

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
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
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

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. 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 (161–163). The Policy Recommendations for the Periodic Health Exam published by the American Academy of Family Physicians take a more neutral stance, recommending against routine screening in patients less than 60 years old without any specific provisions (164). 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 (163,165). Utility analysis based on decision modeling has demonstrated that routine periodic screening for mild

hypothyroidism may become more cost-effective with increasing age (166).

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 (167). Another study that evaluated elderly patients presenting with suspected dementia revealed that hypothyroidism was the second most common undiagnosed disorder contributing to cognitive impairment (168). A similar study reported that measurement of TSH levels identified hypothyroidism in 3.6% of elderly adults presenting for evaluation of mental status changes (169). 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 (170). These findings are not surprising in light of 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 (171).

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