Diagnosis and Management of Hypothyroidism in Women

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Introduction

Thyroid disorders are common in women. These disorders involve either functional impairment, such as hypothyroidism, or structural abnormalities such as thyroid nodules and thyroid cancer. In the present discussion I will focus on functional abnormalities, with an emphasis on conditions that alter their frequency, clinical presentation or treatment.

Thyroid Physiology

The thyroid gland actively traps iodide, converts iodide to iodine, and couples iodine to iodothyronines to generate thyroxine (T_4) and triiodothyronine (T_3) (Figure).[1] (For the remainder of this article, for purposes of simplicity, the general term iodine will be used to refer to iodide and iodine.) The majority of T_4 and T_3 is stored within the colloid (attached to thyroglobulin) but, when needed, can be released and then secreted into the circulation. Pituitary

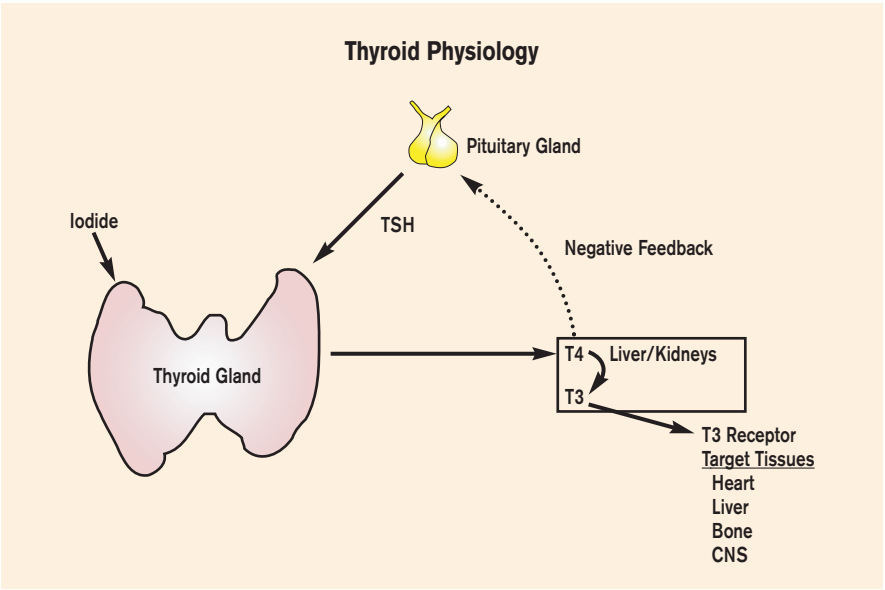

Figure. The thyroid gland actively traps iodide, converts iodide to iodine, and couples iodine to iodothyronines to generate T_4 and T_3. TSH regulates each step of thyroid hormone synthesis. T_4 is converted to T_3 by deiodinase enzymes, located mainly in the liver and kidney.

thyrotropin (thyroid-stimulating hormone, TSH) regulates each step of thyroid hormone synthesis. In the circulation, T_4 and T_3 are bound to proteins (thyroxine-binding globulin, prealbumin and albumin) such that only approximately .03% of T_4 and .3% of T_3 is free or unbound.[2] It is the unbound fraction that is active and accounts for biologic activity. T_4 is converted to T_3 by deiodinase enzymes, located mainly in the liver and kidney. Theoretically, regulation of conversion of T_4 to T_3 represents a homeostatic mechanism by which the body regulates thyroid hormone action. It is believed that T_4 is chiefly a prohormone and T_3 accounts for virtually all of thyroid hormone action in adults. In fact, there are three separate, but related, selenium-dependent deiodinase enzymes, denoted as D1, D2 and D3. D1 is primarily expressed in the liver, kidneys and thyroid gland; its major function is to convert T_4 to T_3. D2 is thought to account for local tissue T_3 generation, and is present largely in the central nervous system, pituitary, brown fat, adipose tissue, skeletal muscle, and thyroid tissue. D3 is important in metabolizing thyroid hormone, and is located in brain, placenta, uterine and fetal tissues. D3 inactivates T_3.

Specific thyroid hormone receptors are located in the nucleus and mediate transcriptional activity, resulting in a myriad of actions attributed to thyroid hormones. Of course, there is a very closely regulated inverse relationship between T_4/T_3 and TSH, such that a small change in T_4/T_3 will result in a magnified change in TSH. Basal TSH is elevated in primary hypothyroidism and suppressed (usually undetectable) in patients with hyperthyroidism.

Iodine. Iodine is an important element that is required for normal thyroid hormone synthesis and secretion, and for maintenance of a euthyroid state. There is equilibration between iodine intake and urinary output. The minimum adult daily iodine requirement is 150 µg; however, over the last several decades in the United States, concern has arisen about excess iodine intake. Recently, this concern has evolved into a discussion of who is likely to have iodine deficiency. Pregnant women seem at particular risk for iodine deficiency, probably due to low intake and enhanced metabolism; thus, it is important to ensure adequate iodine intake in these patients. Iodine is found in many foods; there is a reasonable amount in seafood and it is used as a preservative in bread, flour and pastries.[3,4] In addition, iodine is added to iodized salt. However, these sources may not contribute significantly to an individual' s intake, depending on the type and amount of food eaten. Milk has recently been proven to contain sufficient iodine, probably related to iodine contamination arising from cleansing udders.[5]

Despite these multiple possible sources of iodine, the National Health and Nutrition Examination Survey (NHANES III) indicated that dietary iodine intake was decreasing and now averages about 145 µg/day. In fact, approximately 10% to 15% of women of child-bearing age have urinary iodine concentrations lower than 50 µg/day.[3,4] This value is below the recommended daily allowance for adults (150 µg) and subsequently places these women at risk for iodine deficiency, goiter and hypothyroidism.

The NHANES III is extremely important and useful. Conducted from 1988 to 1994, the study was designed to give normative data for nutrition and health status of the normal noninstitutionalized population throughout the United States.[3,4] Approximately 30,000 individuals were examined and the survey represented, but did not include, subjects from all states and the District of Columbia.

Laboratory Studies

Clinically, the thyroid function tests that are widely available and should be routinely employed are free T_4, T_3 (free T_3 or total T_3), and TSH (Table 1).[6,7] Free T_4 assays measure or assess the unbound, active portion of T_4. These assays have improved over recent years but, in essence, use a variety of different techniques. These assays do not directly measure free T_4, but provide estimates that are appropriate and accurate in most circumstances. Unfortunately, different assays may result in variable results, and each assay seems potentially to give misleading results, at least to some

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extent, particularly when assessing free T_4 in hospitalized patients.

It is theoretically desirable to measure free T_3, rather than total T_3, but free T_3 assays seem to be even more problematic. Depending on the individual circumstances, a clinician might prefer either a total T_3 or a free T_3, with the understanding that total T_3 is normally elevated in women receiving estrogen-containing compounds because estrogen increases thyroxine-binding globulin.

TSH is measured by a sensitive assay but, of course, the value is meaningful only when a patient has a normal pituitary gland. TSH values must be interpreted with caution in hospitalized, systemically ill patients because these patients may manifest "euthyroid sick syndrome," in which metabolism and, probably, secretion of T_4 and T_3 are altered, possibly as a homeostatic mechanism to help conserve energy.

In addition to thyroid function tests, measurement of serum thyroglobulin antibodies and peroxidase antibodies is frequently helpful in determining that a patient has Hashimoto's thyroiditis. Routine laboratory studies such as a complete blood count and a comprehensive metabolic profile should also be obtained because hypothyroidism can affect multiple organ systems and, on rare occasions, there may be an associated autoimmune disorder. In addition, I frequently order a thyroid sonogram to ensure that there are not anatomical abnormalities such as a discrete thyroid nodule, which requires a fine-needle aspiration. Obtaining a thyroid sonogram is especially important in patients with palpable thyroid abnormalities. I generally recommend that a fine-needle aspiration be performed in thyroid nodules 1 cm or larger, although this approach is controversial. A list of laboratory studies that may be useful in patients with suspected hypothyroidism is presented in Table 1.

Table 1.
Laboratory Studies that May be Useful in Patients with Suspected Hypothyroidism

Free T4/T3 (preferred) over total measurements
TSH
Total T4/T3
Thyroid peroxidase antibodies
Thyroid sonogram
Radioactive iodine uptake and scan (rarely useful)
When secondary hypothyroidism is suspected:
Cortisol, prolactin, FSH, LH levels
MRI of pituitary gland
Appropriate hormonal stimulation tests may also be utilized.

Normal range for TSH. TSH is the major serum determinant of biochemical thyroid dysfunction. Obviously, primary hypothyroidism is associated with an elevated TSH level. The critical question then becomes: what is the normal range for TSH? This issue has recently come under intense scrutiny, and is surprisingly controversial. The NHANES III determined the 2.5 to 97.5 percentile of TSH in a special population.[3,4,8] The investigators excluded subjects with a personal or family history of thyroid disease, those with visible or palpable goiter, patients with positive thyroid antibodies, and those taking medications known to influence thyroid function. They reasoned that thyroid dysfunction is so common that previous "normal" ranges likely included individuals with mild hypothyroidism. Therefore, their attempt to determine the normal range was more vigorous. A normal range, so determined, was .47 to 4.15 µIU/mL for men and .41 to 4.09 µIU/mL for women. Considered together, the normal range was .45 to 4.12 µIU/mL, with the median TSH being 1.39 µIU/mL. This rigorously derived normal range is thought to represent a significant improvement but there are several features that require additional comment. The normal range still should only be considered as a reference range and values outside this range should be repeated. In one study, monthly measurements of T_4, T_3, and TSH were taken over the course of a year, and the results indicated that the variation of a given test in a single individual was minimal.[9] Although values clustered tightly around a given value, ranges varied for each individual. For example, one patient's TSH values might have ranged between .5 and 1.2 µIU/mL, whereas another patient's values might cluster between 2.0 and 2.4 µIU/mL. Therefore, a small change in T_4 or T_3 is well within the normal range, but is considered significant for a given patient if there is a significant change in TSH. As a result, serum TSH becomes the most accurate sensor of ambient T_4/T_3 levels in an individual patient. TSH values normally vary throughout the day, rising at about 10 or 11 pm, so it is important to repeat minimally abnormal values several times.

Hypothyroidism

Prevalence. Hypothyroidism is a common disorder. The Colorado Health Fair study[10] showed that 9.5% of 25,862 individuals tested had a TSH greater than 5 µIU/mL, and 74% of these had levels between 5.1 and 10 µIU/mL. The ages of the study population ranged from 18 to over 74 years, with about 68% between ages 45 and 74. The study population was 55.8% female and 44.2% male. The Framingham study[11] of 2,139 subjects older than age 60 demonstrated that 13.6% of women

and 5.7% of men had a TSH greater than 5 µIU/mL. The NHANES III[3] (n = 17,353) showed hypothyroidism in 10% of women and 4% of men older than age 60. Thyroid peroxidase antibodies were present in about 15% to 25% of subjects.

Signs and symptoms. The typical findings of hypothyroidism include fatigue, cold intolerance, constipation, dry skin, thinning hair, difficulty concentrating, bradycardia, hypothermia, slow speech, slow relaxation phase of reflexes, hypoglycemia and hypogonadism. In rare instances, cardiac and pleural effusions may occur. Of course, individual manifestations may vary.

Additional features that may be associated with hypothyroidism include elevated cholesterol, goiter, a personal or family history of autoimmune thyroid disease, insidious weight gain or unexplained infertility. Hypothyroidism is especially common in postmenopausal women.

Etiology: Primary hypothyroidism. The most common cause of hypothyroidism is autoimmune thyroid disease (Hashimoto's thyroiditis) (Table 2).[12] A goiter may be present. This disorder is associated with the development of antiperoxidase or antithyroglobulin antibodies. Rarely, a patient may exhibit Graves' ophthalmopathy. Additional causes include hypothyroidism following radioactive iodine (^{131}I) therapy for hyperthyroidism, surgical thyroidectomy, and antithyroid drugs. Amiodarone, an antiarrhythmic medication, is an increasingly frequent cause of hypothyroidism. Subacute thyroiditis is usually associated with a tender thyroid gland.

Postpartum thyroiditis occurs in about 8% of women following gestation, typically within 6 to 12 months of delivery. Postpartum thyroiditis and subacute thyroiditis usually have an evolving course. Subacute thyroiditis initially manifests as hyperthyroidism with thyroid gland tenderness, which then evolves into hypothyroidism and eventually returns to euthyroidism. Postpartum thyroiditis has a more variable course and can present as hyperthyroidism or hypothyroidism, after which thyroid function tests usually normalize. In a review of 287 patients in 11 studies, 38% of patients presented with hypothyroidism, 36% with hyperthyroidism, and 25% originally presented with hyperthyroidism that evolved into hypothyroidism.[13-19] Women with type 1 diabetes mellitus are predisposed to postpartum thyroiditis and as many as 25% of such patients may develop it. Postpartum thyroiditis usually resolves and the patient remains euthyroid. However, in about 10% of cases more permanent thyroid disease ensues.

Postpartum thyroiditis must be differentiated from lymphocytic hypophysitis, which also can occur in the postpartum period. Autoimmune lymphocytic hypophysitis may manifest as infiltration and destruction of the parenchyma of the pituitary and infundibulum. It generally occurs during pregnancy or the postpartum period. Symptoms of hypopituitarism or an enlarging mass lesion may occur in the absence of obstetric hemorrhage or prior history of menstrual difficulties or infertility. Hyperprolactinemia and diabetes insipidus may also occur. Spontaneous regression and resumption of partial or normal pituitary function may occur, although many patients progress to chronic panhypopituitarism. In contrast, postpartum thyroiditis only involves the thyroid gland, without evidence of a mass lesion in the pituitary, or of the involvement of pituitary hormones (other than the thyroid axis).

When amiodarone administration causes hypothyroidism it probably occurs mainly by the release of iodine contained within the molecule. In the United States, hypothyroidism is the most common amiodarone-associated thyroid abnormality. In areas of the world with iodine deficiency, hyperthyroidism is more common. External radiation to the head and neck area (for example, to treat Hodgkin' s disease or laryngeal cancer) also can cause hypothyroidism, although this may take several years to develop.

Table 2.
Causes of Hypothyroidism

Hashimoto's thyroiditis
Thyroiditis (postpartum, silent, subacute)
Amiodarone
Iodine load (eg, radioactive dyes)
Iodine deficiency
External radiation to head and neck
Thyroidectomy
Infiltrative disorders such as sarcoid or hemochromatosis
Isolated TSH deficiency
Secondary hypothyroidism: pituitary tumor
Hypothalamic hypothyroidism (rare): infiltrative disorders such as sarcoid or hemochromatosis

Secondary Hypothyroidism

Occasionally, hypothyroidism is not primary (ie, thyroidal in origin) but is secondary; that is, due to a hypothalamic or pituitary cause. Secondary hypothyroidism is suspected when there is evidence of a pituitary lesion, such as visual field changes or headache, and when there is an abnormality of another pituitary axis, such as elevated prolactin, perhaps with breast secretion, irregular menses or amenorrhea, or adrenal insufficiency. Furthermore, the serum TSH is expected to be low or inappropriately normal in the context of a decreased free T_4 and, usually, T_3. A pituitary tumor must always be excluded in this circumstance, although rare causes include infiltrative diseases, such

as hemochromatosis and sarcoidosis, as well as isolated TSH deficiency. From a clinical perspective, it is important to obtain pituitary function tests and a radiologic assessment, such as pituitary magnetic resonance imaging (MRI), to exclude the presence of a pituitary tumor.

Elevated TSH: Other Causes

An elevated TSH is important evidence of primary hypothyroidism; however, there are several caveats regarding its interpretation. Systemic illness of any type can transiently alter TSH secretion and an elevated TSH can occur, especially when a seriously ill patient is in the recovery phase. To ensure proper diagnosis and avoid inappropriate diagnosis, elevated TSH should only cautiously be interpreted in any systemically ill, hospitalized patient.[1,20] The topic of interpretation of thyroid function tests in critically ill patients is beyond the scope of the present article. However, in general, levothyroxine therapy should be considered in an ill, hospitalized patient if the serum TSH concentration is higher than 10 µIU/mL, especially if repeated in several days, and also when it occurs in conjunction with appropriate clinical findings and decreased free T_4 and T_3.

Unusual causes of an elevated TSH that may not represent authentic hypothyroidism include TSH diurnal variation, the presence of interfering antibodies, resistance to T_3/T_4, and the presence of a TSH-secreting pituitary tumor. TSH rises late in the evening, at around 10 pm; however, this increase rarely causes confusion because most TSH values are drawn between 8 am and 5 pm. Heterophilic antibodies can develop in patients, especially if they are exposed to or handle animals. Depending on the assay used, these antibodies will cause a markedly abnormal (either high or low) TSH that seems discordant from the free T_4/T_3 and clinical findings. Thyroid hormone resistance is a familial entity in which a mutation occurs in the T_3/T_4 receptor. This disease can present in a variable manner but usually the free T_4 and T_3 are elevated in the context of an inappropriately normal or elevated TSH. Other family members may also exhibit the same findings. It is important to consider these rare causes of an abnormal TSH, but it is much more common for a patient with an elevated TSH to actually have primary hypothyroidism.

Pregnancy and Hypothyroidism

Thyroid function and the interpretation of thyroid function tests in pregnancy is an important, but complex, topic.[2,13,14,21] Estrogen administration or pregnancy increases thyroxine binding globulin, and, as a result, Total T_4 normally increases. It is preferable to measure Free T_4, Free T_3 and TSH when possible, as these hormones are not as influenced by thyroxine-binding globulin (TBG) abnormalities. However, during pregnancy free T_4 measurements may show a decrease in certain assays, and care must be taken to utilize a trimester-specific pregnancy normal range for comparison. Pregnant patients with TSH-receptor antibodies may pass these antibodies across the placenta, and a neonate may demonstrate hypothyroidism or hyperthyroidism. Thyroid-stimulating immunoglobulins (TSI) should be measured in pregnant women with active Graves' disease and in selected patients with Hashimoto's thyroiditis. Thyroid peroxidase and thyroglobulin antibodies are not thought to cause neonatal abnormalities.

It is important to keep TSH within the normal range in pregnant hypothyroid women receiving levothyroxine. Haddow et al[22] noted that an untreated elevated TSH during pregnancy was associated with about an IQ of approximately 7 points lower in the child (measured at about age 9 years). If the mother was treated with levothyroxine the subsequent IQ of the child was not different than that of the control. Although this study has received much attention, it has inherent issues that, in my opinion, require confirmation. For example, the TSH was measured only once in the midtrimester and it is not known what the TSH level was throughout pregnancy. In addition, the serum TSH level achieved in levothyroxine-treated patients is unknown. Also, the babies' thyroid function tests were not measured for many years and, lastly, this was a small retrospective study.

In a summary of 4,123 women, there was evidence that the miscarriage rate was 23% in women with thyroid antibodies as compared to 8% in women who were antibody-negative.[17,23] Fetal deaths also seem to correlate with TSH levels; women with a TSH level greater than or equal to 6 µIU/mL had a 3.8% fetal death rate and women with a normal TSH level had a 0.9% fetal death rate.

A separate issue is whether levothyroxine dosage requirements increase in pregnant hypothyroid women taking levothyroxine. Alexander et al[2] observed that there was an increase in levothyroxine dosage requirements in 17 of 20 such pregnancies. The mean levothyroxine requirement increased 47% during the first half of pregnancy and plateaued by week 16. The increased requirement was maintained until delivery. A separate study, however, did not demonstrate such a high frequency of increased levothyroxine dosage requirements in pregnant women.[24] In both of these studies, levothyoxine requirements seem to increase in thyroidectomized patients more consistently than in patients with primary hypothyroidism.

It is difficult to draw clinical conclusions from these divergent studies. However, it seems important to try to avoid an elevated TSH during pregnancy. Further, it is clear that some (perhaps most) thyroidectomized patients, and possibly patients with primary hypothyroidism, may have increased levothyroxine requirements during pregnancy. This issue is complicated by the fact it takes 4 to 6 weeks for a change in dose to equilibrate, and for the TSH to accurately represent tissue stores. However, by that time, the requirements may have increased again. Given these confounding issues, I

recommend that a hypothyroid woman taking levothyroxine have her thyroid function tested monthly during pregnancy. Her levothyroxine dose should be changed as appropriate. If the TSH level is markedly abnormal (greater than 10 µIU/mL) (and perhaps in other circumstances), I would even recommend repeating thyroid function tests in 2 weeks to make sure the TSH is decreasing appropriately. Unfortunately, there are no evidence-based guidelines for this personal approach.

Subclinical Hypothyroidism

Subclinical hypothyroidism is defined as the presence of an elevated TSH in the context of a normal free T_4 and T_3. This topic has become interesting and controversial, in large part because most patients today are diagnosed with mild or subclinical hypothyroidism rather than with overt hyperthyroidism, which is manifested by an elevated TSH with a decrease in free T_4/T_3.[25,26] Subclinical hypothyroidism is inherently a vague term but it should not be thought of as synonymous with mild hypothyroidism. Rather, subclinical hypothyroidism represents a continuum of disease in which the TSH rises but the T_4/T_3 levels remain within the normal range. My comments above relating to the "normal range" should be considered. That is, if an individual' s own tightly regulated free T_4 level happens to normally reside in the lower portion of the free T_4 "normal range", a small decrease in free T_4, of perhaps 10% to 20%, will be associated with a decreased free T_4 and an elevated TSH. We will categorize this patient as having "overt hypothyroidism". On the other hand, if an individual' s tightly regulated free T_4 value happens to normally reside in the upper portion of the "normal range", and then decrease 50% but still remain within the "normal range", we will characterize this as subclinical hypothyroidism. In theory, the individual in the first example will have "less hypothyroidism" (due to a smaller decrement in free T_4) than the individual in the second example. As a result, caution should be employed in the interpretation and analysis of patients with subclinical hypothyroidism.

Independent Consensus Findings: Subclinical Hypothyroidism

An independent consensus conference was convened to review the literature on this topic and to make recommendations regarding treatment.[25,26] The reader is referred to the original publications from this consensus panel. I will summarize some of the highlights here.

It was thought appropriate to categorize subclinical hypothyroidism into five general topics, which theoretically constitute reasons to treat patients. These categories are: (1) to prevent progression to overt hypothyroidism; (2) alleviate symptoms; (3) decrease lipid levels; (4) improve cardiac function; and (5) improve depression and cognition.

Prevent progression to overt hypothyroidism. In a prospective study of 87 women analyzed over 9.2 years, Huber et al[27] found that the frequency of developing overt hypothyroidism was 0% if the baseline TSH was 4 to 6 µIU/mL, 43% if the baseline TSH was 6 to 12 µIU/mL, and 77% if the baseline TSH was greater than 12 µIU/mL. This study has to be considered with the understanding that these patients had previously been treated for hyperthyroidism, which may have predisposed them to develop hypothyroidism, as compared to a population who had never had previous thyroid disease.

A separate study by Diez and Iglesias[28] showed that 27% (total N = 107) of patients over age 55 with subclinical hypothyroidism progressed to overt hypothyroidism over 6 to 72 months (mean 31 months). Women progressed to overt hypothyroidism more frequently than men, and the presence of thyroid antibodies also increased the likelihood of progression. Of great interest was the fact that in 37% of patients who presented with subclinical hypothyroidism, TSH values later normalized. The absence of thyroid antibodies made it more likely that the serum TSH would normalize. In 52% of patients with initial TSH levels of 5.0 to 9.9 µIU/mL, TSH normalized, whereas only 13% of patients with initial TSH levels of 10.0 to 14.9 µIU/mL eventually had TSH normalized. This remarkable study indicates the importance of repeating thyroid function tests (if clinically feasible) over several weeks or months before initiating therapy.

Alleviate symptoms. Clinically, patients and physicians believe that a multitude of possible symptoms can accompany hypothyroidism. However, these symptoms are vague and, as noted, most patients today have subclinical rather than overt disease. It has been difficult to prove that subclinical hypothyroidism is associated with specific symptoms. Several blinded placebo controlled studies have revealed variable results and the conclusion is that it has not yet been proven that subclinical hypothyroidism is associated with specific symptoms, which resolve when treated with levothyroxine. Of course, thyroid function tests should be obtained in patients with symptoms that may possibly be related. However, even if a patient has subclinical hypothyroidism and is treated, each of the symptoms may not resolve, and if they did a placebo effect could not be ruled out.

Decrease lipid levels. It is well known that overt hypothyroidism is associated with elevated cholesterol levels. It is a different matter to unequivocally prove that subclinical hypothyroidism is associated with elevated cholesterol values that respond to levothyroxine treatment. Most, but not all, controlled studies show a small but discernable decrease in total cholesterol or LDL by normalizing TSH.[29] Meier et al[30] showed a small but statistically significant decrease in LDL, as compared to placebo, especially in patients with a TSH greater than 12 µIU/mL and in patients with an elevated LDL. Overall, it is thought that subclinical hypothyroidism is associated with a mildly elevated LDL that decreases slightly (but significantly) with levothyroxine treatment.

Improve cardiac function. Most studies assessing cardiac or vascular function have focused on surrogate markers. For instance, carotid intima media thickness is decreased by restoration of TSH to normal.[31] The Rotterdam study assessed 1,149 women and found that subclinical hypothyroidism was associated with a 1.7 times increased risk of developing aortic atherosclerosis and a 2.3 increased risk of developing a myocardial infarction.[32] Other risk factors were corrected for in this analysis. This important study was basically confirmed by another study in which 257 patients with subclinical hypothyroidism were followed over a 10-year period without levothyroxine treatment.[33] In men, subclinical hypothyroidism was associated with ischemic heart disease independent of age, systolic blood pressure, body mass index, cholesterol, smoking, erythrocyte sedimentation rate, or presence of diabetes mellitus. The hazard ratio for ischemic cardiac mortality in men was increased significantly to 1.9 to 2.1, but it was not significantly increased in women.

Improve cognition. The area of correlating cognition with subclinical hypothyroidism or its treatment is extremely difficult to assess. Basically, no evidence-based conclusions can be made.

Consensus panel conclusions on treatment. The consensus panel convened to examine the literature on subclinical thyroid disease came to several conclusions. As a general consideration, to recommend screening and treatment several specific criteria must be met. There must be evidence that the disease is associated with adverse clinical outcomes (not surrogates). There must be evidence that treatment of disease reverses those outcomes and there must be evidence that the benefits of treatment outweigh the risks. There is insufficient evidence, based on the criteria noted, to recommend general population screening for TSH. There is sufficient evidence, however, to recommend that individuals who are found to have a serum TSH greater than 10 µIU/mL be treated with levothyroxine. There is insufficient evidence to expect therapeutic benefit when the TSH is between 4.5 and 10 µIU/mL. However, it is recognized that some of these patients will benefit from treatment and that the decision to treat is an individual decision between the physician and patient. An elevated TSH should, of course, be confirmed. In the controversial TSH range of 4.5 to 10 µIU/mL, I generally repeat the thyroid function tests several times over several weeks or even months to ensure it is stable. If the TSH is consistently in this range, and especially if thyroid antibodies are present, I would discuss the issue with the patient and would tend to recommend levothyroxine therapy.

Treatment of Hypothyroidism

Primary hypothyroidism is treated with levothyroxine in a dose sufficient to normalize the TSH. Secondary hypothyroidism is also treated with levothyroxine although, of course, in this situation free T_4/T_3 are depended upon, rather than TSH, and additional pituitary hormone replacement may be needed. The initial dose of levothyroxine is an estimate but it is reasonable to utilize 1.7 µg/kg/day.[34] Thyroid function tests are repeated in 4 to 6 weeks and then the dose is modified, as appropriate, to normalize the TSH. TSH is the major hormone monitored, although its values are interpreted in light of free T_4/T_3 and the clinical context. Hypothyroid patients may require a Free T_4 higher than the normal range to normalize their TSH value. T_3 replacement should not be used either alone or in combination with levothyroxine replacement.

Levothyroxine should be taken alone, and not concurrently with other medications; specifically, cholestyramine, sucralfate, ferrous sulfate, soy, aluminum hydroxide and raloxifene. The administration of estrogen-containing compounds to hypothyroid patients taking a stable dose of levothyroxine may increase her levothyroxine requirements.[35] Conversely, stopping an estrogen-containing compound may decrease levothyroxine requirements. Similar effects may occur with raloxifene.[36]

Thyroid function should be tested routinely, perhaps annually, in patients taking levothyroxine. Even when closely monitored, about 20% of patients will be over-treated and about 20% will be under-treated. More frequent monitoring may be indicated if a patient has symptoms that may reflect altered thyroid status.

Summary and Conclusions

This article reviewed various aspects of the diagnosis, prevalence and treatment of hypothyroidism, with emphasis on special considerations. There are very few large-scale prospective articles on which to form an evidence-based opinion so, unfortunately, any recommended approach in this area is inherently subjective. Perhaps in the future this circumstance will change. ■

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