

Clinician's Review of Thyroid and Parathyroid Disease

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Abstract

Thyroid and parathyroid disorders are common but timely diagnosis can be difficult due to the subclinical nature of symptoms in the early stages of disease. Clinicians face many challenges when treating previously unrecognized thyroid and parathyroid disease as delays in treatment initiation often come at the expense of other organ systems being affected. Prompt recognition and treatment of thyroid and parathyroid disorders can have a beneficial impact on health outcomes and can help reduce the economic burden associated with the treatment of advanced disease. This review will discuss the key diagnostic considerations, clinical manifestations and treatment of primary hypothyroidism, hyperthyroidism, and primary hyperparathyroidism.

Abbreviations: ATA: American Thyroid Association; BMD: Bone Mineral Density; Ca/Cr: Calcium Clearance to Creatinine Clearance ratio; CASR: Calcium Sensing Receptor; CT: Computed Tomography; FHH: Familial Hypocalciuric Hypocalcemia; LT3: Liothyronine; LT4: Levothyroxine; MEN: Multiple Endocrine Neoplasia; MIBI-SPECT: Methoxyisobutyl Isonitrile Single-Photon Emission Computed Tomography; PHPT: Primary Hyperparathyroidism; PTH: Parathyroid Hormone; PTHrp: Parathyroid Hormone Related Peptide; PZL: Poly-Zinc-Liothyronine; RAI: Radioactive Iodine; T3: Triiodothyronine; T4: Thyroxine; TgAb: Thyroglobulin Antibody; TKI: Tyrosine Kinase Inhibitor; TPOAb: Thyroid Peroxidase Antibody; TSH: Thyroid Stimulating Hormone; TSHRAb: Thyroid Stimulating Hormone Receptor Antibodies; TRH: Thyrotropin Releasing Hormone

Thyroid Disorders

Introduction

The presentation of thyroid disease is on a spectrum with clinical presentations and disease severity ranging from subclinical to critical. The principal function of the thyroid gland is to produce T₃ (triiodothyronine) and T₄ (thyroxine). The hypothalamus and pituitary glands release thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) respectively, and this stimulates the release of T₃ and T₄ directly from the thyroid gland. The hypothalamic-pituitary-thyroid axis is regulated by negative feedback. Thus, sufficient production or overproduction of T₃ and T₄ lead to reduced secretion of TRH and TSH. Thyroid hormones play a role in the regulation of metabolism, body temperature, digestion, cognition, muscle strength and cardiac contractility. Primary thyroid disease develops when there is a deficiency or overabundance of T₃ and/or T₄. Prompt recognition and treatment of thyroid disease can help mitigate metabolic disturbances and prevent disease in target organs.

Causes of hypothyroidism

Hypothyroidism can be the direct result of exposure to medications and/or treatments for other disease states such as cancer or hyperthyroidism. Surgical removal of the thyroid gland and radioactive iodine use for the treatment of hyperthyroidism, nodular thyroid disease and thyroid cancer can result in the development of hypothyroidism. External beam radiation treatments for head and neck cancers and lymphoma can lead to the subsequent development of hypothyroidism due to the impact radiation exposure has on the viability of thyroid follicular cells. With increased use of tyrosine kinase inhibitors (TKI) for the treatment of solid tumors, we are now seeing hypothyroidism develop because of the effects this class can have on glandular vascularity and the upregulation of type 3 deiodinase [1-2]. Immune modulatory effects of this drug class have also been attributed to the development of hypothyroidism. The hypothyroidism that develops with TKI use can be preceded by a hyperthyroid state in which typically transient and self-limiting. There is associated inflammation of the thyroid gland and this can lead to

eventual failure of the gland to produce sufficient T4 and T3.

Iodine deficiency remains the most common cause of hypothyroidism worldwide and in iodine replete regions on the world, chronic autoimmune thyroiditis (Hashimoto's thyroiditis) is the most common cause of hypothyroidism [3]. Autoimmune thyroid diseases (including Hashimoto's thyroiditis) are more common in women than in men and are often seen in the presence of other autoimmune conditions such as type 1 diabetes, systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, and Addison's disease. Individuals with a family history of autoimmune disease also have a higher prevalence of autoimmune thyroid disease [4]. Elevated titers of anti-thyroid antibodies: anti-thyroglobulin antibodies (TgAb), antimicrosomal/anti-thyroid peroxidase antibodies (TPOAb), and TSH receptor antibodies (TSHRAb) are indicative of autoimmune thyroid disease [5]. Hashimoto's is typically associated with elevated titers of TPOAb and/or TgAb and the spontaneous disappearance of these antibody levels is rare.

Patients can remain biochemically euthyroid even in the presence of elevated antibody titers. Those who develop subclinical or overt hypothyroidism require clinical evaluation to determine if thyroid hormone replacement therapy is indicated.

Clinical features and laboratory findings associated with hypothyroidism

Hypothyroidism can be subclinical or overt. Subclinical hypothyroidism is defined by a TSH level above the normal range of reference with a normal T4 level. Overt hypothyroidism occurs when the TSH level is elevated, typically above 10 mIU/L in the presence of a low T4 level [5]. The clinical presentation of hypothyroidism can range from asymptomatic-subclinical disease to critical presentations in which patients are obtunded or comatose. Typical symptoms associated with primary hypothyroidism are weight gain, cold intolerance, fatigue, depressed mood, fluid retention, constipation, skin/hair/nail changes. The metabolic consequences of thyroid disease include dyslipidemia, reduced basal metabolic rate and increased creatine kinase production. Symptoms and metabolic disturbances can take several weeks or months to manifest and they are not always present at the time of diagnosis. Some patients have clinical features that more closely mimic hyperthyroidism despite being biochemically hypothyroid. The clinical presentation of an individual with hypothyroidism oftentimes correlates with biochemical severity. However, there may be discordance between clinical presentation and severity of hypothyroidism. For example, someone with a TSH level of 100 mIU/L could present in myxedema coma or may present with minimal evidence of symptoms. Pre-existing

underlying health conditions, age and the duration of undiagnosed/untreated thyroid disease all play a role in the clinical presentation of hypothyroidism.

Treatment of hypothyroidism

The most recent guidelines published by the American Thyroid Association (ATA) in 2014, indicate TSH is the most reliable measure of the adequacy or inadequacy of thyroid hormone replacement therapy [6]. The ATA recommends using a TSH target range of 0.4-4.0 mIU/L [6]. There is consensus that treatment of primary hypothyroidism is indicated when the TSH level exceeds 10 mIU/L [7]. However, there remains a paucity of data via randomized controlled trials to support the benefit of treating primary hypothyroidism when the TSH level is 4.5-10 mIU/L. A meta-analysis performed by Rodondi et al. showed there is a clinically significant increase in cardiovascular morbidity and mortality when the TSH level is >10mIU/L [8]. Other studies have shown that for individuals with underlying cardiovascular disease or risk factors for atherosclerotic cardiovascular disease, there may be benefit in treatment when the threshold for treatment is adjusted to a TSH level of 4.5-10 mIU/L [9,10]. Studies have confirmed beneficial effects on cholesterol levels, endothelial function, and intima media thickness with treatment [11-13].

T4 therapy is the mainstay for treatment of primary hypothyroidism. T4 is more abundant than T3 peripherally and T3 is more biologically active. T4 is converted to T3 by deiodinase enzymes in the body. Some experts believe there are patients who do not efficiently convert T4 to T3 and these individuals may benefit from treatment with combination T4/T3 replacement therapy. Combination therapy can be achieved by adding a pure T3 preparation to T4 therapy or through the use of desiccated thyroid hormone preparations. Desiccated preparations contain both T4 and T3 but tend to be T3 predominant. The ratio of T4 to T3 is inconsistent and this can pose challenges when making therapeutic adjustments based on lab values. Combination therapy may be the appropriate choice for selected patients but is not the gold-standard due to lack of reproducible evidence showing benefits for symptom and disease management. The decision to commence combination replacement should take factors such as age and cardiac risk factors into consideration. Consultation with an endocrinologist is advised when structural thyroid disease such as nodules or goiter are present, when other endocrinopathies (such as pituitary or adrenal disease) are present and for patients who fail to achieve and maintain a euthyroid state or when the etiology of hypothyroidism is iatrogenic [7].

Causes of hyperthyroidism

There are multiple conditions that can cause hyperthyroidism. The most common cause is an

autoimmune condition called Graves' disease. This condition results when TSH receptor antibodies (TSHRab) stimulate the release of T4 and T3 from the thyroid gland [14]. Other causes of hyperthyroidism are toxic adenoma, thyroiditis, germ cell tumors and iodine loads. The latter is underrecognized but important to highlight. The contrast used for angiography and computed tomography (CT) is iodine-rich and can provoke the onset of hyperthyroidism in susceptible individuals. Similarly, iodine rich drugs such as amiodarone can cause hyperthyroidism. The thyroid gland uses the iodine in these iodine-rich preparations for substrate and this drives hormone synthesis. Treatment recommendations for hyperthyroidism differ based on the underlying etiology – this will soon be discussed in more detail.

Clinical features and laboratory findings associated with hyperthyroidism

Hyperthyroidism can be subclinical or overt and the

clinical presentation is on a spectrum with severity ranging from asymptomatic disease to thyroid storm. In subclinical hyperthyroidism, the TSH level is below the reference range but the T4 and T3 levels remain normal. Overt hyperthyroidism denotes a low TSH level and elevated T4 and/or T3 levels and often presents with some combination of gastrointestinal, metabolic, cardiovascular, musculoskeletal, ophthalmologic, and neuropsychiatric symptomatology.

Thyroid storm is a life-threatening form of hyperthyroidism which requires medical treatment in the acute-care setting. Burch and Wartofsky developed a thyroid storm scoring scale that is used to help differentiate thyrotoxicosis from thyroid storm [15]. The scoring system assigns point values based on the severity of clinical findings in the following categories: thermoregulatory dysfunction, central nervous system effects, gastrointestinal-hepatic dysfunction, cardiovascular dysfunction, heart failure and precipitant history (Table 1). A score of 45 points or higher

Table 1: Thyroid Storm Diagnostic Criteria [15].

<p>Temperature (°F/°C)</p> <p>99 to 99.9 / 37.2 to 37.7 5 pts</p> <p>100 to 100.9 / 37.8 to 38.2 10 pts</p> <p>101 to 101.9 / 38.3 to 38.8 15 pts</p> <p>102 to 102.9 / 38.9 to 39.4 20 pts</p> <p>103 to 103.9 / 39.4 to 39.9 25 pts</p> <p>≥104.0 / ≥40.0 30 pts</p>	<p>Cardiovascular Effects</p> <p>Tachycardia</p> <p>99 to 109 5 pts</p> <p>110 to 119 10 pts</p> <p>120 to 129 15 pts</p> <p>130 to 139 20 pts</p> <p>≥140 25 pts</p> <p>Atrial fibrillation 10 pts</p>
<p>Central Nervous System Effects</p> <p>Agitation 10 pts</p> <p>Delirium 20 pts</p> <p>Psychosis 20 pts</p> <p>Extreme lethargy 20 pts</p> <p>Seizure 30 pts</p> <p>Coma 30 pts</p>	<p>Heart Failure</p> <p>Pedal edema 5 pts</p> <p>Bibasilar rales 10 pts</p> <p>Pulmonary edema 15 pts</p>
<p>Gastrointestinal-Hepatic Effects</p> <p>Diarrhea 10 pts</p> <p>Nausea/Vomiting 10 pts</p> <p>Abdominal Pain 10 pts</p> <p>Unexplained Jaundice 20 pts</p>	<p>Precipitant history</p> <p>Negative 0 pts</p> <p>Positive 10 pts</p>

is suggestive of thyroid storm, a score of 25 to 44 supports the diagnosis, and a score of less than 25 makes thyroid storm less likely [15].

Treatment of hyperthyroidism

The most recent guidelines published by the ATA in 2016, for the management of hyperthyroidism recommend the underlying etiology of hyperthyroidism be determined prior to commencing treatment [16]. The treatment approach for hyperthyroidism varies based on the underlying etiology. Thionamides can be used to treat hyperthyroidism caused by Graves' disease and most other causes of hyperthyroidism but radioactive iodine therapy is the gold standard for the treatment of Graves' and toxic adenoma(s). Thyroid scans performed with I-123, I-131 or Technetium are helpful in defining the degree of hyperthyroidism and determining the underlying etiology of hyperthyroidism. Thyroid uptake scans in patient's with thyroiditis, classically have very low or absent uptake. Thus, radioactive iodine (RAI) therapy is not indicated. Supportive measures are recommended. Most cases of thyroiditis are self-limiting, but some will progress to overt hypothyroidism and require thyroid hormone replacement therapy temporarily or permanently. Toxic nodules will have localized increased iodine and technetium uptake and are thus amenable to treatment with RAI. Similarly, Graves' will have diffusely increased uptake and RAI can be pursued before or after a trial of thionamide therapy. Methimazole is the thionamide of choice for patients with Graves' who are not in the first trimester of pregnancy, in thyroid storm and have not had drug-reactions to methimazole [16].

The decision of whether or not to commence thionamide therapy prior to administering RAI is made after taking many factors into consideration such as age, severity of thyrotoxicosis, cardiac risk factors (RAI can provoke myocardial infarction in patients with uncontrolled hyperthyroidism and underlying coronary artery disease) and pregnancy status. In women who are candidates for RAI, a pregnancy test should be obtained and confirmed negative, 48 hours prior to treatment [16].

Supportive therapies such as beta-blockers and glucocorticoids are used to help ameliorate cardiovascular and musculoskeletal symptoms such as palpitations and neck pain. Glucocorticoids can also be used to help reduce peripheral conversion of T4 to T3.

There are special considerations when treating hyperthyroidism in women who are pregnant. RAI is contraindicated during pregnancy and should not be administered in women who are lactating. Thionamides are used to treat hyperthyroidism during pregnancy and the choice of thionamide varies based on pre-pregnancy treatment modality (if applicable) and based on trimester associated teratogenic considerations.

In addition to careful monitoring of thyroid function, the clinician will also need to periodically assess liver enzyme levels and white blood cell counts as hepatotoxicity and agranulocytosis are well recognized potential complications of thionamide therapy.

Controversies and future considerations in thyroid disease management

The diagnosis and treatment of newly diagnosed thyroid disease in hospitalized patients remains controversial as there are many factors (including acute illness) that may cause thyroid hormone levels to be abnormal in this population. Inappropriate treatment initiation in these cases can have life-threatening consequences so it is important to be sure treatment is initiated for organic thyroid disease and not non-thyroidal illness syndrome [6]. With the exception of critically ill patients with hypothyroidism, such as those with myxedema in whom intravenous thyroid hormone replacement is recommended, oral levothyroxine therapy is the recommended therapy for hospitalized patients with hypothyroidism. Patients who are unable to tolerate oral replacement can receive enteral or intravenous replacement. The ATA recommends using an intravenous equivalent that is 75% of the calculated oral dose [6].

Another controversy in hypothyroidism management is the combination of liothyronine (LT3) and levothyroxine (LT4) in patients who continue to have hypothyroid symptoms despite being biochemically euthyroid. The Pharmacokinetic properties of T3, can complicate the clinician's ability to dose-adjust appropriately and can affect the patient's treatment response. Endogenous T3 levels are very stable in the blood and have <10% variability during the day [17]. However, LT3 peaks in the blood within 3-4 hours of dosing and this has clinical implications with regard to symptom management in patients with hypothyroidism [17].

In 2018, a group of researchers from Rush University found that the administration of a metal coordinated form of LT3 ($Zn[T3][H_2O]_n$), known as poly-zinc-liothyronine (PZL) in mice resulted in restoration of the physiologic properties of T3. The serum peak was delayed and the duration of action of LT3 was extended [17]. Clinical trials are needed to assess the safety and clinical implications of PZL use in humans but this discovery has the potential to change the way we manage individuals with hypothyroidism.

Key points

- Treatment of primary hypothyroidism is indicated when the TSH level exceeds 10 mIU/L. The benefit of treating primary hypothyroidism when the TSH level is 4.5-10 mIU/L is less clear.

- For individuals with underlying cardiovascular disease or risk factors for atherosclerotic cardiovascular disease, there may be benefit in treatment when the TSH level is 4.5-10 mIU/L.
- T4 therapy is the mainstay for treatment of primary hypothyroidism.
- Overt hyperthyroidism often presents with some combination of gastrointestinal, metabolic, cardiovascular, musculoskeletal, ophthalmologic and neuropsychiatric symptomatology.
- There are special considerations when treating hyperthyroidism in a woman who is pregnant.
- Thyroid dysfunction can present in a variety of ways and prompt recognition of clinical features and initiation of the appropriate treatment can help mitigate disease progression.

Hyperparathyroidism

Introduction

The parathyroid glands secrete parathyroid hormone (PTH). PTH regulates calcium levels in the body by stimulating the release of calcium from bones and the excretion of calcium in the urine [14]. There are four parathyroid glands and an enlargement of one or more of the glands will lead to overproduction of PTH. This is what occurs in primary hyperparathyroidism and hypercalcemia is typically the result. 80% of patients with PHPT have underlying parathyroid adenoma [18]. Less common causes of hyperparathyroidism are due to 4-gland hyperplasia and carcinoma [18-19].

PHPT is the most common cause of hypercalcemia and most cases are sporadic [19]. There are also well studied gene defects that cause hyperparathyroidism in association with endocrine syndromes such as multiple endocrine neoplasia (MEN).

This review will focus on the typical and atypical presentations of primary hyperparathyroidism (PHPT), diagnostic evaluation, major clinical manifestations and treatment of PHPT. Secondary causes of PTH elevation, such as vitamin D deficiency, chronic kidney disease and malabsorption syndromes (i.e. celiac disease) will not be discussed but should be excluded during the initial evaluation.

Diagnosis of primary hyperparathyroidism and diagnostic considerations

Primary hyperparathyroidism is the most common cause of hypercalcemia and the prevalence is estimated to be 1 to 7 cases per 1000 adults [20-23]. Women are 2-3 times

more likely to develop the condition than men [24]. PHPT should be suspected when serum calcium levels are elevated and the PTH level is elevated or inappropriately normal. The latter is indicative of aberrant parathyroid regulation of serum calcium levels [19]. Calcium and parathyroid hormone levels should be tested simultaneously, and the measurement of serum calcium should be adjusted for albumin as 40% of calcium is bound to serum proteins, mainly albumin [25]. The serum albumin-corrected calcium level can be normal in PHPT, so it is important to order a serum ionized calcium level in these cases [25]. Normocalcemic hyperparathyroidism is an atypical form of mild parathyroid disease and presents with high levels of parathyroid hormone and normal serum calcium levels. Normocalcemic hyperparathyroidism can progress to PHPT. Criterion for surgical management will be discussed later and the guidelines are the same for asymptomatic PHPT and normocalcemic hyperparathyroidism.

Clinicians must consider non-PTH mediated causes of hypercalcemia when evaluating patients with hypercalcemia. Hypercalcemia can be mediated by underlying malignancy and this is the second most common cause of serum calcium elevation [19]. The PTH level is suppressed when hypercalcemia is caused by malignancy and the parathyroid hormone peptide (PTHrp) is elevated. It is very important to distinguish PHPT from other causes of hypercalcemia as the clinical outcome depends on prompt recognition and initiation of the appropriate treatment(s).

The differential for PHPT should also include iatrogenic causes of hypercalcemia and PTH elevation. Patients on thiazides and/or lithium therapies can have PTH elevation and hypercalcemia. The mechanisms for each are different but the unifying factor in each case is that many of these patients have underlying PHPT that is unmasked by thiazide or lithium use. It is important to withdraw the medication and follow the serum calcium level for several months (typically 3-6 months) [19]. If hypercalcemia and PTH elevation are persistent despite medication-withdrawal, a repeat evaluation to confirm hyperparathyroidism should be performed. Guidance from a psychiatrist is recommended when considering lithium withdrawal as there are several psychiatric implications which need to be considered.

Familial Hypocalciuric Hypercalcemia (FHH) is a rare autosomal dominant disorder that results in an inactivating mutation of the calcium sensing receptor (CASR) gene and should also be on the differential in patients being evaluated for PTH-dependent hypercalcemia. The inactivation of the calcium sensing receptor (CASR) gene, raises the threshold for serum calcium suppression of PTH secretion [26]. This ultimately leads to increased renal calcium reabsorption and subsequent hypocalciuria. Calculation of the calcium clearance to creatinine clearance ratio (Ca/

Cr), which is usually less than 0.01 in FHH, can be used to help distinguish this condition from PHPT [19]. Another important distinguishing factor is that the average patient with PHPT is 50-60 years old and patients with FHH tend to be children or young adults [18,19]. Because FHH is a genetic defect, surgery is not indicated. Parathyroidectomy is the definitive treatment for PHPT, so it is very important to distinguish PHPT from FHH so that patients with FHH do not undergo an unnecessary surgery.

Clinical manifestations and complications

Chronically elevated serum calcium levels can lead to the development of nephrolithiasis. Kidney stones are present in 15-20% of newly diagnosed cases of PHPT [25]. Several other musculoskeletal, gastrointestinal, and psychiatric symptoms including bone and joint pain, fractures, constipation, nausea/vomiting, depression and altered sensorium can be present. Untreated PHPT can have several adverse cardiovascular implications. The risk of developing calcific disease in the vessels due to long-standing exposure to high serum calcium levels is well recognized. It is also important to highlight the relationship between excess PTH levels and the development of cardiac arrhythmias, impaired vasodilation, and the development of cardiac myocyte hypertrophy with subsequent left ventricular hypertrophy [27].

Treatment of primary hyperparathyroidism

Parathyroidectomy is recommended for patients who have symptomatic disease: nephrolithiasis, fractures, and/

or symptomatic hypercalcemia. Surgery can be performed via a minimally invasive approach with appropriate pre-operative localization of the parathyroid adenoma(s). This is typically done via methoxyisobutyl isonitrile single-photon emission computed tomography (MIBI-SPECT) imaging and/or parathyroid ultrasound. If pre-operative imaging is non-localizing, 4-gland exploration is performed. For patients who are not appropriate surgical candidates due to age or co-morbidities that would complicate the ability to undergo surgery safely, medical management with long-term monitoring of calcium levels, kidney function and bone density is recommended. Management using cinacalcet should be considered if bone mineral density (BMD) is normal and bisphosphonate therapy can be considered if BMD is low.

Recommendations for the management of asymptomatic PHPT are summarized in Table 2. Parathyroidectomy is indicated if the patient meets any one of the criteria for surgical management.

Key points

- Hyperparathyroidism can present with hypercalcemia or normocalcemia.
- Normocalcemic hyperparathyroidism and asymptomatic PHPT have the same criteria for surgical intervention.
- For those who are not appropriate surgical candidates, consider bisphosphonate or cinacalcet use.

Table 2: Guidelines for surgical management of PHPT in asymptomatic patients [28].

Measurement	Clinical Parameters
Age (years)	<50
Serum Calcium	At least 1.0 mg/dL (0.25 mmol/L) greater than the upper limit of normal
Renal Considerations	<ul style="list-style-type: none"> ◦ eGFR <60mL/min ◦ Radiographic evidence of nephrolithiasis or nephrocalcinosis (CT or ultrasound) ◦ 24-hour urine calcium >400 mg/day (>10mmol/day) and confirmation of increased stone risk via biochemical stone ◦ risk analysis
Bone Density	<ul style="list-style-type: none"> ◦ Osteoporosis (lumbar spine, total hip, femoral neck, or distal 1/3 radius) ◦ Radiographic evidence of vertebral fracture (CT, MRI or VFA)

eGFR: Estimated Glomerular Filtration Rate; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; VFA: Vertebral Fracture Assessment.

- When surgery is not indicated, long-term surveillance for worsening hypercalcemia, renal failure and reduction in bone mineral density is recommended.
- Untreated PHPT can adversely impact multiple organ systems: gastrointestinal, renal, musculoskeletal, neurologic and cardiovascular.

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