

Thyroid Dysfunctions and its Monitoring

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ABSTRACT

The prevalence of hypothyroidism is three times higher among women than men. The prevalence in an unselected community population of young, middle aged and elderly individuals is about 1.4 percent and the estimated annual incidence rate is one to two per 1,000 women. Surveys of geriatric populations have yielded estimated prevalence rates for overt hypothyroidism of 0.2 percent to 3 percent. The presentation of symptoms in the elderly may be atypical or absent. The prevalence of subclinical hypothyroidism is estimated to be between 4.0–8.5% of the adult US population without known thyroid disease, and the prevalence increases with age. Up to 20% of women over the age of 60 are estimated to have subclinical hypothyroidism. Caucasians are more likely to have subclinical hypothyroidism than non-Caucasians. The risk is highest in those with type I diabetes mellitus, a family history of thyroid disease or head/neck cancers treated with external beam radiation. Other risk factors include previous radioactive iodine treatment or thyroid surgery. Interestingly, about 20% of patients on thyroid medications are both over replaced and under replaced. Because of the high incidence of thyroid disease, The American Thyroid Association recommends measuring thyroid function on all adults beginning at age 35 years and every 5 years thereafter noting that more frequent screening may be appropriate in high risk groups. The treatment of subclinical hypothyroidism has been controversial but more recent data suggest there are increased risks of ischemic heart disease in untreated patients and that a more aggressive approach to treatment would be appropriate. In contrast, subclinical hyperthyroidism has more well understood risks of atrial fibrillation and flutter and so should be more aggressively treated.

Keywords: Hypothyroidism, Thyroid Gland, Goiter, thyroxine-binding globulin

INTRODUCTION

The thyroid gland, located below the larynx, is the largest endocrine organ, and is essential to mammalian life. The thyroid gland produces hormones, which help in the regulation of metabolism, growth and development, and even reproduction^[1]. To maintain normal thyroid function, the hypothalamus and the pituitary gland both impact thyroid status. Known as the hypothalamic-pituitary-thyroid axis, this link between the three is what

regulates proper thyroid hormone synthesis and release. The system is a negative-feed process in which the level of circulating thyroid hormone (both T₄ and T₃) signals the hypothalamus to synthesize and release thyroid-releasing hormone (TRH) or suppress it. The level of thyroid-releasing hormone in turn balances the release of TSH. When more TSH is needed, thyroid-releasing hormone binds to receptors in the pituitary gland that cause the release of TSH. The release of TSH causes the

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thyroid to stimulate the expression of the sodium/iodide symporter (NIS), which is responsible for iodide transport and therefore iodine uptake, the enzyme thyroid peroxidase, and thyroglobulin. In addition, TSH also helps in the generation of H₂O₂. All of these uses of TSH cause more thyroid hormones to be produced and released^[2]. Less TSH causes less thyroid hormone to be produced and released from the thyroid gland, causing TRH suppression. .

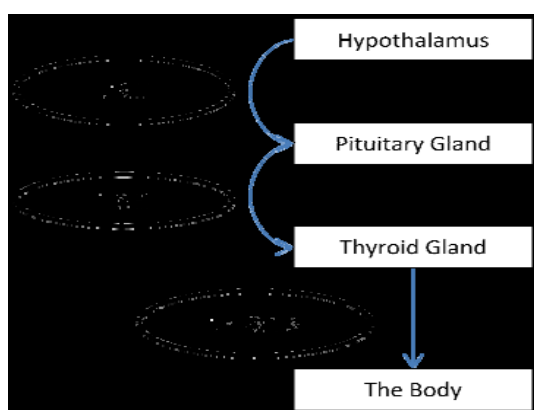


Figure 1. Hypothalamic-Pituitary-Thyroid axis.

Within the thyroid gland, thyroid hormone synthesis requires iodine and the enzyme thyroid peroxidase to turn thyroglobulin (Tg) into thyroxine and triiodothyronine, T₄ and T₃, respectively. Thyroxine and triiodothyronine are then released into the bloodstream, where they are part of protein synthesis and metabolic processes in a multitude of cells and tissues

The regulation of thyroid hormones is a complex process. In a person with healthy thyroid function, the presence of excess or lack of iodine, for example, leads the thyroid gland to make and release more or less of its hormones. The level of hormone in circulation signals the suppression or the synthesis of other hormones like TRH and TSH that in turn help maintain thyroid hormone balance. Since thyroid hormones are not water-soluble they bind to proteins when they are released from the thyroid gland. The majority travels in the

bloodstream bound to the proteins thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA) and albumin. Free thyroxine, fT₄, is the small amount (about 0.03%) of thyroid hormone that is not bound to a protein^[3]. Similarly, fT₃ is the triiodothyronine that is not bound to a protein. While there is more thyroxine in the thyroid gland and circulating in the body, triiodothyronine (T₃) is the bioactive form of the two. In addition to being released from the thyroid gland, T₃ and 3, 3', 5'-triiodothyronine (rT₃) are also formed from thyroxine locally in the cells by deiodination. Greer (1990)³ states that in individuals with healthy thyroid function 20% of T₃ is produced in the thyroid gland, while 80% is formed from thyroxine peripherally (p. 236).

THYROID FUNCTION

The term euthyroid is used to refer to individuals with normal thyroid function. Different studies use some combination of the following criteria to decide who is considered euthyroid. Most studies will primarily check for thyroid autoantibodies, TSH levels, fT₄ levels and previous thyroid disease as elements to determine thyroid status^[4-6]. If all information is readily available to the investigators, a person can be determined euthyroid if:

- (1) they do not have a previous or current diagnosis of thyroid disorders or dysfunction.
- (2) are not taking thyroid hormone therapy or medications for thyroid diseases.
- (3) Do not have positive thyroid autoantibodies (anti-Tg and TPOAb) in the Serum.
- (4) Have TSH levels, fT₄ levels and fT₃ levels within the reference ranges.

Abnormal thyroid function, which leads to the body making too little or too much hormone, can be due to different issues. Autoimmune thyroid disorders (AITD) are largely attributed to genetics^[7], while other forms of hypothyroidism and hyperthyroidism can be

iodine-induced^[8] or caused by medications that interfere with thyroid function. Hypothyroidism occurs when the thyroid gland does not make enough thyroid hormones. It can be detected through serum TSH tests that show levels of TSH above the reference range. The most severe form of hypothyroidism is myxedema, where the body starts to shut down. This form of hypothyroidism may occur after many years of a person suffering from the dysfunction^[9]. On the other hand, hyperthyroidism occurs when the body makes too much thyroid hormone and the thyroid gland is said to be “overactive”. The dysfunction can be diagnosed through serum TSH, T4, and T3 tests, which reveal low levels of TSH and higher levels of T4 and T3 than the reference ranges. Besides autoimmune disease, hyperthyroidism can be caused, temporarily, by lower overall immune response (e.g. when a person is fighting a viral infection), the individual is suffering from thyroid inflammation (thyroiditis), or due to a thyroid nodule or goiter forming^[10]. In addition to these diseases, an individual can develop thyroid cancer. Thyroid nodules can be either benign or cancerous. A thyroid ultrasound and biopsy is used to diagnose cancer, and a sensitive test is used to check for thyroid carcinoma recurrence, where serum thyroglobulin (Tg) levels are examined. While thyroid cancer is a common endocrine-related cancer, it is rare that a person is diagnosed as having this type of carcinoma. According to the American Thyroid Association (2008a)^[11], the incidence of thyroid cancer in the United States is 20,000 cases per year. Thyroid carcinoma can be managed through surgical removal of the thyroid and continued use of thyroid hormone therapy.

FACTORS THAT AFFECT THYROID FUNCTION

Different factors affect thyroid function. The present study was able to include urinary iodine concentration, gender, age, smoking and race as variables in the analysis due to their known potential to be confounders when studying

thyroid function. Additionally, education, physical activity level, daily caloric intake and poverty status were included because they are known risk factors for BMI. While other known risk factors of thyroid function are known, these are not included in the study due to the unavailability of data.

Iodine

Studies have shown that iodine is a vital component of thyroid hormone synthesis, and therefore is of critical importance in thyroid function^[12]. Without the proper balance of iodine intake, thyroid function suffers greatly. Iodine is needed in thyroid hormone synthesis to turn thyroglobulin into thyroxine or triiodothyronine, T4 or T3, respectively. Too little iodine will cause the thyroid gland to produce less hormone, while too much will lead to an excess of hormone. Iodine deficiency is still a big problem across the world^[13]. The effects range from different size goiters to the very serious complication called cretinism. Since the 1990's, the U.S. has been considered iodine sufficient. However, excess iodine intake is of concern because it may lead to thyroid dysfunction. The effects of excess iodine intake range from hyperthyroidism to hypothyroidism and chronic autoimmune thyroiditis (CAT)^[14]. Research shows that in populations where there is iodine deficiency or excess, overt hyperthyroidism and hypothyroidism exist^[15]. For example, in areas of iodine deficiency such as in Aalborg, Denmark where there is a moderate iodine deficiency, and in Copenhagen, Denmark where there is a mild iodine deficiency,^[16] Pedersen et al. (2002), found that incidence rates of overt hyperthyroidism were much higher in Aalborg than those in Copenhagen. The reverse was also true, where more cases of overt hypothyroidism existed in Copenhagen than in Aalborg^[16]. Some studies have found iodine intake to be directly related to serum TSH levels^[17,14,18]. Laurberg et al. (1998),^[19] found

that serum TSH levels were low in Jutland, Denmark, an area known to have low iodine intake levels, whereas Iceland, an area known to have high iodine intake levels had high TSH values. Similarly, ^[20] Vejbjerg et al. (2009) also found higher median serum TSH levels after iodine intake increased in the population due to mandatory salt iodization.

While iodine deficiency causes more damage than iodine excess, both extremes are detrimental to a population's health. In studies of thyroid hormones and obesity, iodine may be a key component in understanding this relationship.

Gender, Age and Race

It has been well documented that a difference in thyroid function/dysfunction exists between males and females^[21].

noted that women were different from men in terms of thyroid function due to the effect of pregnancy and estrogen on thyroid function, as well as their susceptibility to autoimmune thyroid disease. Higher prevalence rates of thyroid disease have been found in females, especially in premenopausal women ^[22]. In their study using data from the National Health and Nutrition Examination Survey III (NHANES III: 1988-1994), Hollowell et al. (2002) ^[23] reported a significantly higher percent of females with TSH levels > 11.45 mIU/liter than males in both the total population studied and in the subgroup of disease free individuals. Additionally, all populations showed that there was a higher percentage of females with TSH levels < 0.4 mIU/liter, as well ²³(Hollowell et al., 2002). While the present study included gender as a covariate in the analysis, the variable was not found to be an effect modifier of TSH levels and BMI. This may be because the population being studied had normal TSH levels, where differences between the genders have been found when looking at thyroid dysfunction. This may also be due to the fact that the present study evaluated adults between 20 and 49

years of age, which, for the most part may not include a high percent of post-menopausal women^[24]. Shon, Jung, Kim, & Lee (2008) also found a difference between males and females when looking at TSH levels and obesity. Their findings were in agreement with other studies that showed higher levels of TSH in euthyroid women compared to euthyroid men. Age has also been shown to affect thyroid function. As people age, thyroid hormone synthesis is impacted. While studies like the one done by Hollowell et al. (2002) ^[23] have shown that TSH levels increase with age when iodine intake is sufficient in a population, findings are contradicting. For example, Laurberg et al. (2006)¹⁹ found that in the first cohort, TSH levels decreased with age, but the association was not seen when participants with thyroid abnormalities were excluded. A third characteristic that has been documented as a modifier of TSH levels is race. Studies have shown that different racial groups show different levels of serum TSH. Hollowell et al. (2002) ^[23] found that more whites than blacks had TSH levels above the normal range, while more blacks than whites showed TSH levels below the normal range. A significant association between race and TSH levels was found among 809 patients (with TSH levels between 0-5mU/L) in a study conducted in 1991, after adjusting for age, sex and chronic medical problems and/or medication use^[25] (Schechtman, Kallenberg, Hirsch, & Shumacher, 1991). Findings showed that whites were more likely to have higher levels of TSH as compared to blacks. The study also pointed out that it was in agreement with other studies that had been previously published. Moreover, a current study done among a population in Brazil demonstrated that prevalence of hypothyroidism was higher among white participants as compared to mulatto and black participants ^[26](Sichieri et al., 2007). Results showed that on average, TSH values were 22% lower for blacks than for whites (finding was

statistically significant with a $p=001$). The current study found that the relationship between serum TSH levels and BMI was different for different racial categories.

Smoking

The literature points to a pattern showing TSH levels being lower in smokers compared to non-smokers^[27]. Additionally, smoking cessation has been associated with an increase in weight. Furthermore, smoking could interfere with iodine intake by way of thiocyanate inhibition of the NIS or sodium/iodide symporter, which is the protein responsible for iodide transport by the thyroid (this topic is beyond the scope of the present study)^{19,2} (Laurberg et al., 2006; Miot et al., 2010). Smoking status is therefore seen as an effect modifier or confounder of the relationship between BMI and TSH levels^[21,28,29]. Thus, some studies have stratified the data by smoking status, have only included those who are non-smokers or have adjusted for smoking status in their analysis. The study by Nyren et al. (2006)²⁹ found that in non-smokers, BMI and TSH levels were positively associated. Furthermore, the follow up cohort also showed that among non-smokers only, an association existed between a change in TSH and a change in BMI. Investigators of this study suggest that smoking may mask the relationship between BMI and TSH levels. While Makepeace et al. (2008)^[30] did not find a relationship between TSH and BMI, the study did find that TSH levels were significantly lower in current smokers than non-smokers or former smokers.

Obesity

The obesity epidemic we are facing as a nation is alarming. Currently, estimates show that about 68% of adults in the United States are overweight and obese^[31]. The problems related with obesity have been well documented in numerous studies. Many studies have looked at the impact of environmental factors on weight, while others have looked at the genetic aspect

and psychological and/or behavioral aspects related to weight. A third focus of research in obesity is the hormonal aspect that contributes to body weight. The area of hormonal influence, specifically thyroid hormones, on weight is the focus of the current study.

Thyroid Function and Weight

There are different ways that thyroid hormones have been said to affect weight. First, they are thought of as hormones that contribute to energy expenditure and thermogenesis. Additionally, some researchers have suggested that increased levels of TSH are an adaptive mechanism due to increase adiposity^[32]. Others have suggested that being obese may lead to thyroid hormone resistance in peripheral metabolism. These mechanisms are beyond the scope of this study; however a brief explanation is provided regarding the major role of thyroid hormones in resting energy expenditure (REE). Thyroid hormones are critical to energy expenditure and thermogenesis. Triiodothyronine (T3) and thyroxine (T4) deiodinized to T3 are both used by cells to increase the metabolic rate known as adaptive thermogenesis. This complex mechanism—which has been documented by others—allows for humans and other mammals to increase the metabolic rate, thus creating more heat to maintain proper energy homeostasis^[33]. In human adults, skeletal muscle provides a place for thermogenesis to occur. Thyroid hormones have been found to play an important role in energy expenditure in these cells. They are part of complex pathways and processes that lead to increasing ATP and energy expenditure. A decrease in thyroid hormone would therefore lead to slower metabolic rate. This is seen in the condition known as hypothyroidism. The opposite is true for people with the condition known as hyperthyroidism, where metabolic rate increases and loss of body fat is seen. Al-Adsani, Hoffer, & Silva (1997)^[34] found significant changes in resting energy

expenditure (REE) when there were small changes in T4 dosage of patients who were on chronic thyroid hormone replacement. They used TSH as the indicator for thyroid status since TSH “reflects an end effect of thyroid hormone” and showed how REE decreased as TSH levels increased. The investigators noted that this kind of change found in REE could account for weight gain over a 5-10 year time span. Significant findings between REE and TSH levels further confirm that TSH levels are an important factor to consider when looking at weight and obesity in our population. This is of high importance considering that these changes in REE are seen when changes happen within the normal range of TSH levels. Thyroid hormones have been found to affect weight, even when hormone levels are within the normal range. Knudsen et al. (2005)^[35] found a significant positive association between TSH levels and BMI. Other investigators have also found positive associations between TSH levels and obesity in their studies. For example, a recent study among euthyroid individuals showed that TSH levels were significantly higher among obese

participants compared to lean participants^[36] (Nannipieri et al., 2009). Bastemir et al. (2007)^[37] also found that the degree of obesity as measured by BMI was associated with higher TSH levels. While Rotondi et al. (2009)^[38] did not find a significant association between BMI and TSH in euthyroid morbidly obese patients compared to euthyroid normal weight (henceforth “normoweight”) patients, findings did show that TSH levels were higher in the morbidly obese group relative to the normoweight group. Furthermore, Iacobellis et al. (2005) also found that in euthyroid individuals, TSH levels and BMI were positively correlated. Additionally, the study also found that after adjusting for BMI, TSH levels and Leptin levels were also correlated. They suggested that TSH could therefore be an early marker for energy balance in individuals with

severe obesity^[39] (Iacobellis et al., 2005). Studies have also found significant associations between thyroid hormones and other obesity-related measures such as waist circumference and weight in kilograms. De Pergola et al. (2007)²⁸ found that TSH levels were positively correlated with waist circumference in a study of 201 overweight and obese women who were euthyroid. Interestingly, this study also found TSH to be negatively correlated with age, something that other studies have found to be a positive association²¹ (Blount et al., 2006). Similarly, Fox et al. (2008)^[40] also found a positive association between TSH and weight in kilograms in a cohort of euthyroid individuals. The study was able to assess the association over time given that it was a prospective design. Findings showed that over time, when TSH levels increased, weight also increased^[40] (Fox et al., 2008). In the same manner, the study by Sari, Balci, Altunbas, & Karayalcin (2003)^[41] also showed an association between TSH and weight. As with the study by Fox et al. (2008)^[40], the prospective design of the study by Sari et al. (2003)^[41] allowed for evaluation of change over time. The study found that those who lost more than 10 percent body weight showed lowered levels of TSH at follow up. A few studies did result in no association between TSH levels and BMI^[30,42,24] (Makepeace et al., 2008; Manji et al., 2006; Shon et al., 2008). However, the study by Makepeace et al. (2008) did find that levels of TSH were lower among smokers. Their findings on lower TSH levels among smokers were consistent with the literature. The study by^[42] Manji et al. (2006) had a sample size of 401 euthyroid men and women; however, a potential limitation of the study was that the participants had been referred to the clinic for thyroid nodules or goiter. The investigators classified them as euthyroid because their serum TSH levels were within the normal range. Nevertheless, most other studies exclude subjects with confirmed goiters or thyroid nodules when looking at

euthyroid individuals, since these usually occur when thyroid dysfunction is present or iodine levels are not sufficient. Lastly, the study by Shon et al. (2008) did acknowledge that their findings with regards to TSH and BMI did not agree with findings of other studies. However, they found that TSH levels were higher in euthyroid women than in men, which is consistent with the literature. Despite the scarcity of studies about thyroid function and obesity in euthyroid individuals, the recent literature does point to a pattern that suggests thyroid hormones, such as TSH levels within the normal range, affect, to an extent, the weight status of individuals. Investigators need to study this area more closely to gain better understanding of the role these hormones play even when individuals are deemed healthy. While many more studies are needed to confirm this—especially prospective designs—the literature thus far points in this direction. The present study adds to the body of knowledge in the topic and uses data from a large study population that represents individuals across the nation. As more studies are conducted in the area of thyroid hormones and obesity in euthyroid individuals, there is hope to fully understand another potential facet in the complex chronic disease that is obesity. The knowledge gained will better prepare public health officials and other health providers in dealing with a growing epidemic in the United States as well as other parts of the world.

Thyroid Stimulating Hormone (TSH)

Thyroid stimulating hormone (TSH) is the most sensitive and specific test for the investigation and management of primary thyroid dysfunction

Patients with thyrotoxicosis usually have a TSH value < 0.1 mU/L

- Thyroid antibodies are indicated in cases of hypothyroidism (TSH > 5 mU/L) due to

suspected autoimmune thyroid disease. Serum antibody (anti-TPO) testing should only be performed once for the diagnosis. Serial testing has no clinical utility. Obesity is a growing problem, not only in the United States, but globally. Obesity has increased over the last few decades and currently, the Centers for Disease Control and Prevention (CDC) estimates that about 68% of the US adult population is considered overweight or obese ^[31](Flegal, Carroll, Ogden, & Curtin, 2010). Currently, efforts to understand the multi-faceted problem are of top priority in public health. Many factors have been found to affect a person's weight, including lifestyle choices like nutritional behaviour and physical activity, as well as genetics and environmental factors—for example, where someone lives and food availability in the community. Likewise, risk factors associated with being overweight or obese have also been studied. Obesity increases the risk for cardiovascular disease, diabetes, cancers and metabolic syndrome, to name a few. It reduces the quality of life as well as overall life expectancy, and is responsible for a large portion of healthcare costs in America. It is important to understand all the risk factors that contribute to obesity, as well as understand all the co-morbidities that arise with being overweight and obese since the majority of the population suffers from the disease. The study of hormones, especially thyroid hormones and their association with obesity has been well documented in individuals with thyroid disorders. People who have thyroid dysfunction have been found to also suffer from weight problems ^[22](Bunevicius, Peceliuniene, Mickuviene, Girdler, & Bunevicius, 2008). Overt hypothyroidism is known to be related to weight gain, while overt hyperthyroidism leads to weight loss. Studies on euthyroid, or people with normal thyroid function, are scarce. However, most studies that have been done on euthyroid individuals have shown that there is a

significant association between BMI and thyroid function. More studies are needed to fully understand the extent of the association and translate the findings into practical use in the clinical setting. The regulation of thyroid hormones is a complex process. In a person with healthy thyroid function, the presence of excess or lack of iodine, for example, leads the thyroid gland to make and release more or less of its hormones. The level of hormone in circulation signals the suppression or the synthesis of other hormones like TRH and TSH that in turn help maintain thyroid hormone balance.

Since thyroid hormones are not water-soluble, they bind to proteins when they are released from the thyroid gland. The majority travels in the bloodstream bound to the proteins thyroxin-binding globulin (TBG), thyroxine binding prealbumin (TBPA) and albumin. Free thyroxine, fT4, is the small amount (about 0.03%) of thyroid hormone that is not bound to a protein (Greer, 1990)³. Similarly, fT3 is the triiodothyronine that is not bound to a protein. While there is more thyroxine in the thyroid gland and circulating in the body, triiodothyronine (T3) is the bioactive form of the two. In addition to being released from the thyroid gland, T3 and 3, 3', 5'-triiodothyronine (rT3) are also formed from thyroxine locally in the cells by deiodination. Greer (1990)³ states that in individuals with healthy thyroid function 20% of T3 is produced in the thyroid gland,

while 80% is formed from thyroxine peripherally (p. 236).

Thyroid Function Tests: Diagnoses and Monitoring of Thyroid Function Disorders in Adults

Scope

This guideline applies to:

- The detection of thyroid dysfunction in adults (individuals 19 years of age and over)
- monitoring adult patients treated for thyroid function disorders.

Diagnostic Codes: 244 (Hypothyroidism), 242 (Hyperthyroidism)

Prevention and Risk Factors

Routine thyroid function testing is not recommended in asymptomatic adults. However, testing may be indicated when non-specific signs and symptoms are present in patients at risk for thyroid disease.

Risk factors for thyroid disease ^[43]

- personal history of thyroid disease
- strong family history of thyroid disease
- diagnosis of autoimmune disease
- past history of neck irradiation
- drug therapies such as lithium and amiodarone
- women over age 50
- elderly patients
- women 6 weeks to 6 months post-partum

Diagnosis/Investigation | Signs/Symptoms ^[43-48]

Hypothyroidism	Hyperthyroidism
Weight gain	Weight loss
Hair loss	Hair loss
Lethargy	Palpitations / Tachycardia / Atrial fibrillation
Menstrual irregularities (menorrhagia)	Menstrual irregularities (amenorrhea/oligomenorrhea)
Cognitive impairment	Widened pulse pressure
Depression	Nervousness and tremor
Constipation	Muscular weakness
Goitre	Goitre
Dry skin	Heat intolerance, diaphoresis, clammy hands
Cold intolerance	Hypertension

Tests

Thyroid Stimulating Hormone (TSH)

Measurement of TSH has become the principal test for the evaluation of thyroid function in most circumstances^[44]. **A TSH value within the reference interval excludes majority of cases of primary overt thyroid disease^[45].** If TSH is abnormal, confirm the diagnosis with free T4 (fT4). Where risk factors exist, consider free T3 (fT3) when fT4 is normal and thyrotoxicosis is suspected. Laboratories in BC usually retain specimens for 5 to 7 days in case add-on testing is required. See Tables 1 and 2 for potential causes.

Causes of high thyroid-stimulating hormone (TSH)

1. Hypothyroidism
2. Recovery from severe illness
3. Pituitary excess due to pituitary tumours causing secondary hyperthyroidism (very rare)

Causes of low thyroid-stimulating hormone (TSH)

1. Hyperthyroid State

A. Both T3 and T4 elevated

- i) Graves' disease
- ii) Toxic multinodular goiter

B. Only T3 elevated with normal T4

- i) T3 toxicosis (e.g. Autonomous nodule)
- ii) Exogenous T3 ingestions (liothyronine)

C. Only T4 elevated with normal T3

- i) Hyperthyroidism patient with nausea, vomiting and starvation causing decreased conversion of T4 to T3.

2. Hypothyroid State

- i) Pituitary or hypothalamic disease (both T4 and T3 low)

3. Euthyroid State

- i) Sick euthyroid (both T3, T4 low, rT3* elevated)
- ii) Drugs such as glucocorticoids, octreotide, and dopamine

Free Thyroxine (fT4) and Free Triiodothyronine (fT3)

Measurements of fT4 and fT3 have replaced measurements of total T4 and total T3 levels. Laboratories are permitted to substitute free hormone assays when total T3 or T4 have been ordered. **Measurement of fT3 in patients with suspected hyperthyroidism is rarely indicated.** This is reserved for situations where hyperthyroidism is suspected clinically and TSH is suppressed, but the fT4 is not elevated^[47]. **Measurement of fT3 is not indicated in hypothyroidism.**

More frequent measurement of thyroid function may be useful when there is a discrepancy between the results of the initial thyroid function test and clinical findings. In most cases, repeating the same test is less useful than ordering a different test (e.g. if a TSH result does not appear to correlate with the patient's clinical status, it may be more appropriate to follow with a fT4 measurement). Consultation with a laboratory physician is appropriate when the test results do not correlate with clinical findings.

MONITORING

Hypothyroidism: Since TSH values change slowly^[48], frequent repeat testing is unnecessary. TSH may be repeated after at least 6-12 weeks following a change in thyroid hormone replacement dose or a change in a patient's clinical status. Once the TSH has normalized with treatment, it should be checked annually unless clinically indicated. This would confirm adequacy of treatment dose and compliance with therapy.

Hyperthyroidism: To monitor patients on treatment for Graves' disease or other causes of hyperthyroidism, allow at least three months before repeating TSH levels since pituitary secretion of TSH may be suppressed for prolonged periods following hyperthyroidism. If a biochemical measurement of thyroid status is required during this time period, fT4 is preferred^[43,48].

Hypothalamic or pituitary disease: TSH is only useful as a measure of thyroid disease if the hypothalamic-pituitary-thyroid axis is intact. When pituitary or hypothalamic disease is suspected, fT4 measurement is preferred to assess adequacy of thyroid replacement therapy.

Subclinical Thyroid Disease

Typically patients with subclinical thyroid diseases are asymptomatic, but have a TSH outside the reference interval and a free thyroxine within the reference interval.

In **subclinical hypothyroidism**, the TSH level may be borderline elevated in the presence of normal levels of fT4^[49]. Treatment for subclinical hypothyroidism is recommended when:

- TSH greater than 10mU/L;
- TSH is above the upper reference interval limit, but ≤ 10 mU/L and any of the following are present:
 - elevated thyroid peroxidase (TPO) antibodies
 - goitre
 - strong family history of autoimmune disease
 - pregnancy (see pregnancy section below)

The prevalence of **subclinical hypothyroidism** in the general population is between 4% and 8%^[50]. Every year, 2% to 5% of patients with subclinical hypothyroidism progress to overt hypothyroidism^[51]. In recent reviews, thyroid hormone therapy for subclinical hypothyroidism did not result in improved survival or quality of life^[51,52]. Monitoring of TSH in untreated patients at 12 month intervals is indicated. Routine screening for subclinical hypothyroidism is not recommended. Clinicians should have a low threshold for obtaining a serum TSH in women who have vague suggestive symptoms, who are pregnant or anticipating becoming pregnant, or who have a strong family history of autoimmune thyroid disease.

In subclinical hyperthyroidism, the TSH level may be borderline suppressed in the presence of normal levels of fT4^[53]. Subclinical hyperthyroidism is less common, with a prevalence of 0.6% -1.1%. In elderly patients with TSH < 0.1 mU/L, the relative risk for atrial fibrillation increases threefold^[54-56]. Post-menopausal women with subclinical hyperthyroidism may have an increased rate of bone loss. In the elderly there is a higher cardiovascular risk and an increased risk of fracture. Patients with atrial fibrillation and osteoporosis should be screened for hyperthyroidism. Treatment of subclinical hyperthyroidism should be considered in the elderly^[57]. Patients with subclinical hyperthyroidism due to multi-nodular goitre or functioning adenoma are unlikely to normalize and are therefore more likely to benefit from treatment. Follow up testing with TSH and fT4 6-12 months later is recommended^[58].

Thyroid Disease in Pregnancy

a) Pre-pregnancy and early pregnancy: TSH screening for hypothyroidism is indicated in women who are planning pregnancy or are in early pregnancy if they have a goitre or strong family history of thyroid disease^[59]. If hypothyroidism has been diagnosed before pregnancy,^[60] treatment should be adjusted to achieve a TSH level not higher than 2.5 mU/L before pregnancy and T4 re-measured within 30-40 days^[60].

b) Pregnancy: A high index of suspicion for thyroid disease during pregnancy is warranted. Research data support a possible connection between untreated maternal hypothyroidism and neuropsychological impairment in the offspring^[60-62]. TSH may be suppressed as a normal finding within the first trimester of pregnancy. A normal fT4 generally excludes hyperthyroidism^[43]. Thyroxine replacement dosage may increase by 25-50% during pregnancy, particularly in the first trimester. In patients on thyroxine replacement,

measurement of TSH at least during each trimester is recommended^[63]. It is recommended that thyroxine dose be adjusted to keep TSH between 0.5-2.5 mU/L in the first trimester and 0.5- 3.0 mU/L in the second and third trimesters^[62]. Hyperthyroid patients should have specialist consultation when contemplating pregnancy or during pregnancy.

c) Post pregnancy: After delivery, most hypothyroid women need a decrease in the thyroxine dosage they received during pregnancy^[60]. Post-partum thyroiditis (PPT) may occur in 5-10% of women, but there are insufficient data to recommend screening of all women. PPT is an auto-immune disorder and the presence of anti-TPO antibodies increases the risk of disease^[64]. Women that are TPO antibody positive should have a TSH performed at 3 and 6 months post-partum^[60]. PPT is often mild and transient. The disorder may present as hyperthyroidism followed by hypothyroidism and subsequent recovery of normal thyroid function. Some women may present with hypothyroidism without a hyperthyroid interval and may remain hypothyroid. There is an increased incidence of Graves' disease in the post-partum interval and not all hyperthyroidism is post-partum thyroiditis. There is a significant risk for recurrent post-partum thyroiditis in subsequent pregnancies. Women with a history of PPT have an increased risk of developing permanent primary hypothyroidism in 5-10 years post PPT episode. Evidence suggests an annual^[60] TSH in these patients.

BACKGROUND

According to the Canadian Task Force on the Periodic Health Examination community surveys have reported prevalence rates of overt hyperthyroidism of less than 1.9%, the rates being comparable in elderly populations^[64,65]. If "sub-clinical" cases are included, the prevalence rate can be as high as 2.7%. In a well conducted

community study, the annual incidence rate of overt hyperthyroidism was estimated to be 2 to 3 per 1,000 women. The prevalence of hypothyroidism is three times higher among women than men. The prevalence in an unselected community population of young, middle aged and elderly individuals is about 1.4 percent and the estimated annual incidence rate is one to two per 1,000 women. Surveys of geriatric populations have yielded estimated prevalence rates for overt hypothyroidism of 0.2 percent to 3 percent^[64]. The presentation of symptoms in the elderly may be atypical or absent^[65]. The prevalence of subclinical hypothyroidism is estimated to be between 4.0–8.5% of the adult US population without known thyroid disease, and the prevalence increases with age^[66]. Up to 20% of women over the age of 60 are estimated to have subclinical hypothyroidism. Caucasians are more likely to have subclinical hypothyroidism than non-Caucasians. The risk is highest in those with type I diabetes mellitus, a family history of thyroid disease or head/neck cancers treated with external beam radiation. Other risk factors include previous radioactive iodine treatment or thyroid surgery. Interestingly, about 20% of patients on thyroid medications are both over replaced and underreplaced. Because of the high incidence of thyroid disease, The American Thyroid Association recommends measuring thyroid function on all adults beginning at age 35 years and every 5 years thereafter noting that more frequent screening may be appropriate in high risk groups^[67]. The treatment of subclinical hypothyroidism has been controversial^[68,69] but more recent data suggest there are increased risks of ischemic heart disease in untreated patients and that a more aggressive approach to treatment would be appropriate^[70]. In contrast, subclinical hyperthyroidism has more well understood risks of atrial fibrillation and flutter and so should be more aggressively treated^[71,72].

Thyroid disease in pregnancy requires special attention and follow up. Of particular concern is the effect of hypothyroidism on neuropsychological development of the child^[73]. Thus, many women on thyroxine replacement require as much as a 50% increase in dose during pregnancy. Some authorities have suggested immediate increases in dose upon diagnosing pregnancy to avoid sequelae of hypothyroidism^[74].

Several drugs in common use have significant effects on the thyroid. Amiodarone, by virtue of its containing two iodine atoms, may induce iodide like effects of hypo- or hyperthyroidism,

with abnormalities being more common if there is underlying autoimmune thyroid disease. Hypothyroidism is more common than hyperthyroidism^[75,76]. Lithium can cause goiter, hypothyroidism, and possibly hyperthyroidism, with hypothyroidism being the most common sequela^[77]. Interferon alfa-2b may cause hyper- or hypothyroidism^[78].

In the treatment of thyroid cancer, suppression of TSH (a growth factor for normal and malignant thyroid cells) results in approximately a 40% reduction in recurrence rates of thyroid cancer^[79]. Therefore the treatment target is an undetectable TSH.

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