20. Screening for Thyroid Disease

RECOMMENDATION

Routine screening for thyroid disease with thyroid function tests is not recommended for asymptomatic children or adults. There is insufficient evidence to recommend for or against screening for thyroid disease with thyroid function tests in high-risk patients, but recommendations may be made on other grounds (see ***Clinical Intervention***). Clinicians should remain alert to subtle symptoms and signs of thyroid dysfunction when examining such patients. Screening for congenital hypothyroidism is discussed in Chapter 45.

Burden of Suffering

Hyperthyroidism and hypothyroidism together account for considerable morbidity in the U.S. The total prevalence of these two disorders in adolescents and adults is estimated to be 1–4%; prevalence is higher in women and persons with Down syndrome, and increases with increasing age.[1–10] The annual incidence in adults has been estimated to be 0.05–0.1% for hyperthyroidism and 0.08–0.2% for hypothyroidism, with the higher incidences cited occurring in elderly women.[2,11] In adolescents, an incidence of 0.06%/year for these two disorders has been reported.[5] Symptoms of thyroid dysfunction, involving the nervous, cardiovascular, and gastrointestinal systems, may have an important impact on health and behavior.[12] Rarely, fatalities may occur due to thyroid storm in hyperthyroidism and myxedema coma in hypothyroidism.[13] Thyroid dysfunction during pregnancy is associated with an increased risk of adverse maternal and fetal outcomes.[14–18] Most patients with thyroid dysfunction will present with typical clinical symptoms and signs within a few months of disease onset, although overt disease may occasionally be overlooked. Studies in which asymptomatic adults of all ages were screened in the clinical setting, often using older, less sensitive tests, detected previously unsuspected thyroid disease in 0.6–0.9% of persons screened.[2,3,19,20]

The clinical diagnosis of thyroid dysfunction can be more difficult in certain high-prevalence populations, including the elderly, those with Down syndrome, and postpartum women, possibly delaying treatment and risking complications.[13] Older persons may experience apathetic hyperthyroidism, without the goiter, ophthalmopathy, and signs of sympathetic nervous system hyperactivity typically seen in younger persons.[21] Typical

symptoms and signs of hypothyroidism, like fatigue, constipation, dry skin, and poor concentration, may be confused with symptoms of aging,[22] and may also occur less frequently in elderly hypothyroid patients.[23] Screening persons 60 years or older in the clinical setting detects previously unsuspected hyperthyroidism in 0.1–0.9% and hypothyroidism in 0.7–2.1%.[2,19,24–27] The clinical diagnosis of hypothyroidism may also be overlooked in patients with Down syndrome because some symptoms and signs, such as slow speech, thick tongue, and slow mentation, are typical findings of both conditions.[6,7] Screening persons with Down syndrome has detected previously unrecognized thyroid disease, primarily hypothyroidism, in 2.9% (range 0–6.5%).[6,7,28] Screening reveals thyroid dysfunction, primarily thyroiditis, in 4–6% of postpartum women.[29–32] This dysfunction is sometimes accompanied by nonspecific symptoms, such as fatigue, palpitations, impaired concentration, or depression,[31,33,34] that may be mistakenly attributed to the postpartum condition. Women with a personal or family history of thyroid or autoimmune disease, or with thyroid antibodies, are at increased risk for postpartum thyroid dysfunction.[16,30,35–37] Postpartum thyroid dysfunction is usually transient, but it may require short-term treatment to control symptoms.

Subclinical thyroid dysfunction as typically defined in the literature is a biochemical abnormality,[38] characterized by an abnormal level of thyroid-stimulating hormone (TSH) with otherwise normal thyroid tests and no clinical symptoms. Subclinical hypothyroidism, recognized by an elevated TSH level, is seen in 6–8% of adult women and 3% of adult men.[1] As with overt disease, the prevalence is higher in the elderly and in persons with Down syndrome.[6,7,24,25,27,28,39–41] Progression to overt hypothyroidism occurred in ≤ 2% of patients who had subclinical hypothyroidism without evidence of thyroid autoimmunity or prior thyroid-related disorders and who were followed for 2–15 years; in those with thyroid antibodies, however, progression occurs in about 5–7%/year, and in as many as 20–24%/year in elderly patients with antibodies.[25,28,39,42–45] Other than the risk of developing overt hypothyroidism, the importance of subclinical hypothyroidism is unknown. Case series have suggested adverse effects of an isolated elevated TSH level on blood lipid profile, myocardial function, and neuropsychiatric function,[22,46–48] but controlled observational studies have reported conflicting evidence regarding an association between subclinical hypothyroidism and any of these adverse effects.[49–54]

Subclinical hyperthyroidism, recognized by a subnormal TSH level, is seen in 0.2–5% of the elderly population; ≤ 1%/year progress to overt disease.[11,40,55,56] Subnormal levels of TSH are often transient, returning to normal without intervention.[3,25,57] There is limited evidence of risk from subclinical hyperthyroidism except when it is due to excessive thyroxine replacement. Case series have reported subclinical hyperthyroidism in a

number of patients with atrial fibrillation.[58–61] Older controlled observational studies found no association between subclinical hyperthyroidism and atrial fibrillation,[62,63] but a significant association was reported in one carefully controlled cohort study that used a sensitive TSH assay.[57] One controlled study reported a significantly lower total cholesterol level in patients with a subnormal TSH level,[51] suggesting a possible benefit of this condition.

Accuracy of Screening Tests

Thyroid function tests to detect thyroid disease, including total thyroxine (TT_4), free thyroxine (FT_4), and TSH, are influenced by a variety of diagnostic and biologic factors that may affect their accuracy. For example, while TT_4 is usually elevated in hyperthyroidism, it misses 5% of cases that are due to triiodothyronine (T_3) toxicosis.[64] TT_4 concentration is strongly influenced by the concentrations and binding affinities of thyroxine-binding globulin and other thyroid-binding proteins.[38] Falsely abnormal TT_4 results often occur with conditions that affect these proteins, such as pregnancy, use of certain drugs, and nonthyroidal illness.[38,64] FT_4 has the advantage over TT_4 of being independent of thyroid-binding protein concentrations. Equilibrium dialysis (ED), regarded as the reference method for FT_4, is not suitable for routine screening due to its high cost.[38,65] Immunoassay or index (FTI) methods to estimate FT_4 are simpler, less expensive than ED, and have specificities of 93–99% compared to ED;[20,66–68] these methods are not always independent of thyroid-binding protein concentrations, however,[38,69] and they may show substantial interlaboratory variation.[65] TT_4 and FT_4 cannot be reliably measured in ill patients, because a substantial proportion will have abnormal thyroid function in the absence of true thyroid disease, due to "sick euthyroid syndrome."[69–71] Screening with TT_4 or FT_4 will generate many false-positive results in healthy populations.[2,19,20,71] With test specificities in the mid-90% range or lower, the low prevalence of previously unsuspected thyroid disease means that the likelihood of disease given an abnormal test will be quite low. In one study, thyroid disease requiring treatment was found in only 13% of those with abnormal FTI results.[20] Because TT_4 and FT_4 are normal by definition in subclinical thyroid dysfunction, they are not useful as screening tests for this condition.

The immunometric ("sensitive") TSH (sTSH) assays detect low as well as high serum TSH levels, and have become the standard for detecting hyperthyroidism and hypothyroidism. They therefore offer promise as first-line thyroid screening tests. In unselected populations, sTSH has a sensitivity of 89–95% and specificity of 90–96% for overt thyroid dysfunction, as compared to reference standards incorporating clinical history, ex-

amination, repeat measurement, and/or additional testing including thyrotropin-releasing hormone tests.[3,40,68] In an asymptomatic older population, the likelihood of thyroid disease given an abnormal sTSH was only 7%, however, reflecting the low prevalence of disease in healthy people.[40] Acutely ill patients, pregnant women, and persons using certain drugs such as glucocorticoids may have false-positive sTSH results,[38,72,73] although specificity is better than for TT_4 and FT_4 when the three tests have been directly compared.[38,74] Newer sTSH assays reduce but do not eliminate false-positive diagnoses in such patients.[75–77] sTSH may respond slowly to abrupt changes in thyroid function,[38] such as those that occur after treatment for hyperthyroidism, but such changes are not generally relevant to the screening of asymptomatic patients.

Effectiveness of Early Detection

Screening for occult thyroid dysfunction in adults would be valuable if there were clinical benefits of early treatment, including relief of previously unrecognized symptoms. We found no studies evaluating the treatment of hyperthyroidism detected by screening in asymptomatic persons, or of subclinical hyperthyroidism in persons with atrial fibrillation. Uncertainties about the benefits of treating hyperthyroidism detected by screening are particularly important because of the costs and potential adverse effects (e.g., agranulocytosis, induced hypothyroidism, surgical complications) of treatment with antithyroid medications, radioactive iodine ablation, or subtotal thyroidectomy.[78,79]

Several studies have evaluated the effectiveness of treating patients with subclinical hypothyroidism. Most of the subjects had previously identified thyroid disease, however, and the results may not apply to asymptomatic patients identified only by screening. In a randomized placebo-controlled trial of 33 women with subclinical hypothyroidism, all with a past history of treated hyperthyroidism, there were significant improvements in myocardial contractility and in previously unrecognized symptoms, but no significant changes in basal metabolic rate, pulse, body weight, skin texture, or serum lipid levels.[80] The long-term clinical importance of subtle changes in myocardial contractility is unknown. An uncontrolled experiment in 17 women identified by screening found a significantly improved mean clinical symptom score after treatment, mixed effects on myocardial function, and no effect on cholesterol, resting heart rate, body mass, or blood pressure.[81] Methodologic flaws make it difficult to interpret the results of this study. Uncontrolled experiments in adult patients, mostly women, with subclinical hypothyroidism due to previously identified thyroid disease have reported variable improvement in myocardial function but little effect on lipoproteins with thyroxine treatment.[82–89] A randomized con-

trolled trial measuring the effects of thyroid replacement on quality of life, lipids, neuropsychological function, bone mineral density, and myocardial function in elderly patients with subclinical hypothyroidism is ongoing (personal communication, Dr. R. Jaeshke, St. Joseph's Hospital, Hamilton, Ontario, August 4, 1995).

In children and adults with Down syndrome and subclinical hypothyroidism, a double-blind crossover placebo-controlled trial failed to document any cognitive, social, or physical changes attributable to 8–14 weeks of thyroxine treatment,[41] although treatment duration may have been inadequate to effect change. There is otherwise little evidence regarding the benefits of early intervention in these individuals.

Thyroxine replacement therapy can have adverse effects with even moderate degrees of overtreatment (as detected by low TSH or high TT_4 levels), including decreased bone density compared to matched controls.[90–93] Reduced bone density could increase the risk of fractures in the elderly, but one large series found no significant difference in risk for fractures (or for ischemic heart disease) in treated patients with normal TSH levels compared to those with suppressed TSH due to overtreatment.[94] The fracture rate in the two groups was the same as in the general population, while the risk of ischemic heart disease was higher in treated patients irrespective of TSH levels. The study was not designed to determine whether the latter finding was due to treatment or to the underlying disease, however. A small randomized controlled trial in postmenopausal women with subclinical hypothyroidism found no bone density reduction after 14 months of appropriate thyroxine treatment.[95] Evidence therefore suggests against an adverse impact of appropriate thyroxine treatment.

Recommendations of Other Groups

No organizations recommend routine screening for thyroid disease in the general population, except screening newborns for congenital hypothyroidism (see Chapter 45). The American Academy of Family Physicians (AAFP)[96] and the American Association of Clinical Endocrinologists[97] recommend measuring thyroid function periodically in all older women. The policy of the AAFP is currently under review. The Canadian Task Force on the Periodic Health Examination recommends maintaining a high index of clinical suspicion for nonspecific symptoms consistent with hypothyroidism when examining perimenopausal and postmenopausal women.[98] The American College of Physicians recommends screening women over age 50 with one or more general symptoms that could be caused by thyroid disease.[99] The American College of Obstetricians and Gynecologists recommends that physicians and patients be aware of the symptoms and risk factors for postpartum thyroid dysfunction, and evaluate patients when in-

dicated.[100] The American Academy of Pediatrics recommends that children with Down syndrome have thyroid screening tests at 4–6 and 12 months of age, and annually thereafter.[101] The American Thyroid Association recommends screening thyroid function in elderly patients, postpartum women, and all patients with autoimmune disease or with a strong family history of thyroid disease, using serum TSH measurement.[64,102]

Discussion

The prevalence of unsuspected thyroid disease in healthy people in the general population is very low. Despite the high specificity of thyroid function tests such as the newer TSH assays, their routine use in the asymptomatic general population results in many false-positive results. Because of the low prevalence of unsuspected disease, only 1 in 5–10 persons with abnormal screening tests will prove to have thyroid disease. Given the low risk, the lack of evidence that treatment of subclinical thyroid disease identified by screening results in important health benefits, and the potential adverse effects of treatment, screening the asymptomatic general population is not recommended.

The prevalence of thyroid disease is higher in certain populations, including elderly persons (particularly women), persons with Down syndrome, and postpartum women, and these patients might be candidates for thyroid function testing if the results could provide an explanation for nonspecific and insidious symptoms, such as fatigue, memory impairment, or depression, that might be attributed mistakenly to other medical or psychiatric causes. Clinicians should therefore maintain a high index of suspicion for such nonspecific symptoms, and for thyroid disease when these types of symptoms are found, when examining high-risk patients. There is, however, little evidence that routinely screening high-risk patients results in important clinical benefits.

CLINICAL INTERVENTION

Routine screening for thyroid disease with thyroid function tests is not recommended for asymptomatic children or adults (“D” recommendation). This recommendation does not mean that clinicians should not monitor thyroid function in patients with a previous history of thyroid disease. There is insufficient evidence to recommend for or against screening for thyroid disease with thyroid function tests in high-risk patients, including elderly persons, postpartum women, and persons with Down syndrome, but recommendations may be made on other grounds, such as the higher prevalence of disease and the increased likelihood that symptoms of thyroid disease will be overlooked in these patients (“C” recommendation).

Clinicians should remain alert for subtle or nonspecific symptoms of thyroid dysfunction when examining such patients, and maintain a low threshold for diagnostic evaluation of thyroid function. Examples of such symptoms include easy fatiguability, weight gain, dry skin or hair, cold intolerance, difficulty concentrating, depression, nervousness, and palpitations. If screening is performed, the preferred test is measurement of thyroid-stimulating hormone (TSH) using a sensitive immunometric or similar assay, because of its superior sensitivity and specificity. Screening for congenital hypothyroidism is discussed in Chapter 45.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Carolyn DiGuiseppi, MD, MPH.

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