The Clinical Consequences and Diagnosis of Hypothyroidism

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ABBREVIATIONS: CVD = coronary vascular disease; FT_3 = free T_3; FT_4 = free T_4; T_3 = triiodothyronine; T_4 = thyroxine; TPO = thyroid peroxidase; TPOAb = thyroid peroxidase antibody; TSH = thyroid stimulating hormone.

INDEX TERMS: coronary vascular disease; hypothyroidism.

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Thyroid dysfunction is the most prevalent endocrine disorder, affecting more than 21 million Americans. The annual healthcare costs known to be associated with thyroid dysfunction exceed 10 billion dollars annually.[1] Manifestations of untreated thyroid dysfunction include coronary heart disease, osteoporosis, atrial fibrillation, cognitive impairment, and depression. These sequelae of undiagnosed thyroid dysfunction are among the major causes of mortality, morbidity, and diminished quality of life among older adults. In addition to the individual costs of such morbidity, including functional limitations and disruption of caring giving responsibilities, the healthcare costs associated with caring for individuals with heart disease, stroke, and hip fracture attributed to uncontrolled thyroid dysfunction are substantial. For example, coronary vascular disease (CVD) is the leading cause of mortality in developed countries, with more than 697,000 deaths in 1999 in the United States. In addition, CVD is a leading cause of morbidity, functional limitations, and reduced quality of life among affected individuals.[2]

Thyroid dysfunction can be divided into two general categories: 1) hyperthyroidism, characterized by increased thyroid hormones with decreased thyroid stimulating hormone (TSH) and 2) hypothyroidism, characterized by decreased thyroid hormones with increased TSH. Hypothyroidism is more common; between 10% to 20% of postmenopausal women have evidence of hypothyroidism which can have significant clinical consequences.[3-7] Hypothyroidism can be further subdivided into overt and subclinical (mild) disorders. Because the signs and symptoms of hypothyroidism are vague and nonspecific, many cases are not identified and go undiagnosed, prompting interest in routine screening for thyroid dysfunction. This article will review thyroid gland physiology, pathophysiology, clinical features, prevalence, clinical implications, laboratory diagnosis, treatment, and screening for hypothyroidism, with particular emphasis on subclinical dysfunction.

THYROID GLAND PHYSIOLOGY

The thyroid gland provides the primary control of basal metabolism throughout the body, producing thyroxine (T_4), and the more active triiodothyronine (T_3). Thyroid hormones circulate in the serum reversibly bound to proteins such as thyroid hormone binding globulin and albumin. Both free T_4 (FT_4) and free T_3 (FT_3) enter across the cell membrane, bind to nuclear receptors, and influence gene expression. At the cellular level, thyroid hormone increases carbohydrate and lipid catabolism and stimulates protein synthesis. Among the aspects of homeostasis influenced by thyroid hormone are thermogenesis, glycogen and fat storage, bone resorption and remodeling, bowel motility, blood volume, systemic vascular resistance, cardiac contractility, and heart rate.

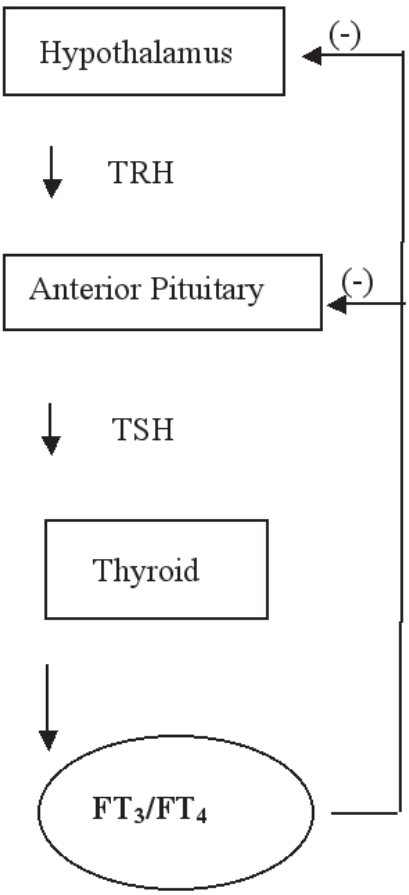
Every person has his or her own specific, genetically predetermined FT_4/FT_3 set-point that is regulated by the hypothalamus and the anterior pituitary via negative feedback (Figure 1).[8] Decreasing levels of FT_4/FT_3 in the circulation, seen in hypothyroidism, results in increased production of TSH by the anterior pituitary. TSH acts on the epithelium of thyroid gland follicles and increases iodine uptake and thyroxine synthesis. Rising FT_4/FT_3 suppresses thyrotropin releasing hor-

mone and TSH. Small changes in the individual's FT_4/FT_3 set-point, while well within the normal range, can trigger an inversely amplified log/linear response in the secretion of TSH from the pituitary gland. Often TSH will be abnormal well before any significant changes in thyroid function are observed.

PATHOPHYSIOLOGY

Primary hypothyroidism can be biochemically categorized as overt or subclinical depending on the serum concentrations of FT_4/FT_3. Overt hypothyroidism is characterized by elevated TSH and decreased FT_4/FT_3 concentrations. Subclinical hypothyroidism, in which TSH is also elevated but FT_4/FT_3 are normal, is believed to be a subtle and early indicator of thyroid dysfunction.[9] In fact, subclinical hypothyroidism is a strong predictor of future overt hypothyroidism, suggesting that for some individuals, subclinical hypothyroidism lies along a continuum of thyroid dysfunction. While individuals with subclinical hypothyroidism have FT_4 concentrations within the population reference range, the presence of an abnormal TSH suggests that their FT_4 is not 'normal' for them.[8] Based on laboratory testing, subclinical hypothyroidism can be subcategorized by TSH concentration and by the presence of thyroid peroxidase antibodies called TPOAb. The majority of individuals (55% to 85%) have mild elevations of TSH, between 5 mU/L to 10 mU/L.[10] Most people (50% to 83%) in this group do not have significant levels of TPOAb.[10] However, when TSH is greater than 10 mU/L, most individuals (80%) have detectable TPOAb. The presence of high levels of TPOAb (>20 IU/mL) is so strongly predictive of overt disease that it has been proposed that individuals with subclinical hypothyroidism and high TPOAb levels be classified as having 'impending' overt disease.[10] The rate of progression from subclinical hypothyroidism to overt disease varies from 3% to 20% per year.[11] Approximately 5.5% of individuals with subclinical hypothyroidism spontaneously regress to having a TSH in the normal range after a year of observation.[6]

Figure 1. Regulation of thyroid hormones by feedback inhibition to the hypothalamus



The most common cause of primary hypothyroidism in developed countries is autoimmune thyroiditis, also referred to as Hashimoto's disease.[12,13] The next most common cause of hypothyroidism is over-treatment of hyperthyroidism with radiation and surgery. Autoimmune thyroiditis involves the gradual destruction of the thyroid gland via abnormal T-cell function.[12] Defective T-cells recognize thyroid antigen in combination with specific major histocompatibility complex antigens. Thyroid targeted T-helper cells present these antigens to B-cells resulting in production of a range of antithyroid antibodies. These antibodies are often directed against both thyroglobulin, the precursor of thyroid hormones stored in the lumen of thyroid follicles, and thyroid peroxidase (TPO), located on the microvilli of the epithelial cells that line the follicle. TPO is required for iodination of the tyrosine residue in thyroglobulin that forms T_3 and T_4, and TPOAb is the most commonly identified antithyroid antibody.[4] The presence of TPOAb is a risk factor for overt disease and TPOAb and TSH levels parallel one another with higher TSH concentrations correlating with higher TPOAb titer and vice versa.[14-16]

CASE STUDY

The following case study illustrates a typical presentation and diagnosis of subclinical hypothyroidism. A 63-year-old Caucasian woman presents to her family medicine physician complaining of fatigue over the last three to five years. She reports that she is so tired after work that she does not have the energy to fix dinner and usually goes bed early without eating. Despite eating less, she has gained 43 pounds

over the last three years. The physical examination is normal. Her physician tells her that there is nothing to worry about and that her fatigue and weight gain are normal changes for a woman her age. She is advised to exercise more and eat less bread and pasta. Later that month, she attends a health fair at the county health department where she is screened for breast, cervical, and colon cancer, diabetes, hypertension, hyperlipidemia, and thyroid disease. The laboratory results on a fasting sample reveal the following results (Table 1).

She is referred to her local physician for follow up and further blood tests reveal a FT_4 of 1.7 ng/dL (reference interval 0.8-2.3 ng/dL). She is placed on 0.05 mg levothyroxine daily. Four months later she returns to the physician, having lost ten pounds and reports that she is has regained her energy and "feels 100% better". The thyroid function and lipid tests are repeated at that time (Table 2).

The woman will continue to receive daily levothyroxine and return to her physician on a yearly basis.

CLINICAL FEATURES

Common symptoms of hypothyroidism include fatigue, depression, cognitive impairment, cold intolerance, dry skin, constipation, and weight gain (Table 3).[17] Patients often have increased total and LDL cholesterol, increased triglycerides, and decreased HDL. Because the signs and symptoms are nonspecific and the onset often insidious, diminished thyroid function is likely to remain undiagnosed because the symptoms are attributed to the inevitable consequences of aging, particularly in post-menopausal women.

PREVALENCE

Hypothyroidism is a common disorder, affecting 4.6% of the U.S. population.[4] Subclinical hypothyroidism is more common than overt disease, especially in older females.[3,5,7] Several studies have defined the prevalence of subclinical hypothyroidism in women as more than five times that of overt disease, ranging from 8.0% to 21.0% in various population studies.[3-5,18-20] TSH and TPOAb elevation increase with age, are more common among women from the fourth decade on, and are more likely to affect whites and Mexican Americans than African Americans.[4] Individuals with a history of treated hyperthyroidism, neck surgery or neck irradiation, or autoimmune disorders such as type I diabetes have an increased risk for developing hypothyroidism. In addition, medications such as lithium, corticosteroids, dopamine, beta-blockers, amiodarone, and interferon can suppress thyroid function.[21]

CLINICAL IMPLICATIONS

The primary complication of untreated hypothyroidism is an increased risk for developing atherosclerosis. The link between hypothyroidism and atherosclerosis is multifactorial and includes lipid abnormalities and autoimmune processes. Decreased thyroid hormones increase total and LDL cholesterol by increasing endogenous cholesterol synthesis, decreasing lipoprotein lipase activity, increasing LDL oxidation, and decreasing hepatic LDL receptors.[22-24] Large population studies of individuals with overt hypothyroidism have noted significantly elevated total cholesterol and LDL cholesterol compared to euthyroid controls.[25] Smaller studies have similar findings with several also noting elevation of triglycerides.[26,27] The literature on the effect of subclinical hypothyroidism on lipid metabolism and risk for atherosclerosis is often summarized as conflicting.[11,28] Several groups have identified significant lipid abnormalities in subclinical disease only when TSH was greater than 10 mIU/L.[10,24,29,30] Across the spectrum of subclinical hypothyroidism there are trends for higher levels of total cholesterol, LDL, and triglycerides, as well as lower HDL with increasing severity correlated with TSH concentration. The relationship between subclinical hypothyroidism and cardiovascular risk in two large population based studies yielded discordant results. In

Table 1. Test results

Test	Result	Reference interval
Glucose	73	65-110 mg/dL
Total cholesterol	245	<200 mg/dL
LDL cholesterol	180	1-129 mg/dL
HDL cholesterol	35	40-59 mg/dL
Triglycerides	160	1-149 mg/dL
TSH	11.72	0.46-4.68 mU/L

Table 2. Followup test results

Test	Result	Reference interval
Total cholesterol	214	<200 mg/dL
LDL cholesterol	128	1-129 mg/dL
HDL cholesterol	60	40-59 mg/dL
Triglycerides	130	1-149 mg/dL
TSH	2.57	0.46-4.68 mU/L
FT_4	1.3	0.8-2.3 ng/dL

Table 3. Clinical manifestations of hypothyroidism*

Symptoms
- Fatigue
- Lethargy
- Sleepiness
- Mental impairment
- Depression
- Cold intolerance
- Hoarseness
- Dry skin
- Decreased perspiration
- Weight gain
- Decreased appetite
- Constipation
- Menstrual disturbances
- Arthralgia
- Paresthesia

Signs
- Slow movements
- Slow speech
- Hoarseness
- Bradycardia
- Dry skin
- Nonpitting edema (myxedema)
- Hyporeflexia
- Delayed relaxation of reflexes

Symptoms and signs associated with specific causes of hypothroidism
- Diffuse or nodular goiter
- Chronic autoimmune thyroiditis
- Ingestion of antithyroid substances or iodine deficiency

Symptom and signs of pituitary or hypothalamic tumor
- Headache
- Visual Impairment
- Deficiency or excess of pituitary hormones other than TSH

*Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, Eighth Edition. Lewis E Braverman, Robert D Utiger, editors. 2000. Philadelphia. Lippincott Williams and Wilkins. Reprinted with permission.

a 20-year follow-up study of individuals in England with thyroid dysfunction, death from cardiovascular disease was not significantly increased for those with subclinical hypothyroidism when compared to normal controls.[5] However, in a recent study of middle aged women, those with subclinical hypothyroidism were twice as likely to have atherosclerosis compared to normal controls.[3] Variability in the relationship between lipid profile, atherosclerotic risk, and thyroid function may be attributable to divergent definitions of subclinical hypothyroidism, inappropriate control groups, functional limits of older laboratory tests for TSH and thyroid hormones, and diversity within studied populations with regard to age, sex, smoking status, and ethnicity.[31]

In addition to hyperlipidemia as a risk factor for atherosclerosis, individuals with hypothyroidism have evidence of immune-mediated endothelial dysfunction, where the severity is associated with increased TSH level and with increasing TPOAb concentration.[32,33] In general, autoantibodies and associated immune complexes are associated with hypertension, platelet aggregation, increased vascular permeability, and endothelial dysfunction, all leading to increased risk of thrombosis and atherosclerosis.[34,35] Endothelial dysfunction is an interrelated process of vascular endothelial damage that includes inflammation, abnormal platelet aggregation, increased adhesion of monocytes, and increased proliferation of vascular smooth muscle cells, all important components in the development of atherosclerosis, intravascular thrombosis, and plaque- and clot-related emboli.[35]

LABORATORY DIAGNOSIS

Due to the limited utility of patient history and clinical examination for making a diagnosis, the determination of thyroid function status is based on laboratory tests for serum TSH, FT_4, and TPOAb. Third generation TSH assays with functional sensitivity below 0.02 mIU/L are recommended as the most sensitive and specific tests for detecting thyroid dysfunction in ambulatory individuals.[21] The diurnal fluctuation seen with individual TSH concentrations usually occurs well within the normal reference interval and does not necessitate specific scheduling of specimen collection.[21] TSH is most often measured using non-isotopic immunometric assays on automated analyzers.[21] Interference from heterophillic antibodies can falsely increase TSH concentrations, necessitating the need for dilution studies or repeating the assay using a different method. The recently published document from the National Academy of Clinical Biochemistry (NACB), "Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease" contains guide-

lines for establishing functional sensitivity, between-run precision, and determination of reference intervals.[21]

The use of serum TSH to screen for thyroid dysfunction assumes the individual has normal pituitary and hypothalamic function and has stable thyroid status. Pituitary or hypothalamic disease can cause central hypothyroidism in which TSH is abnormally glycosylated resulting in decreased biological activity but normal immunoreactivity in laboratory tests. Rarely, a pituitary tumor may secrete TSH with normal immunoreactivity, but increased biological activity resulting in hyperthyroidism. Recent treatment of, or transition from, hypo- and hyperthyroidism can result in diagnostically misleading TSH concentrations.[21] In addition, hospitalized patients with nonthyroidal illness can have transient abnormalities in TSH concentrations. Individuals receiving levothyroxine replacement therapy for hypothyroidism should wait at least six to eight weeks following initiation of therapy to allow pituitary re-equilibrium before measuring TSH concentrations.[21]

Reflexively testing FT_4 on samples with abnormal TSH represents an efficient and effective way to diagnose thyroid dysfunction and allows the classification into subclinical or overt hypo- and hyper-thyroidism. FT_4, unlike total T_4, is unaffected by common protein binding abnormalities and is diagnostically more accurate. In addition, in ambulatory patients, FT_4 is relatively unaffected by acute and chronic non-thyroidal illness.[21] FT_4 can be measured with direct assays in reference laboratories using physical separation of free and bound hormone by equilibrium dialysis, ultrafiltration, or gel filtration methods. Alternatively, free hormone estimates can be determined indirectly in the clinical laboratory using one or two-step immunoassays or mathematic calculations involving protein uptake methods. Depending on the methodology, the indirect assays can have interferences from abnormal concentrations of serum binding proteins. The limitations of the various assays for FT_4 are discussed in detail in the NACB document.[21]

Because autoimmunity is a hallmark of hypothyroidism, antithyroid antibodies, especially TPOAb, can be used as a marker of disease activity and progression. TPOAb is the most sensitive test for detecting autoimmune thyroid dysfunction with greater than 95% of patients with Hashimoto's thyroiditis having elevated TPOAb.[21] TPOAb elevation may precede increases in TSH and signal early thyroid gland destruction.[22] The NACB recommends that sensitive, specific, automated TPOAb immunoassays replace the older antimicrosomal antibody agglutination tests. The TPOAb methods currently available vary significantly in sensitivity and specificity, indicating a need for international standardization of this test.[21]

TREATMENT

Hypothyroidism is treated by providing the patient with a daily dose of synthetic thyroid hormone called levothyroxine. Most cases of overt hypothyroidism are treated to decrease the risk of atherosclerosis. The decision to treat subclinical hypothyroidism is controversial, as randomized treatment trials have had varied outcomes.[11] The arguments for treating subclinical hypothyroidism are to prevent the development to overt disease, to improve hyperlipidemia, and to improve patient symptomology. Others argue that the improvement in lipid levels is slight and that over treatment can lead to hyperthyroidism.[29,36] It has been proposed that patients with subclinical hypothyroidism receive treatment if their TSH is >10 mU/L and TPOAb are present or if a goiter is present.[28]

SCREENING PROGRAMS

Screening at-risk populations (elderly persons, women) for thyroid dysfunction using serum TSH has been proposed because many of the signs and symptoms of mild disease are nonspecific and evidence exists of chronic complications from untreated cases. The American Thyroid Association, a professional association of physicians and scientists, recommends that all adults be screened using serum TSH beginning at age 35 and every five years thereafter.[37] The American College of Physicians supports screening women older than 50 years of age for thyroid disease.[38] Recently, Congress commissioned the National Academy of Science to conduct a study on coverage of routine thyroid screening for Medicare beneficiaries. The study report, "Medicare Coverage of Routine Screening for Thyroid Disease" was published in 2003 by the Institute of Medicine.[11] The report concluded that at the present time, Medicare should not cover screening for thyroid dysfunction due to a lack of sufficient evidence of either benefit or harm. The report recommended that further research be performed to provide definitive answers.

SUMMARY

Hypothyroidism represents a common disorder especially in older women. Left untreated, it can lead to abnormalities in lipid metabolism and subsequent progression to overt hypothyroidism, with significant clinical consequences of myocardial infarction and stroke. More research needs to be performed to investigate the link between subclinical hypothyroidism and cardiovascular disease risk and to evaluate the health and economic outcomes of randomized trials of TSH screening.[11]

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