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REVIEW

Hypothyroidism in Adult Women: The Utility of Targeted vs Universal Thyroid Screening

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Abstract: Hypothyroidism is a common disease that is more prevalent in female populations. The purpose of this paper is to discuss the evidence, risks, and benefits of screening asymptomatic women for hypothyroidism. There is lack of evidence to support clinical management of asymptomatic individuals with an elevated TSH and normal serum thyroxine levels. Patients with subclinical hypothyroidism, especially the elderly, are at risk of overtreatment. Given these considerations, the majority of US and UK professional organizations do not support universal screening. Many do offer caveats for special groups, including pregnant people, who may need screening if there are clinical symptoms or family history of autoimmune disease. In conclusion, targeted screening may be best recommended based on risk factors, symptoms, and clinical suspicion, rather than at a universal level.

Keywords: asymptomatic, subclinical, overt, universal

Introduction

Hypothyroidism is a common, chronic disease of thyroid hormone deficiency. It is characterized by low thyroxine (T4) and triiodothyronine (T3) levels, which in primary hypothyroidism is associated with a high thyroid stimulating hormone (TSH) level due to a lack of feedback inhibition.[1] If left untreated or inadequately treated, hypothyroidism may increase the risk for coronary heart disease, hyperlipidemia, neuropsychiatric conditions, infertility, and be potentially fatal in severe cases, such as myxedema coma.[2] During pregnancy, untreated hypothyroidism can cause fetal anomalies such as cognitive and motor impairment, hearing and speech problems, and low birth weight; maternal effects including increased risk of abortion, gestational hypertension, and postpartum hemorrhage.[3–5] Common symptoms of hypothyroidism include fatigue, cold sensitivity, weight gain, constipation, and depression, but many people lack symptoms significant enough to seek medical attention.[6,7]

The purpose of screening is to detect a condition in an asymptomatic population, with the goal of reducing morbidity and mortality. As outlined by Wilson and Junger, a good screening test must be affordable and acceptable, and the condition must be prevalent and enough of a health burden in the target population to make screening worthwhile; treatment for the condition must be feasible, and intervening early in the detected condition must ultimately result in reduced morbidity and mortality.[7] Additionally, screening tests should be sensitive and specific, and the benefits of detecting and treating the condition must outweigh any risks of screening or of early detection.[8]

While the epidemiologic burden of undiagnosed hypothyroidism remains unclear, there are associations between hypothyroidism and female sex, white race, elderly populations, individuals with autoimmune conditions, and geographic regions with iodine deficiency.[1,6] Hypothyroidism is more prevalent in genetically female populations, with an increased prevalence based on age and concurrent autoimmune conditions.[9] This paper will discuss current recommendations regarding screening for thyroid disease, in light of the potential risks of untreated hypothyroidism, the potential benefits of treatment, and the potential risks of unnecessary treatment.

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Definition and Prevalence

Hypothyroidism as a condition is divided into a few clinical subsets: overt and subclinical, as well as primary and secondary hypothyroidism. Overt hypothyroidism is broadly defined biochemically as an elevation in TSH, generally greater than 4.0–4.5 mIU/L, and a low Free T4, below 0.6–0.8 ng/dL.[10–14] Lab variability and differences in guidelines by professional associations may affect cutoff values. General symptoms of overt hypothyroidism include, weight gain, cold intolerance, coarse hair, constipation, impaired memory, infertility, and muscle weakness.[2] Subclinical hypothyroidism is defined as an elevated TSH, with serum T4 within range.[15] In general, patients are asymptomatic and are only diagnosed through routine bloodwork. While subclinical hypothyroidism may be an early sign of thyroid failure and is an independent risk factor for developing hypothyroidism, current treatment guidelines indicate treating subclinical hypothyroidism only when there is presence of hypothyroid symptoms, TSH > 10.0 mIU/L, high titers of anti-thyroid peroxidase antibodies (anti-TPO), or significant cardiovascular risk.[16,17] Primary versus secondary hypothyroidism is further differentiated based on primary organ dysfunction. Primary hypothyroidism is defined as dysfunction at the thyroid level resulting in elevated TSH and low thyroid hormone, while secondary hypothyroidism is associated with hypothalamic-pituitary disorder manifesting as low thyroid hormone as a result of disproportionately low or low-to-normal TSH.[2]

The prevalence of hypothyroidism varies based on the definition and diagnostic criteria used, as well as patient demographic factors such as age, race and ethnicity, sex, geographic region, iodine exposure, among many other factors. The most cited prevalence data for the United States indicate a prevalence around 5%,[18] with ranges from 3 to 14% depending on the study analyzed.[19] Two comprehensive meta-analyses, based out of Europe, corroborated an estimated prevalence of 5% for both overt and subclinical hypothyroidism.[6,20] Variation is likely largely due to methodology variation, such as diagnostic cut-off differences; however, it is important to note that more recent trials in the US indicate a prevalence closer to 10%.[9] Epidemiologically, the prevalence of hypothyroidism is greatest among white, non-Hispanic females, older aged individuals, and those with a family history of thyroid pathology.[13,15] The reason for this may be due to increased screening in these populations.[21] Other groups of people at an increased risk for hypothyroidism include those with autoimmune conditions, like type 1 diabetes mellitus, family history of thyroid disease, history of head and neck radiation, abnormal thyroid examination, such as goiter, and psychiatric conditions. Certain medications, such as lithium, amiodarone, tyrosine kinase inhibitors, interferon alpha, interleukin-2, and immune-checkpoint inhibitors, are also well known for causing thyroid dysfunction.[19] Within these at-risk populations, clinicians may want to consider monitoring thyroid function tests, such as TSH and free T4, to identify possible thyroid pathology.[22] The current discussion is focused on screening of the asymptomatic, average-risk patient, not those with conditions or on medications associated with thyroid dysfunction.

Laboratory Tests Used to Detect Thyroid Disease

As stated above, thyroid function tests, including TSH, T4, and T3, are the hormones used in the diagnosis of hypothyroidism. Physiologically, thyrotropin-releasing hormone (TRH) is secreted from the hypothalamus to stimulate the anterior pituitary to release TSH. Subsequently, the thyroid gland responds with production of T3 and T4 which act on end organ tissues. T3 is the bioactive form of thyroid hormone and is formed from the conversion of T4 in the body's periphery. When diagnosing thyroid dysfunction, TSH is the recommended first-line test. However, in certain cases, such as subclinical thyroid dysfunction or secondary hypothyroidism, TSH may not sufficiently demonstrate the disease picture and free thyroid hormones must be tested as well. For subclinical thyroid dysfunction, a high TSH may indicate overt thyroid dysfunction, where a subsequent normal thyroid hormone is necessary to make the appropriate diagnosis. In secondary hypothyroidism, the disease pathology originates at the hypothalamus and/or pituitary gland, resulting in a low or inappropriately normal TSH. Without a concurrent low T4 level, secondary hypothyroidism may be inappropriately diagnosed as hyperthyroidism or euthyroid.[23]

Current Guidelines

Several major medical organizations in the US and in the UK have consistently recommended against universal screening for hypothyroidism in the general population. In its most recent set of guidelines in 2015, the United States Preventive Services Task Force (USPSTF) addressed nonpregnant, asymptomatic adults and concluded there was insufficient

evidence to evaluate universal screening. In the rationale for the recommendation, they cite the lack of evidence of thyroid screening in reducing morbidity or mortality due to cardiovascular disease, provide clinically meaningful improvements in blood pressure, body mass index (BMI), bone mineral density, lipid levels, or improve cognitive function. They also found inadequate evidence of harms of screening but do include risk of false positives and over-diagnoses and treatment in asymptomatic individuals.[15,24]

In 2021, the USPSTF conducted a literature review to investigate any updates in evidence. Most of the new literature focused on diagnosis and management of subclinical hypothyroidism, while none discussed the benefits and harms in patients with overt thyroid dysfunction identified on screening.[25] Additionally, a review by the Canadian Preventive Task Force structured similarly to that of the USPSTF found no new evidence on the benefits or harms of screening asymptomatic individuals between 2014 and 2018.[26]

The British Association for Clinical Biochemistry, the British Thyroid Association, and the British Thyroid Foundation support "case finding" in women with non-specific symptoms that may be indicative of an underlying thyroid disorder in the UK guidelines published in 2006.[27] They are also aligned with the USPSTF recommendation against routine, universal screening (Table 1). Previously, such unified guidelines did not exist in the UK. The diagnostic criteria for hypothyroidism vary based on recommendation with no uniform consensus on what TSH level defines thyroid pathology. Reference ranges based on NHANES III data indicate that TSH concentrations above 0.4–4.5 mIU/L with below threshold levels of free thyroxine (T4, <57.9 nmol/L) and tri-iodothyronine are most used.[24] Other organizations, such as the US Preventive Services Task Force (USPSTF), classify normal TSH ranges as 0.1–6.5 mU/L.[15]

Principles of Screening

Screening accuracy is variable depending on the level of clinical suspicion and symptomology. For clinically suspected thyroid disease, the serum TSH test has a sensitivity of 98% and a specificity of 92%.[24] When screening asymptomatic patients in a primary care setting, positive predictive value (PPV) and general accuracy of screenings are low.[15] Accuracy is difficult to quantify as external factors, such as nonthyroidal illness, patient age, and gender, may transiently affect TSH levels at the time of screening leading to possible false-positive results. Further, individuals with abnormal TSH on screening may never go on to develop clinically significant thyroid pathology and/or their TSH may revert to normal over time creating true- and false-positive differentiation difficult.[16]

Benefits of Screening

To date, no consensus has been reached on the utility of universal, TSH-based screening for asymptomatic patients to identify thyroid pathology. The goal of asymptomatic screening is to identify and provide treatment for individuals with subclinical hypothyroidism prior to developing harmful disease sequelae; however, with this goal in mind, the benefits of universal screening must outweigh the risks of allowing an undiagnosed condition to progress in an asymptomatic patient – both at an individual patient and population level.

Table 1 Guidelines for Hypothyroidism Screening by U.S. and UK Professional Organizations

Organization	Current Guidelines
USPSTF	Insufficient evidence to evaluate universal screening[24]
AAFP	Support of USPSTF guidelines[10]
ATA, AACE	Case finding in high-risk populations as well as consideration of screening in individuals greater than 60 years of age[22]
British Association for Clinical Biochemistry, the British Thyroid Association, and the British Thyroid Foundation	Do not recommend routine, universal screening; support case finding in women with non-specific symptoms that may be indicative of an underlying thyroid disorder[27]

Abbreviations: USPSTF, United States Preventive Services Task Force; AAFP, American Academy of Family Physicians; ATA, American Thyroid Association; AACE, American Association of Clinical Endocrinology.

One benefit of such proposed screening is for early detection and treatment of thyroid pathology in efforts to reduce hypothyroid-associated morbidity and mortality. Analysis of the efficacy of levothyroxine treatment for subclinical hypothyroidism has generated mixed results. A summary of eight randomized trials assessing treatment of subclinical hypothyroidism indicates that treatment led to symptom reduction among populations with either a history of Graves' disease or a serum TSH > 10mU/L. For other subgroups, evidence was inconclusive regarding whether treatment was effective at reducing symptoms or lowering LDL cholesterol, and therefore cardiac sequelae, in a clinically significant manner.[15]

Regarding the potential benefit of preventing the development of subclinical hypothyroidism to overt hypothyroidism, the Whickham study identified that of 1000 women aged 35 and over screened for thyroid pathology, subclinical hypothyroidism will be present in 80 individuals, with 43 having both a mildly elevated TSH and screen positive for antithyroid antibodies. With 5-years of levothyroxine treatment, overt hypothyroidism will be prevented in 3 out of 43 women, while the remaining 40 patients will take treatment without benefit. Treatment on a 20-year scale would prevent overt hypothyroidism in 29 out of the 43 women, with the 14 women remaining on unnecessary, longitudinal treatment.[16,28]

Drawback of Mass Screening

Increasing Incidence of Subclinical Hypothyroidism

Since hypothyroidism is diagnosed based on laboratory values, typically the TSH, a gray area exists among practitioners for when to initiate treatment. Additionally, the majority diagnosed with hypothyroidism in the US have subclinical disease. Thirty-seven percent of these individuals have been found to convert to a normal TSH, while only 2–3% develop overt hypothyroidism.[29,30] In the rationale for their most current guidelines, the USPTSF stresses that the term "overt" hypothyroidism is again a reflection of TSH level above the cut-off of normal range and is not indicative of symptomatology. If universal screening were to be implemented, it is likely that incidences of both subclinical and overt hypothyroidism would increase. As more people are diagnosed with hypothyroidism based on their TSH values, the question then becomes, what to do next? Current evidence is lacking for whether individuals in the subclinical category should be observed for a period of time and whether long-term morbidity and mortality are affected by initiating early treatment with levothyroxine. One retrospective study found an association between subclinical disease and increased incidence of ischemic heart disease.[31] However, no randomized clinical trial has been performed with treatment versus placebo for this population. In public comment to the USPSTF guidelines, providers raised ethical concerns over enrolling patients into a trial with placebo when a treatment already exists.[24]

False Positives

Associated with the increase in subclinical disease incidence is the potential for greater false-positive results with universal screening. Thyroid hormone production is influenced by medications, illness, and other hormones.[32] For example, a TSH level may be above the normal range if an individual is recovering from a recent illness but may normalize soon after. There is no current guideline for when testing should be repeated. This again brings up whether patients that fall into this possible false-positive category and are asymptomatic should be observed before repeat testing, or if no action should be taken until symptoms develop. The USPSTF has identified the potential for false positives to be a possible harm associated with screening, but evidence to support or refute this harm is lacking.[24]

Potential Overtreatment

In identifying patients with asymptomatic subclinical hypothyroidism on universal screening, the subsequent question is whether to treat them. One potential risk in doing so is inducing iatrogenic hyperthyroidism. Iatrogenic hyperthyroidism through unnecessary supplementation can increase patients' risk of arrhythmias such as atrial fibrillation and bone loss and should be avoided.[33] Excessive thyroid replacement can cause suppression of TSH and result in loss of bone.[34] Elderly patients are particularly susceptible to these harmful side effects, especially those with pre-existing cardiac conditions.[35] To avoid this in elderly patients with diagnosed hypothyroidism, treatment with levothyroxine should be titrated solely with regular monitoring of TSH.[36]

Medical Waste

One factor to consider with universal screening is its cost-effectiveness. Choosing Wisely is a campaign launched by the American Board of Internal Medicine in 2012 that discusses tests or procedures called into question for their utility by specialists in various fields. Regarding TSH screening, Choosing Wisely reports a recommendation from the American Society of Clinical Pathology to avoid testing in annual visits for asymptomatic adults, regardless of age, due to lack of evidence that it improves patient care. They go on to suggest that this testing may be appropriate in patients who are at high risk or show signs of thyroid disease, on par with clinical practice guidelines from several professional associations.[37]

While a cost-effectiveness analysis for universal TSH screening has not been performed, studies have been produced for certain populations. One study argued that screening for subclinical hypothyroidism in pregnant people is cost-effective, showing with their model that 589.3 quality-adjusted life years (QALYs) are gained for every 100,000 pregnant people screened. Greater than 500 QALYs is generally used as a measure of cost-effectiveness.[38] Another study published in 1998 based on data from the UK National Health Service reported that a favorable cost-effectiveness profile was seen in patients above 60 years if thyroid testing were implemented every three years. The authors acknowledge that this result is impacted by the variability in prevalence of thyroid disease amongst the elderly population.[39] Age-specific TSH cutoffs are typically not used for diagnosing hypothyroidism, which may lead to over-diagnosis in this population. In general, cost-effective analysis is needed for population-based TSH screening, delineated by subclinical, overt, and symptomatic hypothyroidism.

Special Groups

Pregnant People

Untreated thyroid dysfunction in pregnant people is of particular concern due to the risk of neonatal hypothyroidism or hyperthyroidism. Maternal antibodies can cross the placenta and affect the fetal thyroid gland through stimulation or inhibition. While rare, untreated maternal hypothyroidism has been shown to be associated with low birth weight and impaired cognitive development in the offspring. However, similar adverse outcomes have not been reported conclusively in untreated maternal subclinical hypothyroidism. Some papers report an association with increased incidence of gestational diabetes, hypertension, and pre-term birth, but other studies show no such association.[40–43]

In their 2002 guidelines, the American College of Obstetrics and Gynecology (ACOG) recommended the use of clinical judgement based on risks and symptoms of thyroid disease when decided whether to screen pregnant people.[44] In their most recent guidelines in 2020, ACOG is aligned with the ATE and AACE recommendations against universal screening in pregnancy and recommended testing only for pregnant individuals at risk of overt hypothyroidism (family history, type I diabetes, clinical symptoms). In recommending testing for overt disease only, they cite the 2012 CATS randomized controlled trial for screening and treatment of women with subclinical hypothyroidism during pregnancy. This study showed that cognitive function of children of women treated did not improve at 3 or 5 years.[45] They also cite a trial in 2017 which similarly treated pregnant women for subclinical hypothyroidism without evidence of improved cognition for children up to five years of age.[46] Prior to these trials, much debate existed on the impact of maternal subclinical hypothyroidism on health outcomes in their offspring.[47]

Older and Post-Menopausal Women

Although TSH cutoffs are often applied universally across age groups, this level generally increases with age. One paper showed that 14.5% of its cohort aged 80 years or older had a TSH level greater than the general upper limit of 4.5 mIU/L but did not exhibit any signs or symptoms of thyroid dysfunction.[48] Thyroid testing in older adults is commonly ordered for a work-up of fatigue or confusion. One retrospective study using claims data reported that of the 4025 adults older than 65 years who were diagnosed with hypothyroidism, 28% did not receive treatment with levothyroxine.[49] In addition to undertreatment when it was deemed medically necessary, individuals who were not treated may not have exhibited symptoms of thyroid dysfunction. This alludes to the underlying problem of diagnosis based upon lab values rather than correlation with symptomatology. The TRUST trial investigated the impact of subclinical disease on heart failure in the elderly population. Adults 65 years and older were randomized to levothyroxine or placebo with main primary outcomes

measuring systolic and diastolic function. No difference in primary outcomes was found between the treatment versus placebo groups.[50] In post-menopausal women, it can be difficult to distinguish between symptoms due to menopause versus those due to hypothyroidism. Untreated overt hypothyroidism has been associated with osteoporosis, cardiovascular disease, and memory impairment. However, studies assessing cardiac risk in this population are limited, and the extent of effects from subclinical hypothyroidism is unclear.[51] Since estrogen increases levels of thyroxine binding globulin, total T4 levels will be elevated in patients taking hormonal replacement therapy.[52] This should therefore be taken into account when treatment of hypothyroidism is being considered. Further studies using age appropriate TSH cutoff values are needed to understand both the natural history of hypothyroidism in the elderly population and possible health impacts.

Conclusion

Although thyroid screening is routinely performed in clinical practice, the limited evidence supporting this screening in assymptomatic populations calls into question its utility. While the primary goal of early screening is to detect hypothyroidism early in its disease course, connect patients to treatment, and avoid adverse physiological effects, the lack of evidence supporting treatment of subclinical hypothyroid patients, population risks of overtreatment, harms of false positives, and medical waste make it difficult to defend persistent screenings of asymptomatic, nonpregnant adults. Looking ahead, targeted screening may be best recommended based on risk factors, symptoms, and clinical suspicion, rather than at a universal level.

Abbreviations

T4, thyroxine; T3, triiodothyronine; TSH, thyroid stimulating hormone; anti-TPO, anti-thyroid peroxidase antibodies; TRH, thyroid releasing hormone; USPSTF, United States Preventive Services Task Force; AAFP, American Academy of Family Physicians; ATA, American Thyroid Association; AACE, American Association of Clinical Endocrinologists; ACOG, American College of Obstetrics and Gynecology; QALY, quality-adjusted life years; PPV, positive predictive value.

Disclosure

The authors report no conflicts of interest in this work.

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