COLLEGE of AMERICAN PATHOLOGISTS

Evaluating Thyroid Disorders For Clinicians

SYNOPSIS AND RELEVANCE

Thyroid stimulating hormone (TSH) forms the mainstay for assessing thyroid function in most patients. The judicious use of TSH combined with free thyroxine (FT4) levels can help patients by:

1. Accurately classifying thyroid disorders in patients with an intact hypothalamic-pituitary axis.
2. Avoiding over-diagnosis of older patients with mild increases in TSH as hypothyroid.
3. Improving detection of maternal hypothyroidism.
4. Avoiding over-diagnosis of thyroid disease in inpatients who may have been physiologically suppressed TSH.
5. Stratifying the risk of progression from subclinical hypothyroidism to hypothyroidism.

INSIGHTS

1. The initial assessment of thyroid function in most patients should be performed using an algorithm for reflexive testing based on sensitive (sTSH), or third generation, TSH levels (see **Appendix A**):
    - If the TSH is < 0.10mIU/L, suspect hyperthyroidism.
    - If the TSH is borderline low (0.10 - 0.20 mIU/L), measure FT4.
    - If the TSH is > 10 mIU/L, the presumptive diagnosis is hypothyroidism.
    - If the TSH is inconclusive, with mildly elevated TSH levels (4.2 - 10 mIU/L), measure FT4.
        - If the FT4 level is decreased, suspect hypothyroidism.
        - If FT4 level is normal, consider subclinical hypothyroidism (SCH).
2. T3 has no role in the evaluation of hypothyroidism.
3. Routine testing for hypothyroidism in hospitalized patients has low utility unless there is a high index of suspicion.
4. Use trimester-specific reference ranges for TSH in pregnancy. Choose a secondary target (free T4 vs. total T4) to test in pregnancy based on the availability of trimester-specific reference ranges.
5. Simultaneous ordering of free and total T4 and free and total T3 has no utility.
6. In order to stratify risk of progression from SCH to overt hypothyroidism, a one-time measurement of anti-TPO is preferred rather than anti-TG.

BACKGROUND

Thyroid function is controlled by a classical negative endocrine feedback loop of the hypothalamic-pituitary-thyroid axis. Thyrotropin releasing hormone (TRH) is released by the hypothalamus and stimulates the pituitary gland to secrete thyroid stimulating hormone (TSH), which in turn acts on the thyroid gland to secrete thyroxine (T4) and, to a lesser extent, triiodothyronine (T3). Most T3 is produced peripherally by conversion of T4 to T3. TSH, T4 and T3 levels form the mainstay of modern laboratory testing for thyroid disease.

Hypothyroidism, insufficient production of thyroid hormone by the thyroid gland, is most commonly caused worldwide by a lack of dietary iodine and in the United States by autoimmune thyroiditis (Hashimoto thyroiditis). Other causes of primary hypothyroidism include previous thyroidectomy, radioiodine treatment for thyroid tumors, radiation damage from treatment of head and neck cancers, and rarely, medications such as tyrosine kinase inhibitors and checkpoint inhibitors, including programed cell death 1 and anti-cytotoxic T-lymphocyte associated antigen immunotherapy. All of these etiologies lead to decreased levels of T4 and consequent increases in TSH.

Central hypothyroidism occurs when there is insufficient production of TSH, usually as a result of injury to the pituitary-hypothalamic axis from, for example, pituitary or hypothalamic tumors, previous surgery or radiation for pituitary or hypothalamic disease, and lymphocytic or granulomatous hypophysitis. In central hypothyroidism, serum FT4 levels are low, but TSH levels can vary. When TSH and FT4 levels are low, the diagnosis of central hypothyroidism is straightforward.

Symptoms of hypothyroidism include cold intolerance, fatigue, depression, and weight gain. Hypothyroidism increases serum LDL levels and increases the risk of coronary artery disease. If untreated in pregnancy, it can lead to growth delays and intellectual impairment in infants.

Subclinical hypothyroidism (SCH) is defined as a mildly elevated TSH level with a normal value of FT4, and is usually asymptomatic. Its prevalence is between 3% to 8% in the general population without known thyroid disease, and increases with age. Patients with SCH are at risk for overt hypothyroidism. In one study, the rate of progression to hypothyroidism was 2.6% annually if anti-thyroid peroxidase antibodies (anti-TPO) are absent and 4.3% annually if anti-TPO are present. SCH is more common in women, but by the 6th decade, the prevalence is equal in men and women. SCH is associated with anti-thyroid antibodies in up to 80% of cases. Other than in pregnancy, there is no consensus whether SCH requires treatment with levothyroxine, especially when TSH levels are less than 10 mIU/L. Children of women with SCH during pregnancy have been found to more frequently have a reduced intelligence quotient, and these women more frequently have adverse outcomes during pregnancy. There is no conclusive evidence that treatment of SCH with TSH levels between 5.1 and 10 mIU/L leads to reductions in lipid and cholesterol levels or decreases the risk for coronary artery disease.

Hyperthyroidism is due to the inappropriately high synthesis and secretion of thyroid hormones by the thyroid gland. Graves disease is an autoimmune disorder, and is the most common cause of hyperthyroidism. It can lead to enlargement of the thyroid gland and produce symptoms of irritability, heat intolerance, rapid heart rate, diarrhea, weight loss, thickening of the skin over the pretibial area, and Graves ophthalmopathy. Graves disease and all other variants of autoimmune related hyperthyroidism are the result of thyroid stimulating hormone receptor (TSHR) autoantibodies that bind and transactivate the TSH receptor on thyroid cells resulting in uncontrolled production of thyroid hormones without the normal feedback inhibition. These antibodies are known as long-acting-thyroid-stimulating hormone or thyroid-stimulating immunoglobulins (TSI). Some patients with Graves disease have TSHR-blocking antibodies, which do not transactivate the TSH receptor. The severity of Graves disease is determined by the balance between titers of TSI and TSHR-blocking antibodies. TSHR-blocking antibodies, and to lesser extent TSI, can also found in hypothyroidism.

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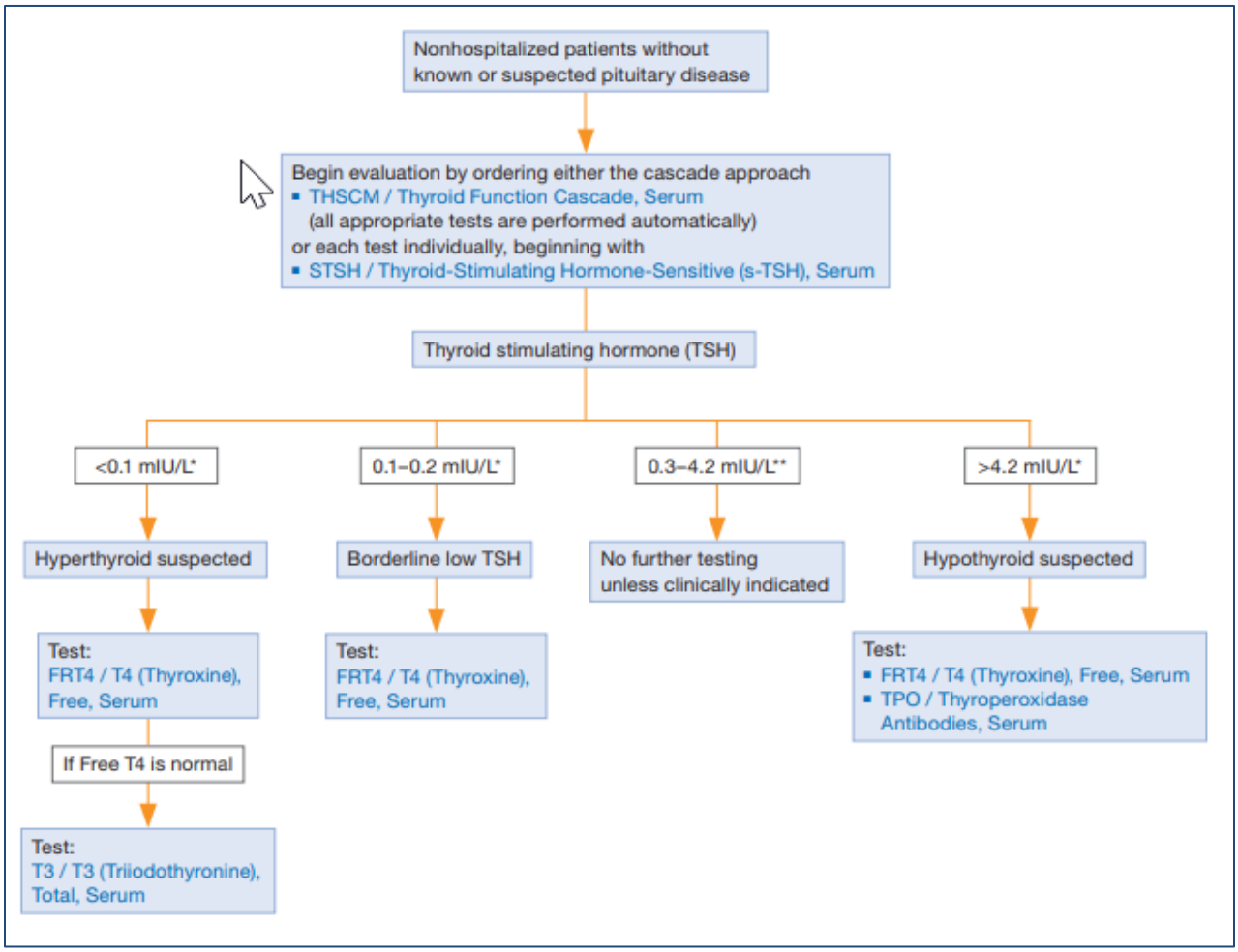
APPENDIX A: THYROID SCREENING ALGORITHM



* For 12 hours before specimen collection for any thyroid test listed in this algorithm, the patient should not take multivitamins or dietary supplements containing biotin (vitamin B7), which is commonly found in hair, skin, and nail supplements and multivitamins.
** Adult s-TSH reference ranges.

Reference: Mayo Foundation for Medical Education and Research. Thyroid function ordering algorithm. Published October 2017 Reviewed 11/2023. Accessed September 5, 2025. https://www.mayocliniclabs.com/it-mmfiles/Thyroid_Function_Ordering_Algorithm.pdf.