MAYO CLINIC

COMMENTARY

Hypothyroidism in Clinical Practice

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Despite weighing just 10 to 20 g in the average adult (or approximately 1-2/10,000th of an average human), the thyroid gland exerts an outsized influence over a broad array of normal physiologic functions, which greatly belies its petite size; this effect reflects the widespread expression of thyroid hormone receptors throughout the human body.[1] When thyroid dysfunction (either hypothyroidism or hyperthyroidism) occurs, significant alterations in normal physiology can result, with the degree of pathology generally related to the degree of dysfunction and the rate at which the dysfunction develops, with more rapid onset associated with greater physiologic perturbation.

Hypothyroidism reflects decreased thyroid function and is one of the most common conditions seen in clinical practice. Hypothyroidism most often results from dysfunction of the thyroid itself (primary hypothyroidism) but can also occur as a result of defects along the hypothalamic/pituitary axis (less common) or from intake of lower-than-required doses of exogenous thyroid hormone in patients with primary hypothyroidism (more common). Overt hypothyroidism, defined as a serum thyrotropin level greater than the upper normal limit with a concomitant serum free thyroxine (T4) value less than the lower normal limit is less common than subclinical hypothyroidism, defined as a thyrotropin value greater than the upper normal limit in association with a serum free T4 value within the reference range. Overall, the presence of overt hypothyroidism and subclinical hypothyroidism increases with age, with both entities more common in women than in men.[2] Estimates of the true prevalence of both overt hypothyroidism and subclinical hypothyroidism in the adult population vary by geographic location but in general range from approximately 0.2% to 1.0% for overt hypothyroidism to as high as approximately 10% for subclinical hypothyroidism, with the prevalence of subclinical hypothyroidism increasing with age, as is discussed later herein.[3]

Because thyroid hormone plays a fundamental role in the regulation of normal metabolism, reduced thyroid hormone levels as occur in hypothyroidism are associated with metabolic slowing and may lead to an array of signs and symptoms, including fatigue, reduced exercise capacity, muscle weakness, weight gain, bradycardia, cold intolerance, slowing of the normal reflex relaxation phase, constipation, depression, and menstrual irregularities (Table). In more severe cases, hypothyroidism can result in pleural or pericardial effusions, or even rhabdomyolysis.

Due to the progressive accumulation of glycosaminoglycans particularly in soft tissues, and as highlighted in the accompanying Letter to the Editor about the Mona Lisa in this issue of *Mayo Clinic Proceedings*, hypothyroidism can also be associated with a panoply of physical traits.[4] These traits include, but are not limited to, edema (particularly of the face), thinning and coarsening of the hair, macroglossia, and the development of carpal tunnel syndrome. In addition to alterations in thyroid indices, abnormalities in other laboratory findings are common in hypothyroidism and can include a decline in renal function, hyperlipidemia, hyponatremia, and a normochromic/normocytic anemia. Although rare, myxedema coma represents the extreme end of the hypothyroidism spectrum and is a life-threatening emergency, the latter resulting from the confluence of severe hypothyroidism with another insult, such as cardiovascular compromise, trauma, or infection, ultimately leading to multiorgan dysfunction.

Abnormal thyroid gland growth is referred to as a goiter. Goiters can occur in individuals who are hypothyroid, hyperthyroid, or euthyroid, although most people with a goiter are euthyroid. When enlargement occurs with displacement of soft tissue structures in the anterior neck, the goiter may be palpable or visible on examination. However, thyroid

TABLE. Signs and Symptoms of Hypothyroidism

Signs	Symptoms
Eyebrow and hair thinning (C)	Fatigue
Skin coarsening (C)	Weight gain
Tendon relaxation phase slowing (C)	Cold intolerance
Facial/periorbital edema (O)	Mental slowing
Macroglossia (O)	Muscle weakness
Bradycardia (O)	Reduced exercise capacity
Pericardial effusion (R)	Constipation
Pleural effusion (R)	Xeroderma
Rhabdomyolysis (R)	Depression
	Menstrual irregularities

C = common; O = occasional; R = rare.

enlargement can also extend inferiorly or posteriorly, in which case the goiter may result in compression or displacement of the trachea, esophagus, or nearby carotid vessels. Globally, iodine deficiency is the most common cause of goiter and is the etiology postulated by the authors of the accompanying Letter to the Editor for the apparent goiter in the Mona Lisa portrait. In contrast, given that iodine sufficiency is generally achieved in the United States due to widespread supplementation of food products, most goiters in the United States are due to autoimmune conditions causing either hypothyroidism (chronic lymphocytic infiltrative thyroiditis, also commonly referred to as Hashimoto's thyroiditis) or hyperthyroidism (Graves disease), or reflect a multinodular goiter.[5] Because most goiters grow slowly, most affected individuals are asymptomatic unless the goiter is sufficiently large to disrupt normal structures in the neck. Care decisions in patients with a goiter are based on biochemical thyroid indices, goiter size, and the presence or absence of nodularity or symptomatic compression of nearby structures. In general, the use of iodinated contrast should be avoided in patients with known goiters to limit the risk of hyperthyroidism development (Jod-Basedow phenomenon).

Given that most clinical manifestations and laboratory abnormalities seen in patients with hypothyroidism are not specific to hypothyroidism per se, formal diagnosis requires serum laboratory assessment. Thyrotropin levels serve as the most sensitive barometer of endogenous thyroid function and are the most useful measure of thyroid status in all persons except rare patients with hypothalamic or pituitary dysfunction as the basis for their hypothyroidism. Importantly, there is general consensus that in many persons, thyrotropin levels rise with progressive age such that some have suggested the use of age-specific values for the thyrotropin upper normal limit, particularly in those older than 70 years.[6] In all patients, the initial finding of an elevated serum thyrotropin level should prompt a repeated thyrotropin assessment in conjunction with concomitant free T4 measurement, with the results determining whether thyroid hormone replacement is warranted. In patients with clinical symptoms consistent with hypothyroidism and in whom a central (hypothalamic or pituitary) etiology is suspected due the presence of a low serum free T4 level in association with an inappropriately low-normal or low serum thyrotropin level, endocrinology referral for further evaluation is warranted.

As noted, subclinical hypothyroidism is defined as a serum thyrotropin value greater than the upper normal limit with a simultaneous free T4 level within the reference range. The risk of subclinical hypothyroidism increases with age in both sexes, with an overall prevalence that is more common in women than in men.[7] Furthermore, a significant percentage of patients with subclinical hypothyroidism will eventually progress to overt hypothyroidism.[8] Most patients with subclinical hypothyroidism have a serum thyrotropin level of less than 10 mIU/L, with most elderly patients having no clinical symptoms of hypothyroidism. Although current recommendations for initiation of thyroid hormone replacement in patients with subclinical hypothyroidism differ geographically and across professional medical societies, most suggest that thyroid hormone replacement should commence when thyrotropin values are greater than 10 mIU/L, with a goal of preventing the development of overt hypothyroidism as well as recognition of the relationship between overt hypothyroidism and cardiovascular disease. Current randomized clinical trial data on the role of thyroid hormone replacement in patients with subclinical hypothyroidism and thyrotropin values between the upper

Mayo Clin Proc. ■ September 2018;93(9):1169-1172 ■ https://doi.org/10.1016/j.mayocp.2018.07.015
www.mayoclinicproceedings.org

normal limit and 10 mIU/L remains conflicting, with some studies, but not others, showing clinical or symptomatic benefit.[9]

In most patients with hypothyroidism, the condition is permanent and necessitates thyroid hormone replacement therapy for life, with a goal of maintaining euthyroidism. Treatment of hypothyroidism is straightforward and can be best accomplished with the synthetic prohormone levothyroxine, also referred to as T4. Thyroxine undergoes natural deiodination in the peripheral tissues to the active form of thyroid hormone, T3, with circulating concentrations of free T3 approximately 1000-fold lower than those of circulating free T4 levels. For nearly all patients, treatment with T4, rather than efforts to provide combination therapy using T4 and T3, is successful as a thyroid hormone replacement method.[10]

Because levothyroxine has a biological half-life of approximately 1 week, once-daily dosing gives near steady-state concentrations of T4 and T3. Full thyroid hormone replacement with levothyroxine is typically approximately 1.6 μg/kg of total body weight provided daily, although in patients with significant obesity, lean body mass may need to be considered for initial calculations to avoid overtreatment. Accordingly, weight gain or loss may necessitate dose adjustment. In most patients, initiation of full thyroid hormone replacement dosing is not necessary; instead, use of a stepwise approach with increasing dosing is advisable. This graduated approach to thyroid hormone replacement is of particular importance in elderly patients, in whom slow upward titration is generally recommended to limit the risks of cardiac ischemia or arrhythmia development. Exceptions to a stepwise approach to thyroid hormone replacement dosing would include, for example, patients with complete thyroidal absence, such as after total thyroidectomy or radioactive iodine thyroid ablation for Graves disease.

Due to the presumptive formation of insoluble and, thus, nonabsorbable complexes that occurs when levothyroxine is bound by a variety of substances, levothyroxine must be ingested in the correct manner to achieve anticipated serum concentrations. Thus, thyroid hormone replacement must occur on an empty stomach, with no other medications or foods beyond water ideally consumed for at least 1 hour after ingestion. Once levothyroxine therapy is initiated or the treatment dose is altered, a repeated thyrotropin measurement should be performed in approximately 6 weeks because this is a sufficient length of time to allow for establishment of a new equilibrium steady state based on the biological half-life of T4 as noted previously herein. On initiation of therapy, most patients with symptomatic hypothyroidism will begin to note improvement within several weeks, although resolution of symptoms even once maintained on a stable dose may not occur for several months. For some patients, symptoms attributed to hypothyroidism may not resolve despite normalization of thyroid indices. In such patients, consideration of a separate etiology may be warranted given that symptoms of hypothyroidism are rather nonspecific.

Finally, special patient populations, including women planning pregnancy, currently pregnant, or immediately postpartum, as well as newborns, exist in which assessment for hypothyroidism is clinically indicated but whose optimized care extends beyond the brief description of issues associated with hypothyroidism as described herein. For these indications, recent guidelines may be consulted.[11,12]

Collectively, hypothyroidism requires recognition as a common clinical issue that can affect virtually all organ systems and should always be considered in the differential diagnosis, especially when caring for older patients. Whether hypothyroidism is sufficient to account for the physical findings noted in the accompanying Letter to the Editor about the Mona Lisa is clearly a fascinating and novel thesis and one that will add to the mystique of this celebrated painting by a genius well-known for leaving recondite clues in his work.

Potential Competing Interests: The author reports no competing interests.

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