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Abstract

Thyroid disorders have various etiologies and presentations. Pertinent treatment needs a conclusive diagnosis and is influenced by variety of coexisting medical conditions. This chapter delineates how to interpret thyroid hormones, referring to various evidence-based clinical guidelines for the management of thyroid disorders. In depth research of relevant literature and evidence-based approach has been taken to simplify interpretation of thyroid hormone levels. Topics addressed include thyroid hormone assays, thyroid antibodies levels, hyper- and hypothyroidism along with thyroid dysfunction in pregnancy.

Introduction

Thyroid is a small butterfly shaped endocrine organ located anteriorly in the lower part of neck. On an average it weighs around 25–30 g in an adult. It produces the thyroid hormones, which are released into the bloodstream and then transported to different tissues in the body. They have an effect on each and every cell and organ of the body. Their main function is to maintain homeostasis in various functions ranging from controlling the metabolic rate, the muscle mass, digestive functions, development of brain, and bone maintenance.

Thyroid gland chiefly synthesizes the hormone thyroxine (T4) and small quantity of triiodothyronine (T3). T3 being the active form with a short half life is converted from T4 with removal of an iodine atom mainly in liver and in small quantities in heart, gut, muscle, and nerves. The gland is controlled by a feedback regulation from the pituitary, which releases thyroid-stimulating hormone (TSH), which in turn is controlled by the thyroid-releasing hormone (TRH) released from the hypothalamus.

Progress in technology over time has improved the sensitivity and specificity of thyroid function test available, and hence permitting an accurate diagnosis of thyroid condition to be made in majority of case. However, analytical inference still stands a major hurdle. The interpretation of thyroid function tests is generally straightforward; through sometimes the reports may seem fairly clear but are in fact misleading. This article aims to address the interpretation of thyroid functions test.

Thyroid-stimulating Hormone

TSH is secreted by anterior pituitary and is central to the negative feedback mechanism for secretion of thyroid hormones. It shows a diurnal variance, presenting a peak soon after midnight and a nadir by late noon, with peak values sometimes even twice the value seen in nadir. TSH may vary in between measurements to the extent of up to 20% without any change in thyroid state.\(^1\)\(^2\)

TSH is now considered as the first diagnostic test for assessment of thyroid condition.\(^3\) It presents as a foremost irregularity in case of thyroid disorders when the other test are normal. When TSH is used to confirm patients with suspected thyroid diseases in an Endocrine clinic it carries high sensitivity of up to 98% and a specificity of up to 92%. But in cases of mass screening the sensitivity and
positive predictive value is low due to underlying diseases or health of the individual screened, hence making the interpretation of test result problematic. As a routine now, value of TSH is considered low when less than 0.1 mU/L and high when more than 6.5 mU/L.

Using TSH as an ace standard does help to categorize patients in over 95% cases. But, TSH alone can be used only if the pituitary thyroid axis is intact. In case of pituitary diseases (hyperthyroidism secondary to TSH producing pituitary adenoma), non-thyroidal illness, HAMA antibody, drugs (glucocorticoids, dopamine), lab results can be misleading and difficult to interpret. Aberrant TSH levels may persist for up to few months even after initiation of thyroid treatment.

The American Thyroid Association recommends routine screening for thyroid disorders in all adults by measurement of serum TSH starting from the age of 35 years and then every 5 years, with more frequent screening in high risk or symptomatic person. The American Association of Clinical Endocrinologists recommend routine measurement of serum TSH in all women of childbearing age before they conceive or during the first trimester of pregnancy (Box 1).

**Thyroid Hormone Assays**

**Serum Thyroxine**

T4 levels are elevated in patients of hyperthyroidism. Hence, in the course of treatment their levels are measured to ascertain the degree of thyroid dysfunction and titration of doses of anti-thyroid medication, because serum TSH values may remain suppressed for a continued duration during the course of therapy.

Serum T4 values are also important in diagnosis of patients suffering from secondary hypothyroidism. Because a case of normal TSH and suppressed T4 should direct the clinical toward a possible diagnosis of secondary hypothyroidism, justifying the assessment of pituitary hormone levels for further investigations.

**Serum Triiodothyronine**

Evaluation of T3 levels is not suggested routinely because of its short half life and normal levels of it influenced by the endocrine homeostasis. Despite this it is of values in cases of T3 toxicosis, in which patients have low TSH, normal T4, and features of hyperthyroidism. This condition is observed in a small fraction of patients suffering from Graves’ disease. A ratio of T3:T4 > 20 ng/mL is indicative of Graves.

**Free Thyroxine and Free Triiodothyronine**

Merely a meagre portion of thyroid hormones circulate in free form not bound to protein. These free form of thyroid hormones are physiologically more important. Their quantification is of value in conditions where levels of thyroid-binding globulin (TBG) are altered. Levels of TBG influence the levels of T3 and T4 in direct proportion.
Interpretation of Thyroid Function Tests

without any change in hormone activity, more TBG falsely more T3, T4, and low TBG presenting as falsely low T3 and T4 (Table 1).

**Free Thyroxine**

fT4 is performed for optimizing thyroxine therapy in patients of newly diagnosed hyperthyroidism. It is also prescribed in diagnosis of secondary hypothyroidism and in cases of end organ thyroid hormone resistance.

**Conditions associated with decreased fT4:**
- Primary hypothyroidism (thyroid hypofunction)
- Secondary hypothyroidism (pituitary hypofunction)
- Tertiary hypothyroidism (hypothalamic hypofunction)

**Conditions associated with increased fT4:**
- Graves’ disease
- Plummer’s disease (toxic thyroid adenoma)
- Early phase of subacute thyroiditis
- Struma ovarii
- Thyrotroph hyper function—secondary hyperthyroidism

**Free Triiodothyronine**

fT3 levels are rarely required.

**Conditions associated with decreased fT3:**
- Critically ill patients
- Patients on high dose steroids
- Patients on beta blockers
- Severe hypothyroidism

**Conditions associated with increased fT3:**
- T3 toxicosis
- Hyperthyroidism

**Thyroid Antibodies**

Estimation of thyroid antibodies is advisable in altered thyroid functions. They help to determine if patient is having an autoimmune thyroid dysfunction. Various antibodies exist against thyroid antigens. The ones of importance include Anti Thyroperoxidase antibody (Anti-TPO Ab), antithyroglobulin antibody and TSH receptor antibody (TSH-RAb).

**Anti-thyroperoxidase Antibody (Anti-TPO Ab)**

Anti-TPO is also known as thyroid microsomal antibodies. They cause hypothyroidism by two distinctive mechanisms. First by blocking the thyroid peroxidase thereby hindering the synthesis of T3 and T4 and secondly by antibody dependent cell toxicity and inflammation of thyroid gland. Anti-TPO Ab levels facilitate in the diagnosis of subclinical hypothyroidism and helps in evaluation of autoimmune thyroiditis.

**TSH Receptor Antibody (TSH-RAb)**

TSH-RAb may either stimulate or block the TSH receptor. If they stimulate they cause Grave’s disease and associated ophthalmopathy. If they act as blocking anti-antibodies they may lead to hypothyroidism.

Measurement of TSH-RAb is helpful in confirming the cause of hyperthyroidism and radioactive iodine therapy is not an option. This assay if of particular importance in managing pregnant patients with Grave’s disease as high concentrations is a fair predictor of fetal and neonatal thyrotoxicosis.

**Thyroglobulin**

It is a large glycoprotein, secreted along with the thyroid hormone. Raised thyroglobulin levels is not a reliable marker or a screening test for thyroid carcinoma; however, it gains importance as an important marker of remaining or recurrent malignancy in patients who undergo total thyroidectomy or radioactive thyroid ablation for papillary or follicular carcinoma.

**Thyroid Function in Pregnancy**

During pregnancy there is a paradigm shift in level of thyroid hormones leading to an increase in T4 levels and a reciprocal decrease in level of TSH. The reason for this physiological change is linked to—
- Human chorionic gonadotropin has an alpha subunit similar to TSH, which binds to TSH receptor. This leads to an increased production of T4, which gives a negative feedback to the pituitary resulting in reduction of TSH.9
- Estrogen produced by the placenta leads to increased secretion of sex hormone binding globulin (SHBG) by the liver. This SHBG increases secretion of T4 from thyroid.
- Pregnancy being a hypermetabolic state leads to increased glomerular filtration rate; hence, increased secretion of T4 by thyroid due to augmented elimination by the kidneys.

**Detecting Thyroid Dysfunction**

There exist an inverse log relationship between TSH and T4 levels. Elevated TSH levels indicate hypothyroidism and low TSH indicate hyperthyroidism.10 Analysis of thyroid function test can be a challenge in case of hypothalamic pituitary disease (low TSH, low T4), systemic illness, starvation (low TSH, low T3).

**Hyperthyroidism**

An elevated fT4 and low TSH is indicative of thyrotoxicosis. Most of the young age group patients with these levels presents as Grave’s disease while the elderly are more prone for nodular thyroid disease.

In cases of subclinical hyperthyroidism TSH levels may be borderline suppressed in the presence of normal fT3 and fT4. Treatment of subclinical hyperthyroidism is warranted in the presence of underlying condition like increased age, cardiac condition like atrial fibrillation, recent history of stroke, and osteoporosis.7

Temporary or short lived thyrotoxicosis can be presented in the form of viral thyroiditis. Most patients have a recent history of viral upper respiratory tract infection. This usually responds to anti-inflammatory medication. Prompt diagnosis of the condition stands as a key to treatment.

A small subset of patients may present with low TSH and normal fT4 thereby representing T3 toxicosis. In these cases measurement of T3 levels is of value. If in case fT3 is not raised then fT4 and TSH should be rechecked.

High fT4 with normal or raised TSH depicts a T4 to T3 conversion defect, or an analysis error.

During the course of treatment, TSH may remain suppressed for varied amount of time; in this case fT4 is measured every 6–8 weeks to monitor the treatment.

**Hypothyroidism**

Elevated TSH levels with low fT4 suggest a diagnosis of primary hypothyroidism, primarily autoimmune in nature but can also be a result of previous surgery or radio iodine ablation of thyroid gland. The prevalence of high TSH with raised antibody levels is more common in elderly women.7

Raised TSH in presence of normal fT4 indicates autoimmune thyroid condition. When TSH levels are more than 4 μIU/mL but less than 10 μIU/mL without any clinical sign, it represents subclinical hypothyroidism. Treatment is warranted in this condition in presence of thyroperoxidase antibody, pregnancy, goitre, or dyslipidemia. TSH levels more that 10 μIU/mL require treatment.

Low or normal TSH usually excludes the diagnosis of primary hypothyroidism. However, presence of low TSH and low fT4, low fT3 should indicate toward secondary hypothyroidism, most commonly seen in cases of Sick Euthyroid syndrome.

Thyroxine replacement in hypothyroid patient should be titrated to maintain a TSH of about 2 μIU/mL. Guidelines recommend that test for thyroid function and changes in dose of thyroxine should not be done before 6 weeks unless clinically indicated because it takes this much time for the body to accomplish reliable T4 levels. Patients who are less compliant to medication usually have tendency to replenish the dose before the scheduled visit. This presents as a raised TSH but normal fT4.

Patients suffering with differentiated thyroid cancers are given suppressive doses of thyroxine to maintain TSH levels below 0.1 μIU/mL to prevent flare ups. Those who initially had a high risk disease but are now disease free post-treatment are advised to maintain TSH levels between 0.1 and 0.5 μIU/mL for at least 5–10 years.7,11

**Sick Euthyroid Syndrome**

This is referred as a thyroid-related change that occurs during systemic illness in the absence of an intrinsic thyroid disease. The syndrome is acute, reversible, and occurs commonly after surgery, starvation and in many acute febrile illnesses. These changes may be observed in up to 75% of hospitalized patients. Any abnormality in hormone level is possible, but the most common observed abnormality is low fT3.
Diseases of thyroid gland are common and initial test to be done for assessment of this condition is serum TSH. fT4 is indicated as a second line test, but the reference range for fT4 and TSH are not universal and reference interval provided by the lab should be acknowledged. Results of thyroid function test are interpreted in light of clinical status of patients: hypothyroid, euthyroid, or hyperthyroid. Subclinical thyroid diseases are commonly encountered and present with an abnormal TSH and normal fT4. Awareness of associated conditions can serve as a guide for further investigations and management. Confounding factors should be excluded before embarking upon further biochemical, radiological, or genetic testing (Table 2).

**Conclusion**

Diseases of thyroid gland are common and initial test to be done for assessment of this condition is serum TSH. fT4 is indicated as a second line test, but the reference range for fT4 and TSH are not universal and reference interval provided by the lab should be acknowledged. Results of thyroid function test are interpreted in light of clinical status of patients: hypothyroid, euthyroid, or hyperthyroid. Subclinical thyroid diseases are commonly encountered and present with an abnormal TSH and normal fT4. Awareness of associated conditions can serve as a guide for further investigations and management. Confounding factors should be excluded before embarking upon further biochemical, radiological, or genetic testing (Table 2).

**References**


**Table 2** Interpretation of thyroid function test

<table>
<thead>
<tr>
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<th>fT4</th>
<th>fT3</th>
<th>Thyroid antibodies</th>
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<tr>
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↔ Normal, ↑ High, ↓ Low
Abstract
Hypothyroidism is associated with myriad of neuropsychiatric manifestations in clinical practice. Due to its variable and wide clinical presentation it sometimes poses a dilemma for the treating physician and consultation—liaison should be considered when treating patients with neurocognitive symptoms.

Introduction
Disorders of Thyroid are one of the common endocrine problems encountered in clinical practice; the hypothalamic-pituitary-thyroidaxis is needed to maintain the normal functioning of various organs and systems, including the central nervous system.

Thyroid dysfunction affects the nervous system and produces a wide and variable spectrum of clinical presentation due to alterations in cognition and emotions. As early as 1888 Clinical Society of London had described myxoedema and its association with behavior and psychological disturbances.

Pathophysiology
The hypometabolism of brain has been postulated to be associated with cognitive decline. Thyroid hormones exert their influence on the central nervous system through a variety of mechanisms like modulation of gene expression of several groups of proteins and the influence on serotonin and noradrenergic neurotransmission. Antithyroid antibodies are also postulated to play a causative role. In autoimmune Hashimoto’s thyroiditis link with Unipolar and Bipolar Depressive disorders is established; however, the exact pathophysiology, role of inflammatory markers or of second messengers is yet to be established and a direct correlation between the more specific marker of the disease, that is, thyroid peroxidase antibodies (TPOAb) or of thyroglobulin antibodies (TGAb) is still an ongoing research.

Epidemiology
Due to improvements in diagnosis and treatment of the hormonal disorders and universal iodine supplementation of common salt the most severe neuropsychiatric syndromes in endocrine diseases are not as frequent as in the past although psychiatric and subtle cognitive disturbances are still seen. Data shows that 1–4% of patients diagnosed with affective disorders have overt hypothyroidism and 4–40% may have subclinical hypothyroidism (SCH). However, majority of patients diagnosed with major depression have normal thyroid function.

Overt Hypothyroidism
Overt hypothyroidism by definition is an elevation of serum thyroid stimulating hormone (TSH) level with a low-free thyroxine (fT4) level. Autoimmune thyroiditis (Hashimoto’s) is the most common cause of...
hypothesis which is commonly seen in middle age females.\textsuperscript{8}

The most common presenting complaints are fatigue and impaired quality of life. Due to advances in interventional and functional imaging the subtle changes in cognition in specific domain like working memory and executive function are now more commonly diagnosed along with the more commonly seen anxiety and depression.

**Neurocognitive Effects Seen in Overt Hypothyroidism**

**Cognition**

Cognition is referred to as mental activities involved in the acquisition, storage, retrieval and use of information.

Memory is most commonly affected domain with specific deficits seen in verbal memory. Hypothyroid individuals have also shown deficits in visuospatial and executive functions.

The other cognitive domains affected include general intelligence, complex attention and concentration, language, learning and memory along with perceptual and visuospatial functions. The frontal lobe executive functions like reasoning, problem solving, decision-making may be affected. There are various psychological tests and measures available for evaluation of these individual cognitive domains.\textsuperscript{4}

In congenital hypothyroidism irreversible cognitive deficits may happen if hypothyroidism is left untreated or intervention started belatedly after the critical window of brain development.

In adolescents who develop hypothyroidism again cognitive domains are affected and those who were treated with Thyroxine Replacement Therapy (TRT) were found to have improved performance on a battery of cognitive tests including reading performance and block design but the patterns of recovery are not definitive.

In adults with hypothyroidism again vocational and occupational pursuit may be affected whereas specific tests of cognitive domains are often seen to be not significantly impaired.

**Dementia**

In geriatric population there may be an overlap of symptoms seen in hypothyroidism and due to old age, itself. Hence, the diagnosis of hypothyroidism may be clinically missed.

Traditionally, Myxoedema used to be known as a reversible cause of dementia in the elderly. There occurs progressive neurocognitive decline leading to impaired social and cognitive functioning. Elderly patients tend to have problems with recent memory though remote memory and overall intelligence remains intact other common problems observed are lack of attention and emotional liability with easy fatigability leading also to a lot of family and caregiver burden.

There is decline in auditory acuity which might contribute indirectly to memory impairment due to sensory deprivation and poor registration usually seen in uncontrolled hypothyroidism which can partially be reversed with thyroxine. TSH levels and risk of developing Alzheimer’s disease may also show some correlation.\textsuperscript{5,12}

**Other Neurological Complications\textsuperscript{10}**

*Cerebellar dysfunction* and motor coordination like ataxia, intention tremors are usually mild and more commonly seen in children and may result in poor outcomes in motor functions in later childhood if delayed treatment or inadequate hormone replacement is done.

**Neuropathy:** Hypothyroidism is associated with peripheral nerve demyelination and decreased nerve conduction velocity (NCV).

Entrapment neuropathy, like Carpal tunnel syndrome and polyneuropathy, is also seen but the bilateral and distal sensorimotor neuropathy is the most common.

With thyroxine replacement therapy the symptoms and signs of neuropathy along with changes in NCV usually normalize in adulthood but those who have symptoms of longer duration may show some residual symptoms of peripheral neuropathy.

**Myopathy** can occur when associated with symptoms or signs of hypothyroidism such as poor linear growth or global developmental delay with pain and muscle weakness along with elevation of creatine phosphokinase.

The delayed acquisition of early motor milestones may be a sign of missed congenital or early acquired hypothyroidism in young children and investigation of thyroid function should be performed in them.

**Hashimoto’s encephalopathy (HE)** is a rare neuroendocrine disorder to be associated with autoimmune thyroiditis (Hashimoto thyroiditis). Hashimoto’s
encephalopathy is frequently seen in women and presents with symptoms of seizures, myoclonus, stroke, and also psychiatric manifestations mainly depressive disorders and even psychosis. These symptoms usually recover with treatment but relapses can also be seen.

Thyroid tests are usually normal. Neuroimaging is often normal. The diagnosis of Hashimoto’s encephalopathy is made with classical clinical picture with positivity of antithyroid peroxidase antibodies. Treatment of Hashimoto’s encephalopathy is corticosteroids.11

Anxiety disorders: These disorders present as restlessness, inability to concentrate, irritability, distraction, increased sweating, muscular tension, and insomnia. The most prevalent anxiety disorders are social anxiety disorder, generalized anxiety and panic disorder, the incidence of which is increased in hyperthyroidism and also in hypothyroidism.2,7

Mood disorders: Depression has a prevalence of 10–15% in the general population and may be more common in people with thyroid disorders. The normal circadian secretion of TSH peaks from 11 pm to 4 am. In depressive patients there is a dysregulation of Hypothalamic-Pituitary-Adrenal axis; hence, the nocturnal surge is absent which may point to functional central hypothyroidism in some depressed patients.

It has been seen that self-knowledge of mildly elevated TSH may be associated with poor quality of life or fatigue known as (“labeling effect”).

Major depressive disorder can also happen in hypothyroidism although more common in hypothyroidism, presence of antithyroid antibodies may have an etiopathological role and severity in causing depression. There are further complications as Lithium the gold standard medicine of Bipolar disorders leads to Hypothyroidism on prolonged use.

Depression is characterized with cognitive distortion in form of hopelessness, helplessness, and worthlessness this may lead to suicidal ideation and in few cases lead to self-harm and suicide.

Many cognitive symptoms like poorer memory, in attentiveness, slower thinking and speech, impaired concentration and apathy is seen in both the diseases. The common symptoms of being easily tired, lack of interest, and pleasure along with loss of appetite, decrease libido, and constipation may pose a difficulty in diagnosis though certain symptoms like weight gain, hypersonmolence or insomnia and impoverished quality of life may give a clue toward diagnosis of hypothyroidism but they are also common in mood disorders. An overlap of anxiety and mood disorders can be seen leading to variety of emotional disturbances.2,7,15

Psychotic disorders: Severe hypothyroidism in 5–15% may present as melancholic depression with mood congruent psychotic features, rarely frank psychosis, delusions, and hallucinations. These features are often seen in Myxedema madness.

Capgras syndrome a delusional disorder has also been associated with hypothyroidism where psychotic symptoms are preceded by symptoms of hypothyroidism even months to years of diagnosis.

Effects of Thyroxine Replacement Therapy on Hypothyroidism

After supplementation of thyroxine replacement therapy there may occur incomplete normalization of subjective neuropsychiatric symptoms even on reaching euthyroid state. There is no rationale of using combination of Levothyroxine (LT4) and Liothyronine (LT3) treatment for hypothyroidism who still complained of depressive symptoms. In these subsets of individual revaluation of other chronic medical condition and consultation liaison with psychiatrist should be sought.

Subclinical Hypothyroidism

“Subclinical” hypothyroidism (SCH) by definition is an elevation of TSH with a normal fT42. In young adults and middle age, the symptoms of depression are more frequent along with mild cognitive impairment, difficulty in learning and selective attention. Subclinical hypothyroidism is prevalent in as many as 20% of post-menopausal women and in older patients many of whom already have some cognitive decline.14 The correction of the subclinical hypothyroid state with neuropsychiatric symptoms still remains elusive.9

There have been no improvements in symptoms of Subclinical hypothyroidism on thyroxine replacement therapy diagnosed with depression who are biochemically euthyroid. Various studies have shown no significant clinical improvement with coadministration of Levothyroxine (LT4) and Selective Serotonin Reuptake
Inhibitors (SSRI) in depressed patients when compared with SSRI alone.9

Congenital hypothyroidism (CH) is a common and treatable cause of preventable intellectual disability with a prevalence of approximately 1 in 2,000–4,000 new born. Thyroxine is an essential hormone during pregnancy especially during first trimester as it is required for fetal brain development at around 12 weeks postconception. Deficiency of thyroxine may lead to abnormal dendrite-genesis and synaptogenesis leading to congenital hypothyroidism in neonates.

Congenital hypothyroidism can impair cognition but also cause arrange of other neurological sequelae including abnormal muscle tone, ataxia and strabismus and motor in coordination the most severe forms of congenital hypothyroidism may include alterations in domains of attention, memory, arithmetic, verbal skills, memory, and behavior.

In severe cases mental retardation, deafness, and spastic diplegia can be seen. There is also presence of other clinical features such as short stature, delayed puberty, and craniofacial abnormalities.

For prevention of neurobehavioral effects of congenital hypothyroidism supplementation of iodine preconceptually may be advised. The immediate goal of thyroxine replacement is to normalize T4 within 2 weeks and TSH within 1 month of birth to ensure growth and neurodevelopmental outcomes as close as possible to their genetic potential.13

Hypothyroidism has also been associated with attention deficit hyperactivity disorder (ADHD) and this may persist even in adults.

The preventive measures of congenital hypothyroidism may be early identification and early initiation of treatment, which has shown improvement in tests for formal intelligence. But certain domains of neurocognition may persist in late childhood and adolescence. Some domains like language, motor skills, attention, and visuospatial processing may be affected even after becoming euthyroid.9,10

Conclusion

Overt hypothyroidism is associated with myriad of symptoms ranging from fatigue affecting quality of life to mood and behavior changes along with cognition. Among the cognitive impairment seen in hypothyroidism is its effect on memory.

Though these changes may be subtle in patients of SCH and may not show major changes on mood and cognition, SCH have been seen to be associated with mild deficits in working memory and executive function especially in elderly.

The treatment with thyroxine replacement is the cornerstone and is always indicated in overt hypothyroidism. There have been improvements in physical symptoms along with resolution of deficits in mood or cognition though complete recovery may not be seen. The treatment of SCH is elusive and it depends upon the decision of treating physician.

The neuropsychiatric symptoms with mild hypothyroidism should be evaluated and treated as independent diagnosis with consultation liaison.

There appears significant merit in recommending universal thyroid screening for all pregnant females along with testing for any young infant or child with global neurocognitive or neuromuscular dysfunction.

Also, emphasis on thyroid testing for patients presenting with neuropsychiatric disorders and conversely assessment of mental health for all patients diagnosed with thyroid disorders can be instrumental for good clinical management as the timely intervention may improve quality of life among thyroid disorder patients with comorbidities.

Neuroplasticity more often favors infant rather than older individual. Thyroxine replacement therapy remains the mainstay of treatment but the extent and duration of recovery especially neurocognitive domains is often incomplete and inconsistent. There is global decline in cognition if thyroxine replacement therapy is delayed or absent. Hence, universal screening of TSH in pregnant women should be emphasized.

References


Abstract
Muscular complaints are common symptoms of thyroid disorder: hypothyroidism or hyperthyroidism. About 79% of hypothyroid patients and 67% of hyperthyroid patients develop neuromuscular symptoms. However, muscle stiffness is more common in hyperthyroidism while muscle weakness is observed commonly both in hypothyroidism and hyperthyroidism. The onset of weakness is usually insidious and proximal muscles are predominantly affected in both types of thyroid myopathy. Thyroid myopathy occurs as a result of either deficiency or overproduction of thyroid hormone, i.e., Thyroxine. Skeletal muscle is a major target of thyroid hormone. Patients with untreated or uncontrolled hypothyroidism and hyperthyroidism can develop severe myopathy resulting in severe functional limitations. These symptoms subside completely with proper diagnosis and appropriate treatment.

Introduction
Abnormal thyroid functions/disorder either too increased or too low can result in neuromuscular manifestations including hypothyroid myopathy, hyperthyroid (thyrotoxic) myopathy, thyrotoxic periodic paralysis, and thyroid associated ophthalmopathy because the skeletal muscle is a major target of thyroid hormone. Muscular complaints are common symptoms of thyroid dysfunction, especially muscle stiffness more so in hyperthyroidism and muscle weakness in both hypothyroidism and hyperthyroidism. The prevalence of neuromuscular manifestations varies between 20% and 50%. Most of these studies were retrospective and were done before FT4 and TSH assays were available.1,2

Types of Myopathy
Hypothyroid Myopathy
Various manifestations of hypothyroidism are observed in clinical practice. Hypothyroid myopathy (HM) occurs as a complication of uncontrolled or untreated hypothyroidism involving about 79% of patients. It is seen in both congenital and acquired hypothyroidism. Sometimes subclinical hypothyroidism manifests as HM. HM can occur at an age but most common age is 40–70 years and involves both sexes. However, females are predominantly affected than males.3

Pathogenesis: The exact pathogenesis of HM is not known. Thyroid hormones markedly influence the cellular metabolism and their deficiency results in cellular functional impairment. Thyroxine (T4) deficiency in hypothyroidism causes:
- Abnormal glycogenolysis
- Reduced mitochondrial oxidation
- Insulin resistant state of the cell

Ultimately this causes selective atrophy of Type 2 muscle fibers (fast twitching type) because these muscle fibers are dependent on glycolysis for energy. Finally, it results in slowing of muscle contraction which may be observed clinically. However, compensatory mechanism
occurs from accumulation of glycosaminoglycans in the muscle further causing muscle hypertrophy. Myopathy symptoms in HM result from low muscle carnitine. Various factors causing muscle involvement in hypothyroidism are due to

- Deposition of glycosaminoglycans
- Low myosin ATPase activity
- Changes in muscle fibers from fast twitching Type 2 to slow twitching Type 1 fibers
- Decrease in ATP turnover in skeletal muscle
- Structural muscle injury. A significant feature is that degree of muscle weakness does not always correlate with the severity of thyroid hormone deficiency. Rise in serum muscle enzymes in the absence of clinical manifestations or structural alterations results from changes in the muscle cell membrane permeability. Thyroid hormone may have a role in regulating gene expression of skeletal muscle proteins like myosin ATPase thus favoring the role of thyroid hormone deficiency in the pathogenesis of TM.4

Thyroid myopathy is of four types:

- Myasthenic syndrome: It is associated with Ptosis and marked weakness. It is commonly seen in children.
- Atrophic type: It is seen in severe muscle atrophy.
- Kocher-Debre-Semelaigne syndrome: It is commonly seen in children. Clinical features include myxedema, short stature, cretinism, and generalized muscle hypertrophy.
- Hoffman syndrome (HS): It occurs in adults. Clinical features include pseudohypertrophy of muscles, proximal muscle weakness, stiffness, and painful spasms. Commonly involved muscles are tongue, arm, and leg muscles. The pathogenesis of pseudohypertrophy is not exactly known but may be due to deposition of glycosaminoglycans and increased muscle fiber size.5 Few cases of HS have been reported from India.6 7 HS was first described by Hoffman in 1897 in an adult who developed muscle stiffness and difficulty in relaxation of muscles after thyroidectomy.8 Usually the cause of HS is primary hypothyroidism (Hashimoto thyroiditis) but rarely secondary. Muscle biopsy is usually not required to confirm the diagnosis. Muscle MRI may be helpful. Prognosis is good in HS. Muscle enlargement usually regresses over time, but may persist in a few cases.

Clinical features of HM include cramps, muscle weakness, myalgia, stiffness, myxedema, and hyporeflexia. Muscle hypertrophy, wasting, and rhabdomyolysis are unusual features.9 Rhabdomyolysis is a rare life threatening complication being precipitated by trauma, exercise, alcohol, and electrolyte disturbances. Rarely HM may present as acute compartment syndrome being precipitated by thrombosis, surgery, trauma, or IV drug abuse.

Differential diagnosis of calf muscle (gastrocnemius) hypertrophy include Duchenne and Becker muscular dystrophy, sarcoidosis granuloma, amyloid, and focal myositis.10

Myoedema is a classical sign of HM but is uncommon and hence is mostly missed by clinicians. It is demonstrated by percussion or applying pressure stimulus with thumb and index finger on the muscles of arm, especially biceps belly. This causes the muscle to form a visible palpable, nontender, firm, localized swelling around the site of stimulus. The swelling reaches its maximum size after 1–2 seconds and gradually subsides over 5–10 seconds so that the muscle regains its normal contour with no palpable localized hardening. The swelling does not spread elsewhere along the muscle. Myoedema is due to prolonged muscle contraction caused by delayed calcium reuptake by the sarcoplasmic reticulum after the stimulus causes release of local calcium. Differential diagnosis of myoedema is from malnutrition, hypoalbuminemia, hypovitaminosis, and hypothyroidism.11

Hyperthyroid Myopathy

Various names are Graves myopathy, thyrotoxic myopathy, Basedow myopathy, or Basedow paraplegia. It was described in early nineteenth century by Graves and Von Basedow documented in severe hyperthyroidism. There are two types of muscle fibers—Type 1 or Slow fibers are required for sustained effort like standing, while Type 2 fibers are fast fibers required for short rapid bursts like sprinting. In hyperthyroidism, there is increased production of ATP and reuptake of calcium. This results in very rapid contraction and relaxation. When this process occurs repeatedly, the structure and mechanics of slow fibers is changed to fast fibers so that muscles lose their endurance, become fatigued, weak, and wasted.

Hyperthyroid (thyrotoxic) myopathy occurs due to overproduction of thyroid hormone, that is, thyroxine.
Thyroid Myopathy—An Update

Etiology includes mostly multinodular goiter and Graves’ disease. Clinical features consist of muscle weakness, fatigue and heat intolerance, difficulty in climbing stairs, and proximal myopathy. If untreated, it can lead to marked debilitating condition and rarely death.\(^\text{12}\)

Hyperthyroid myopathy can be acute or chronic. Acute hyperthyroid myopathy is rare than chronic hyperthyroid myopathy. It occurs due to rapid degradation of muscle fibers so that patients complain of severe muscle pain, muscle cramps, blurring of vision, and bulging eyes. It may present with more severe proximal and distal weakness and rarely quadriplegia with bulbar and respiratory involvement. Patients develop rhabdomyolysis and severe respiratory failure requiring artificial ventilation.

Chronic hyperthyroid myopathy develops after 6 months of onset so that symptoms appear slowly in the form of increased fatigue and difficulty in performing certain tasks. Some patients in thyrotoxic myopathy may have involvement of upper motor neurons related to pyramidal tract dysfunction as well as lower motor neuron symptoms related to peripheral neuropathy. This may overlap with those of amyotrophic lateral sclerosis (ALS).\(^\text{13}\) However, there is no association found between hyperthyroidism and motor neuron disease.

Some patients of hyperthyroid myopathy may present with sensory polyneuropathy, carpal tunnel syndrome, headache, seizures, ischemic cardiovascular disease especially in patients of hyperthyroidism with atrial fibrillation, as well as cerebral venous thrombosis occurring as a result of hypercoagulable state, and auto immune mechanisms. Rarely, Guilla-\textsuperscript{-}\textsuperscript{ain}–\textsuperscript{-}\textsuperscript{Barré} syndrome and chronic inflammatory demyelinating polyneuropathy have been associated with hyperthyroid patients.

Pathophysiology

Excess of thyroid hormone, that is, thyroxine, causes degradation of muscle fibers, especially at the motor end plates of neuromuscular junction. There occurs low level of acetylcholinesterase (AChE), which breaks down ACh in neuromuscular junction. Decrease in AChE blocks degradation of ACh causing ACh to overstimulate motor end plates of muscle fiber. Ultimately overstimulation of motor end plate leads to more sustained muscle contraction resulting in fatigue, muscle weakness and degradation occurring as a result of overproduction of thyroxine.\(^\text{14}\)

Other theory of hyperthyroid myopathy is decrease in protein kinase affinity to cAMP within muscle fibers resulting in increase in cAMP within muscle fibers, which ultimately causes increased release of calcium from muscle fibers’ sarcoplasmic reticulum. Finally, it results in more muscle contractions.\(^\text{15}\)

Chronic hyperthyroid myopathy can be so severe that the patient may develop winging of scapula. If the myopathy progresses untreated, then patient may have involvement of muscles of face, swallowing, and respiration.

**Ocular myopathy:** It is also called dysthyroid ophthalmopathy, or exophthalmic ophthalmoplegia. It is more common in females. It may or may not be associated with chronic thyrotoxic myopathy. It may occur even after treatment for hyperthyroidism. In severe cases it may result in blindness and severe residual deficit.

**Thyrotoxic periodic paralysis:** It is a rare clinical entity mostly occurring in young adult Asian males in age group of 25–30 years. It manifests as sudden episodes of muscle weakness involving muscles of trunk and limbs, developing over a few minutes to hours, and lasting for hours to a few days. It is due to altered muscle membrane excitability secondary to hypokalemia. It reverses spontaneously or requires potassium. Patient may die due to cardiac arrhythmias. Many cases have been reported in the literature.\(^\text{16}\)

**Diagnosis:** Laboratory investigations include CBC, FT3, FT4, TSH, serum sodium, serum potassium, serum calcium, serum phosphorus, blood glucose, blood urea, serum creatinine, serum vitamin B12, serum folic acid, ECG, auto antibodies against thyroid disease, CPK, CPK-MB levels (muscle enzymes), lipid studies, ultrasound of thyroid, hand-held dynamometry, EMG, nerve conduction study, and muscle biopsy, if needed. Normal levels of CPK may reveal early stages of progression while increased levels indicate late stages of progression.

EMG findings of thyroid myopathy include polyphasic action potential with early recruitment full interference pattern. Electromyography (EMG) findings in HM may show low/small amplitude potentials suggesting myopathic changes although it may be normal in half of the patients.

The distal muscles in thyrotoxic patients may show EMG findings of a rather neuropathic process. EMG is used
to diagnose myopathies by comparing muscle contraction responses to electrical stimulus. Response may be normal or myopathic. Muscle biopsy findings in case of HS include muscle fiber hypertrophy, increased nuclei, mucous deposits at places with increased inter fiber ground substance consistent with thyroid myopathy. Muscle biopsy in hyperthyroid myopathy is not specific but may show mild atrophic changes and type 2 fiber predominance. Management of HM consists of thyroid hormone administration and hyperthyroid myopathy treatment consists of antithyroid drugs (propylthiouracil, methimazole), radioactive iodine or surgery in the form of partial or total thyroidectomy. Treatment of thyroid myopathy is carried out by multidisciplinary team consisting of neurologist, endocrinologist, surgeon, ophthalmologist, and physical therapist. Aim in hyperthyroid myopathy is to reduce overproduction of thyroxine from the thyroid gland. While in HM aim is to correct thyroid hormone deficiency by administration of thyroid hormone. Thyroid replacement usually leads to resolution of laboratory abnormalities and symptoms over a few weeks. However, weakness may take months for recovery. Ultimate goal is to restore normal hormone homeostasis.

**Conclusion**

Neuromuscular symptoms and signs are common in 75% of hypothyroid patients and 67% of hyperthyroid patients because the skeletal muscle is a major target of thyroid hormone. It is uncommon for a patient with hypothyroidism to present with muscle weakness as the chief complaint. Patients of hyperthyroid myopathy usually report after the age of 40 years unlike patients of hypothyroidism. Clinical suspicion supported by laboratory investigations is needed to diagnose patients of both hypo- and hyperthyroid myopathy. Weakness in hyperthyroid myopathy develops early but resolves completely during treatment, thus suggesting a functional muscular disorder.

**References**

Abstract
Diabetes and thyroid dysfunction have impact on each other and mutual interdependence has been a matter of interest since long. The prevalence of thyroid disorder in people with diabetes was found to be higher than in general population. Diabetic patients with hyperthyroidism experience a deterioration of glycemic control. Thyroid hormone excess can sometimes precipitate ketoacidosis in diabetic patients. About half of the patients with Grave’s disease exhibit glucose intolerance of variable degree and about 2–3% may develop overt diabetes. Hypothyroidism is the most frequently encountered thyroid disease in patients with diabetes. Studies have found the occurrence of hypothyroidism in 5.7% patients suffering from diabetes. In individuals with T1DM, repetitive events of hypoglycemia hint toward hypothyroidism.

Introduction
The two most often seen endocrine disorders in medical experience are diabetes mellitus and thyroid abnormalities. Thyroid dysfunction is found to occur more frequently in patients with diabetes as compared to the general society.\textsuperscript{1,2} Diabetes and thyroid dysfunction have impact on each other and mutual interdependence has been a matter of interest since long. Increasing body of evidence suggests a pattern of multiform combination of biochemical, inherited, and endocrinal defects leading to this pathophysiological interdependence. Epidemiologic data reveal that thyroid dysfunction is seen in 13.4% of diabetic population. Amongst the patients with diabetes, the subgroup having maximum prevalence of thyroid dysfunction were females with type 1 diabetes (31.4%) and minimum were males with type 2 diabetes (6.0%).\textsuperscript{3} Thyroid hormones play role in metabolism, energy disbursement as well as insulin sensitivity. Vis-a-vis diabetes impacts TSH responsiveness to thyrotropin releasing hormone and causes low T3. The reciprocal interlinkage between thyroid hormone levels and diabetes mellitus has clinical connotation.

Epidemiological studies have shown similar genetic background for diabetes mellitus and thyroid disorders. However, the common genes identification is presently focused on the autoimmune etiology. The closest connection seen amongst type 1 diabetes and autoimmune thyroid diseases have relation with HLA class II sequences.\textsuperscript{3} There is evidence to propose the likelihood of impact of intracellular T3 on insulin sensitivity.\textsuperscript{4}

It is said that rectification of abnormal thyroid status in individuals with diabetes will enhance blood glucose levels, diminish cardiac and other complications chances, and improve overall health. However, there is dearth of unanimity concerning timing and periodicity about thyroid assessment to be conducted in standard approach to diabetes management.\textsuperscript{5}

Hyperthyroidism and Glucose Metabolism
Thyroid hormones may affect glycemia secondary to their influence on glucose metabolism. Hyperthyroidism is known to increase blood sugar levels.\textsuperscript{6}

Increase in thyroid hormones lead to enhanced intestinal absorption of glucose, insulin clearance,
glycogenolysis and gluconeogenesis.\textsuperscript{7} The hepatic glucose output is increased with decreased insulin action and increased lipolysis.\textsuperscript{7}

Hyperthyroid patients encounter decline in blood sugar control if they are also suffering from diabetes mellitus. Thyroid hormone excess can also sometimes precipitate diabetic ketoacidosis in diabetic patients.\textsuperscript{8} Also, the clinical features of hypermetabolic state of thyrotoxicosis and those due to hyperglycemia may be confused among each other leading to missing the diagnosis.

About half the patients of Grave’s disease exhibit glucose intolerance of variable degree and about 2–3\% may develop overt diabetes.\textsuperscript{6}

There is an escalated β-cells reaction to blood sugar levels/catecholamines perhaps secondary to expanded β-cell volume. Patients with elevated thyroid hormones may also have enhanced removal of insulin. Hyperthyroidism leads to increased glucose output from the liver and upregulates glycogenolysis producing glucose intolerance (\textit{Flowchart 1}).\textsuperscript{3,10} It has been advocated that there is hypothalamic sympathetic impact on liver along with enhanced expression of hepatic GLUT 2 transporters with resultant increase of plasma-free fatty acids.\textsuperscript{5} This situation accounts for magnification of elevated blood glucose levels in diabetics. Thyrotoxicosis can also result in state of ketoacidosis in patients with diabetes. This is secondary to the accelerated lipolytic activity and escalated liver β-oxidation.\textsuperscript{7,11}

### Hypothyroidism and Diabetes Mellitus

The most often thyroid disease that we come across in diabetes is hypothyroidism. Studies have found the occurrence of hypothyroidism in 5.7\% patients suffering from diabetes.\textsuperscript{7} The most common etiology in iodine sufficient regions being autoimmune thyroiditis.

In individuals with T1DM, repetitive events of hypoglycemia hint toward hypothyroidism. It has been shown that treatment with thyroxine lowers the blood glucose variations.\textsuperscript{12} It is documented that insulin resistant condition is seen in both overt as well subclinical hypothyroidism.\textsuperscript{13}

The impact of reduced levels of thyroid hormone on metabolism in diabetic patients is contrary to that observed in hyperthyroidism.\textsuperscript{5} Reduced thyroid hormones lead to reduced glucose absorption from gastrointestinal tract. Extended peripheral glucose accretion, lessened hepatic glucose yield, gluconeogenesis and lower peripheral glucose use is witnessed in hypothyroidism.\textsuperscript{5} The insulin stimulated glucose transport and GLUT expression are lowered. Insulin clearance is reduced and less hunger further decreases insulin. A combination of all these metabolic alterations in patients with diabetes and coexistent hypothyroidism lead to reduction in blood sugar with increased frequency of hypoglycemia (\textit{Flowchart 2}).\textsuperscript{14} Studies have also shown reduction and benefit in hypoglycemic episodes following treatment of hypothyroidism.\textsuperscript{15} Studies have correlated hypothyroidism with lowered insulin sensitivity.
Other factors:

- Role of thyroid hormones in lipid metabolism has been studied by many authors.
- They work along with controlling route for energy equilibrium and directly modify insulin equipoise and glucose disbursement by tissues.
- Triggering of melanocortin receptor type 4 (MC4R) brings about lowering of food ingestion and elevation in energy disbursement. Hypothalamic TRH neurons express these receptors which play role in central pathways of energy control.16
- Thyroxine relates to adipocytokines and gut hormones disturbing carbohydrate metabolism.
- Ghrelin hormone which impacts insulin sensitivity has been observed to have counter alliance with T3.
- The β-cell activity of insulin secretion mediated by glucose also is reduced in low thyroid hormone status.

Does Diabetes Mellitus Modify Dysfunctional Thyroid Status?

Diabetic patients have dampened diurnal TSH climax occurring at night. Also, there is weakened TSH response to TRH. Low T3 levels are witnessed in individuals with unchecked diabetes mellitus. It is seen that in diabetic individuals with unrestrained blood glucose, there may be blunted T4 to T3 conversion leading to low T3 state, which corrects with normalization of hyperglycemia.

Evidence suggests that reduced insulin sensitivity and hyperinsulinemia may cause multiplicative sequel on thyroid tissue resulting in thyromegaly and nodularity. Presence of concomitant diabetes also changes therapeutic response to thyroxine in hypothyroidism. Patients with Grave’s orbitopathy have an increased prevalence of type 1 diabetes mellitus as compared to general population. Dysthyroid optic neuropathy has higher occurrence with patients with diabetes mellitus and Grave’s orbitopathy as compared to those without diabetes mellitus.17

Lipid profile disturbances are recognized in patients with hypothyroidism. Elevated total cholesterol, LDL cholesterol, apolipoprotein B, and decreased HDL are the typical findings.15 Altered thyroid status has been correlated with dyslipidemia and insulin resistance in several studies. Literature also shows relation of hypothyroidism and obesity. Blood pressure changes in patients with hypothyroidism have also been studied by authors. Increase in systemic vascular resistance leading to high diastolic blood pressure has been documented in hypothyroidism.20 Studies documenting higher intima media thickness in hypothyroid patients suggest endothelial dysfunction resulting in increased chances of CV risk.

The escalated peripheral vascular resistance and drop in cardiac output witnessed in subclinical and overt hypothyroidism put them to increased susceptibility to nephropathy. The diabetic patients with concurrent low thyroid hormones observed good renal response to therapeutic thyroid correction. Retinopathy seen in patients with diabetes was of greater intensity in subclinical and overt hypothyroid individuals than euthyroid people.21 The above findings of high renal and eye complications documented in coexisting thyroid dysfunction in patients with type 2 diabetes provides rationale for assessing thyroid dysfunction in patients with type 2 diabetes mellitus.

Effect of Metformin on Thyroid Function

Studies document impact of metformin on thyroid function. Metformin given as therapeutic intervention for diabetes resulted in subduing of TSH in a study.22 Another study conducted on thyroid nodules revealed a decrease in nodule size with use of metformin in patients with insulin resistance.23 The studies show the effect to be without any changes in LT4 and LT3. Studies have also shown that following withdrawal of metformin there was some rebound rise in TSH levels.

Does Thyroid Dysfunction Affect Diabetic Complications?

Diabetes is a well established individual predisposing cause for cardiac ailments. Hypothyroidism is known to have independent association with atherosclerotic cardiac diseases.16 Coexistence of these disorders augment the cardiovascular risk of the patient.

Do Hypothyroid Individuals have Factitious Spike in HbA1c?

- Rising HbA1c in hypothyroid patients was witnessed in non-diabetic subjects also in a study.24 The possibility of false spike probably owing to the lower hemoglobin levels in hypothyroid subjects was suggested.
This questions the validity of using glycosylated hemoglobin for diagnosis of diabetes and management in cases with concomitant thyroid abnormalities. Summarizing diabetes mellitus and thyroid cross-linking:

- **Diabetes + Euthyroid**
  - Reduced T3, reduced responsiveness to TRH

- **Diabetes + Hyperthyroid**
  - Glycemic control worsens

- **Non-diabetic + Hyperthyroid**
  - Proceeds to glucose intolerance in half cases

- **Diabetes + Hypothyroidism**
  - More events of hypoglycemia

**Is there any Difference in Diagnosis of Hypothyroidism in Coexistent Diabetes?**

- The elucidation of tests of thyroid function in individuals with unrestrained diabetes may be erroneous.
- Typical alterations include a low-serum T3, a low-serum T4 caused by decreased protein binding, and a low-serum TSH level.
- The similar symptoms of pallor, fatigue, edema, and increase in weight being common to renal disease related to diabetes and hypothyroidism may cause overlooking the diagnosis of the other disorder if one is suspected.

When should we screen diabetics for thyroid dysfunction:

- The significant interdependence seen between thyroid function and metabolic status in T1DM patients warrants timely and adequate monitoring of thyroid levels in these subset of patients.
- Regarding T2DM patients, the consensus regarding thyroid testing is less lucid. There are either no clear cut recommendations regarding once a year screening or in opposition to routine annual estimation of thyroid status in these patients.
- More often testing for thyroid abnormalities in diabetic individuals is approved.
- Similarly, some associations endorse analysis of thyroid status in pregnancy with diabetes. They propose TSH estimation along with palpation of the thyroid gland at identification of diabetes, with systematic observation thereof in individuals with positive results.

On similar grounds, in those with abnormal lipid profile, age more than 50, TSH is proposed.

A recent analysis by Kadiyala et al. suggested a comprehensible perspective to this matter. An initial TSH and TPO antibody assessment in patients with diabetes was advocated. Accordingly a high-risk group could be identified. This group would be consisting of T1DM patients, those with elevated TSH and those with TPO antibody positive. An annual TFT evaluation in this subset would be more likely to be cost effective and yielding desired results.4

**Conclusion**

There is a multifaceted linkage between thyroid defects and diabetes mellitus. In individuals with normal blood glucose status, high thyroid hormones bring about glucose intolerance whereas amongst those with established diabetes the metabolic control gets disturbed. On the other hand, hypothyroidism increases the susceptibility of hypoglycemic episodes in diabetic individuals. Increased insulin resistance is another important feature associated with hypothyroidism. Obscure thyroid defects would have unfavorable consequence not only on diabetes but also on its complications. Therapeutic interventions of subclinical hypothyroidism in patients with diabetes would be advantageous. A structured and well outlined approach to thyroid testing in diabetic subjects is suitable; nevertheless, there is a paucity of categorical specifications in this direction.

**References**

CHAPTER 201
Thyrotoxicosis: Evaluation and Management
Manoj Saluja

Abstract
Thyrotoxicosis, or inappropriately high circulating thyroid hormone concentration causing surplus action at the tissue level, may present as a constellation of clinical manifestations. Causes vary depending on various factors like iodine intake, age, and geography. Diagnosing the entity begins with detailed history and clinical examination aided by tests like thyroid hormone profile, radio and nuclear imaging, Doppler sonogram, serology for antibodies. While management differs according to cause and patient, the target is to control symptoms (beta blockers, glucocorticoids) and treating the cause (surgery, anti-thyroid drugs, radiotherapy). Latest researches on autoimmunity and molecular targets have opened new horizons in term of diagnosis and management as well.

Introduction
Thyrotoxicosis, characterized by inappropriately high circulating thyroid hormone concentration causing surplus action at the tissue level, may present as a constellation of clinical manifestations.\(^1,2\) Hyperthyroidism, a clinical subset of thyrotoxicosis, indicates inappropriately high synthesis and secretion of hormone(s) by the thyroid.\(^1,2\)

Effective management of the disease demands an intricate knowledge of the etiologies, pathophysiology, and treatment options. A basic understanding of approaching a patient, clinical, and lab parameters is important, as is the knowledge about various therapeutic regimens.

Etiology
A multitude of causes have been identified, differing in frequency—depending on iodine intake (Graves' disease predominates in iodine sufficient regions, nodular thyroid disease in iodine deficient regions), age (toxic nodular goiter increases with age; autoimmune thyrotoxicosis is common in young and middle aged), and geography (painless thyroiditis seen in 0.5% of cases in Denmark, 22% in Wisconsin)\(^5\) (Flowchart 1).

Approach to a Patient with Suspected Thyrotoxicosis
Combined and balanced assessment of history, clinical examination, and investigations guides the physician to diagnosis and management.

History
Clinical presentation, like medical and obstetric history, drug and diet intake, familial clustering of similar disease, is important. This provides an organized approach in less time, money, and resources.

Thyrotoxicosis has specific stigmata (Flowchart 2)\(^5\) and may be suspected in presence of given signs and symptoms, concomitant type 1 diabetes/autoimmune diseases, new-onset atrial fibrillation, unexplained anxiety or change in behavior. Thyrotoxicosis typically presents with low thyroid stimulating hormone (TSH),
with (overt) or without (subclinical thyrotoxicosis) raised fT3 and fT4.

The Flowchart 3 shows the approach to a patient with suspected thyrotoxicosis.3

Laboratory Investigations/Imaging

While thyroid profile (TSH, fT3, and fT4) is done to detect the disease, further workup assists in determining the underlying cause.

Radioactive iodine uptake (RAIU) using 123I has become mainstay in diagnosing GD (diffuse uptake of radioactive iodine by the gland) and nodular thyroid disease (focal increased and decreased uptake in TMNG; uptake only in the nodule in TA). Anti-thyroid drugs (ATD) is given only in patients showing increased dye uptake, implying hyperthyroid state (Fig. 1).

Color Flow Doppler Study (CFDS) is safe and efficient, particularly useful when RAIU is contraindicated (pregnancy/breastfeeding). It distinguishes between thyroid hyperactivity (increased flow) from destructive thyroiditis and between the two types of amiodarone-induced thyroiditis (AIT).1

Measurement of TRAb, especially in thyrotoxicosis without nodular signs/orbitopathy, distinguishes between GD and other etiologies. Young age, pre-existing autoimmune diseases, a positive family history are indications for antibody assays. Reduced cost and faster diagnosis have been proven in some studies when compared to RAIU.1

99mTc pertechnetate scan is used in nodular thyroid. Ratio of total T3 to T4 is useful in assessing hyperthyroidism. A hyperactive gland produces more T3 than T4, elevating T3 above the upper limit of normal more than T4. Vice versa is true in thyroiditis1 and thyrotoxicosis factitia (exogenous levothyroxine). Acute phase reactants indicate active inflammation, as in subacute and infectious thyroiditis.

Management

We will discuss management of some of the common etiologies with a protocol for follow-up (Flowchart 4).

Graves’ Disease

Follow two steps—one, symptom control and second, treat the underlying illness. Beta-blockers are used to abate symptoms (caused by overstimulation of beta adrenergic receptors). Propranolol (non-selective) additionally inhibits peripheral conversion of T4 to T3.2 Glucocorticoids may be used in thyroid storm. For the underlying illness, radioactive iodine (RAI), ATD, and thyroidectomy are potential options. ATDs should be stopped 12–18 months after initiation to look for remission—defined as no recurrence of GD after 12 months without treatment (Table 1).2

GD may be associated with ophthalmopathy, but only 5% develop severe symptoms (diplopia, visual field defects, and blurred vision). Mild symptoms like photophobia, irritation, and tearing can be solved using tight fitting sunglasses, saline drops/gel, and application of paper tape (at night) to avoid exposure keratitis. In case of corneal abrasion due to the tape, goggles are recommended. Medical emergency may ensue if orbital edema causes optic nerve compression. In such cases, high dose glucocorticoids and orbital decompression surgery are considered.

Dermopathy—nonpitting erythematous edema on anterior shin is due to glycosaminoglycan accumulation in dermis. High potency local steroid cream with nightly occlusive plastic wraps may be advised.6
Young females may benefit from RAI and surgery more than ATD (better remission rates of former, high teratogenicity of latter), but comorbid condition/pregnancy or refusal to undergo RAI/surgery are indications to initiate ATDs.²

**Toxic Adenoma and Toxic Multinodular Goiter**

Toxic adenoma (TA) (benign monoclonal thyroid tumor) secretes excess thyroid hormones due to activating mutation in TSH receptor gene (increasing adenyl cyclase independent of TSH). TMNG or Plummer’s disease manifests as multiple autonomous nodules. Owing to this pathophysiology, ATDs show less satisfactory results and no remission despite long-term use. RAI and thyroidectomy are feasible and better management options. Selective uptake of the radioactive dye, as opposed to diffuse destruction as seen in GD, makes RAI first-line therapy unless contraindicated.² Risk of persistent hyperthyroidism is 11–20% with RAI and <1% with near-total/total thyroidectomy, but hypothyroidism at 5 years occurs in 16% and 100%, respectively.²

**Miscellaneous**

Amiodarone-induced thyroiditis, caused by direct toxicity of amiodarone and its iodine content, is treated with
long-term high dose ATDs and potassium perchlorate (type-1) or high dose prednisone (40–60 mg/day) for 1–3 months then tapered (type 2). Thyrotropin secreting pituitary adenoma is suspected if raised TSH with high T3, T4 is noted. Pituitary imaging (MRI) confirms the diagnosis. Apart from radiotherapy and/or radiosurgery, several new pharmacotherapies are being explored. Somatostatin receptors 2 and 5 on tumor cells have advocated somatostatin analogues as a possible cure or at least as a preoperative adjunct. They also express dopamine receptors, but agonists have produced variable results.

Hydatidiform mole, choriocarcinoma, testicular germ cell tumor, metastatic follicular thyroid cancer primarily require symptom control and multimodal approach to eradicate the root cause via surgery, radiation, or RAI. Detailed discussion is beyond the scope of this article.

**Thyrotoxicosis without Hyperthyroidism**

Subacute thyroiditis, seen post-viral infections due to antigenic mimicry, is painful but resolves spontaneously over a span of 2–3 months. It undergoes phases of hormonal changes: initially thyrotoxicosis caused by preformed hormone release followed by hypothyroidism due to the lack of new hormone synthesis during the disease period. Painless thyroiditis (seen in iodine sufficient areas), postpartum thyroiditis (seen after delivery/miscarriage) share an autoimmune etiology with a positive family history found more often than not. Supportive treatment is indicated beta-blockers, NSAIDs, and prednisone (for pain relief). During the latter part of disease, levothyroxine should be supplemented and tapered gradually while monitoring the hormone levels every 3–4 weeks. Selenium therapy has been tried in some
cases with inconsistent results.\textsuperscript{2,8} Drug induced thyroiditis (sunitinib, sorafenib, ipilimumab, and pembrolizumab)\textsuperscript{2,9} demands removal of offending agent and beta-blockers.

**Exogenous Thyrotoxicosis**

This may be accidental or intentional (thyrotoxicosis factitia). Intentional overdose needs appropriate counseling\textsuperscript{2} along with beta-blockers, iopanoic acid and cholestyramine. In extreme cases, plasmapheresis may be required.\textsuperscript{2,10}

**Antithyroid Pharmacotherapy**

ATD (methimazole, carbimazole, and propylthiouracil) inhibit formation of iodotyrosines in thyroglobulin (takes 2–8 weeks). PTU remains drug of choice in thyroid storm (due to its peripheral inhibition of T4 to T3) and in first trimester pregnancy. Methimazole and carbimazole have longer duration of action with once daily dosing, ensuring better compliance. Owing to teratogenicity (cutis aplasia), they are less preferred in first trimester of pregnancy, but may be restarted post 12 weeks gestation.\textsuperscript{1,2}

ATDs should be titrated every 4 weeks. Adverse reactions are mild—include fever, rash, urticarial and arthralgia, usually seen within first week of treatment. Grave side effects include agranulocytosis, aplastic anemia, hepatic failure, lupus like vasculitis. Except agranulocytosis, all are more common with PTU. Granulocyte colony-stimulating factor (G-CSF) appears to accelerate recovery in patients with agranulocytosis. Dipping prevalence of these side effects from 30/1,000 to 1/1,000 at the end of 30 and 180 days, respectively, establishes safety in long-term therapy, especially in GD.\textsuperscript{1,2}
Flowchart 4: Management and follow-up of thyrotoxicosis

Hyperthyroidism in adults: management and monitoring

Adult with hyperthyroidism
- Consider antithyroid drugs with supportive treatment while awaiting specialist assessment
- Offer antithyroid drugs in specialist care to people waiting for radioactive iodine or surgery

First-line definitive treatment
- Radioactive iodine
  Offer for:
  - Graves' and toxic multiple nodules
  - Toxic single nodule as an alternative to surgery unless pregnancy, fathering a child within 6 months, thyroid eye disease, compression or suspected thyroid malignancy
- Antithyroid drugs
  Offer for:
  - Graves' (12-to 18-month course) if likely to achieve remission or if other treatments unsuitable
  - Toxic single or multiple nodules (life-long treatment) if other treatments unsuitable
- Surgery (thyroidectomy)
  Offer for:
  - Graves' (total thyroidectomy) if compression or malignancy suspected or if other treatments unsuitable
  - Toxic multiple (total thyroidectomy) or single nodule (hemithyroidectomy) if radioactive iodine unsuitable

Monitoring and ongoing treatment
- Consider measuring TSH, FT4 and FT3 every 6 weeks for first 6 months until TSH normal
- Consider measuring TSH, FT4 and FT3 every 6 weeks until TSH normal then TSH every 3 months
  - Do not monitor full blood count or liver function unless clinical concern
- Consider radioactive iodine or surgery for Graves' with persistent or relapsed hyperthyroidism
- After stopping antithyroid drugs, consider measuring TSH within 8 weeks, then every 3 months for a year, then once a year

Hyperthyroid
- Consider antithyroid drugs until 6 months then more treatment if TSH not normal

Hypothyroid
- Offer levothyroxine if not taking antithyroid drugs

Euthyroid
- Consider measuring TSH at 9 and 12 months and then every 6 months if TSH normal at 12 months

(A) With cascading—measuring FT4 in the same sample if TSH above reference range, and FT4 and FT3 in the same sample if TSH below reference range
Monitoring of liver function and explaining the possible reactions to the patients are quintessential. Up to 750 mg/day of PTU or 20 mg/day of methimazole in lactating mothers does not affect infants’ thyroid function.\(^{11}\)

Severe thyrotoxicosis calls for use of additive therapy with saturated solution of potassium iodide (SSKI) at a dosage of 10 drops twice daily, iopanoic acid at 1 g/day, cholestyramine (enhances enterohepatic clearance of thyroid hormone) up to 12 gm in three divided doses (for 4 weeks).\(^{1,2}\)

### Radioactive Iodine Therapy

RAI is effective, safe, avoids hospitalization with higher cure and lower recurrence rates. It causes thyroid specific fibrosis of the gland over weeks to months.\(^{2,13}\) \(^{131}\)I is administered at 75–200 \(\mu\)Ci/g of estimated thyroid tissue divided by percent of \(^{123}\)I uptake in 24 hours.\(^{1}\)

It is absolutely contraindicated in children (<5 years), pregnancy (as it causes fetal hypothyroidism) and in lactating mothers. Patients are counseled to avoid conception for 3–6 months post RAI therapy. Severe ophthalmopathy could be exacerbated, so is either avoided or given with concomitant glucocorticoid therapy (prednisone 0.4 mg/kg for 1 month with subsequent taper).\(^{2}\) To diminish the risk of worsened thyrotoxicosis, pretreatment with ATD (methimazole than PTU) may be considered for 3–5 days.

### Thyroidectomy

Subtotal, near-total, total thyroidectomies are various options available. Severe hyperthyroidism in children, pregnant females noncompliant or intolerant to ATDs, patients with large goiters, severe ophthalmopathy, suspicious nodules, refractory AIT, and patients with unstable cardiac conditions are common indications.\(^{6}\)

Prior to the surgery, euthyroid state should be achieved using beta-blockers (target heart rate <80/minute), ATDs (4–8 weeks) and stable (cold) iodine treatment. SSKI (1–2 drops daily for 10–14 days) is administered after ATDs and before the procedure. It reduces hormone secretion and decreasing gland vascularity (moderates intraoperative blood loss). Preoperative single dose dexamethasone (8 mg) is suggested avoid post-procedure nausea, vomiting, and pain.\(^{1,2,6}\) Laryngeal nerve injury and hypoparathyroidism are possible complications. Hormone levels are checked every 4–8 weeks and T4 is titrated accordingly (started at 50–75 \(\mu\)g/day).

Endoscopic technique is a novel approach with better cosmetic satisfaction, lesser complications, and reduced time. Any surgical procedure, open, or endoscopic, yields better result if performed by a high-volume thyroid surgeon (>25 surgeries/year).\(^{12}\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Dosing</th>
<th>Remission rate (%)</th>
<th>Adverse effects</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATDs(^a)</td>
<td>Block TPO</td>
<td>Initial dose proportional to degree of elevation of thyroid hormones, symptoms, and goiter size</td>
<td>30–60</td>
<td>Dose and duration dependent Rash, elevated liver enzymes, agranulocytosis (0.3%), vasculitis (&lt;0.1%)</td>
<td>MMI ↑ Risk of congenital abnormalities; recommended in 2nd and 3rd trimester. PTU Lower teratogenic risk, ↑ risk of hepatotoxicity; recommended in 1st trimester All ATDs ↑ Risk of fetal hypothyroidism</td>
</tr>
<tr>
<td>Radioactive iodine (^{131})I</td>
<td>Thyroid follicular cell necrosis</td>
<td>Fixed or calculated dose based on goiter size and uptake</td>
<td>80–90</td>
<td>Worsening thyrotoxicosis/orbitopathy, Thyroiditis</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Thyroid surgery</td>
<td>Removal of thyroid tissue</td>
<td>Total thyroidectomy</td>
<td>100</td>
<td>Hypoparathyroidism, laryngeal nerve injury</td>
<td>Done in 2nd trimester</td>
</tr>
</tbody>
</table>

\(^a\) ATDs, anti-thyroid drugs; MMI, methimazole; PTU, propylthiouracil; TPO, thyroid peroxidase; T3, triiodothyronine; T4, thyroxine; ↑, increased. \(^b\) Blocks TPO and peripheral T4 to T3 conversion.
Pitfalls, Controversies, and Unanswered Questions

Biotin has proven to cause spurious diagnosis of GD, especially at a dose of more than 10 mg/day, hence should be avoided for at least 12 hours prior to testing. Second common pitfall is misdiagnosing iodine deficiency for thyrotoxicosis under the setting of increased radioiodine uptake by the gland. Amplified uptake but normal T3/T4/TSH implies iodine deficiency than endogenous hyperthyroidism.

Treatment of subclinical thyrotoxicosis has been a matter of debate for long. Current guidelines recommend treatment in case TSH is persistently <0.1 Mu/L. Risk reduction of atrial fibrillation and low bone density in postmenopausal women is seen.

Questions concerning optimum dose and duration of ATD in GD, use of ATDs before and after RAI therapy, risk benefit ratio of block replacement regimen during RAI therapy, role of rituximab, lanreotide remain largely unanswered. Immunomodulatory therapy is being tested for GD.

Conclusion

The evaluation for cause should begin from the clinical picture itself to be supported by biochemical tests, nuclear medicine, and ultrasound imaging. Increased gland function remains an important aspect for therapy selection. GD and MNG remain the common causes. Long-term ATDs have replaced RAI and surgery for managing GD, except in special circumstances, while nodular goiter fare less well with ATDs. Thyroiditis constitutes major cause of thyrotoxicosis in absence of a hyperfunctioning gland. Thyroid autoimmunity has huge scope for developing novel therapies, particularly GD by addressing the pathophysiology itself. From redressal of less effective therapies to identifying newer targets at a molecular level, we have definitely come a long way with even better prospects in near future.

References

2. Sharma A, Stan MN. Thyrotoxicosis: Diagnosis and Management; Mayo Clinic Proceedings. 2019;94(6):1048-64.
**Abstract**

Polyuria is defined as urinary output more than 50 mL/kg/day or 3–3.5 L/day. It should be differentiated from increased urinary frequency by proper history and documentation of increased urinary volume. Polyuria can be due to solute diuresis or water diuresis. In most cases of solute diuresis the etiology is evident from history, physical examination and baseline laboratory investigations. For water diuresis a detailed history and physical examination and a number of tests consisting of serum sodium and other electrolytes, paired plasma and urine osmolality, water deprivation test, hypertonic saline infusion, and plasma copeptin levels help establish the diagnosis.

**Introduction**

Polyuria is defined as urinary output more than 50 mL/kg/day or 3–3.5 L/day. It should be differentiated from increased urinary frequency. Polyuria can interrupt daily activities, disturb sleep, and cause bed-wetting in children. The two major types of polyuria are solute and water diuresis.

**Water Homoeostasis**

Extracellular fluid balance is under control of two factors: Antidiuretic hormone (ADH) also known as arginine vasopressin (AVP) and thirst. A rise in serum osmolality (most sensitive to serum sodium) and hypovolemia sensed by baroreceptors stimulate ADH secretion and thirst. ADH (V2) receptors are located at the luminal side of collecting duct of the kidney. On receptor binding, ADH leads to cAMP production with translocation of aquaporin 2 channels to luminal membrane, allowing reabsorption of water from lumen forming concentrated urine. Water moves out of the tubule along the concentration gradient created and maintained by reabsorption of solutes in thick ascending loop of Henle thereby producing hypertonic renal medullary interstitium. The sensation of thirst and ADH secretion is suppressed upon normalization of ECF volume and serum osmolality (280–295 mOsm/kg).

**Determinants of Daily Urine Output**

The daily urine output is dependent on solute load and concentrating ability of the nephron. Polyuria can therefore be solute diuresis, water diuresis, or both.

Solute diuresis due to excess saline/hypertonic saline infusion, protein excess with urea generation, glucose, and mannitol produces concentrated urine. Water diuresis (polyuria-polydipsia syndrome) producing dilute urine is of two types: diabetes insipidus (DI) and primary polydipsia (PP). In central diabetes insipidus (CDI), there is partial or complete ADH deficiency; in nephrogenic DI (NDI), there is resistance ADH action. Excessive water intake in absence of physiological stimulus, often in the background of psychiatric disorders is seen in PP. Sometimes solute and water diuresis coexist, for example, ADH deficiency/resistance with solute diuresis. Chronic
renal failure, infiltrative renal parenchymal disease and relief of longstanding urinary obstruction sometimes have a mixed solute and water diuresis. Sometimes DI is seen in pregnancy due to placental vasopressinase increasing ADH breakdown and transient ADH resistance in second half of pregnancy (Table 1).

**Approach to a Patient with Polyuria**

**History**

A detailed history regarding age and mode of onset, progression, and duration of polyuria and family history should be taken. Polyuria should be differentiated from increased urinary frequency. Hereditary NDI typically has a neonatal presentation; most craniopharyngiomas present in childhood and adolescence; infiltration, tumors, and metastasis present in any age. Polyuria with weight loss with family/personal history of diabetes mellitus suggests diabetes mellitus/uncontrolled hyperglycemia; polyuria after recent acute kidney injury, high protein diet/supplement and after release of urinary tract obstruction suggests urea-induced diuresis. In glucocorticoid excess states, polyuria occurs due to hyperglycemia and protein breakdown with urea generation. A detailed medication history, history of head injury, or central nervous system surgery is important. Mannitol and hypertonic saline cause solute diuresis; many drugs cause NDI. Patients with DI prefer cold water; in CDI symptoms develop almost suddenly (as urine concentrating capacity is maintained until ADH synthesis decreases to 10–15% of normal); in PP symptoms develop gradually. Patients with PP may have coexisting psychiatric illness. These are not precise discriminating criteria and overlap exists in clinical features of CDI, NDI, and PP. The etiology of DI may be evident at presentation. Polyuria in a non-diabetic patient with breast cancer could be due to metastasis to posterior pituitary or hypercalcemia of malignancy. Metastasis to posterior pituitary is more common than to anterior pituitary as the systemic circulation supplies the posterior pituitary whereas the hypophyseal portal system supplies the anterior pituitary. DI due to craniopharyngioma may present with growth retardation and visual impairment.

<table>
<thead>
<tr>
<th>Table 1 Causes of polyuria</th>
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<tr>
<td><strong>Osmotic diuresis</strong></td>
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<tr>
<td>Glucosuria</td>
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<td>Urea diuresis</td>
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<tr>
<td>• Resolving phase of acute kidney injury</td>
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<tr>
<td>• High protein diet</td>
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<tr>
<td>• Glucocorticoid excess → protein breakdown → urea generation</td>
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<tr>
<td>Sodium diuresis</td>
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<tr>
<td>• Large volume of saline/ hypertonic saline</td>
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<td>• Post release of bilateral urinary tract obstruction</td>
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<tr>
<td>Mannitol</td>
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Often the etiology is not obvious on presentation and unfolds as investigations progress, for example, infiltrative disorders, tumors, hypercalcemia, hypokalemia in Bartter syndrome, etc.

In most patients with DI, presence of intact thirst mechanism ensures that sodium levels are within normal. However, DI may present with hypernatremia in patients with limited access to water or unable to express thirst, for example, elderly people living alone, patients admitted in intensive care, infants, and in adipsic (impaired thirst) hypernatremia. Typically, patients with DI visiting a physician in out-patient setting complaining of polyuria have normal sodium levels; whereas those in intensive care setting, infants and elderly living alone may have hypernatremia.

**Physical Examination**

Clinical examination is unremarkable in most cases; however, one should look for wasting (diabetes, malignancy), evidence of glucocorticoid excess, and enlarged kidneys on abdominal palpation. Anthropometric evaluation in a child and confrontation perimetry is to be done when history or physical examination suggests sellar or suprasellar mass. Hypernatremic patients may have irritability, disorientation, unconsciousness, seizures, and focal neurologic deficits.

**Investigations**

**Confirm Polyuria**

While evaluating any case of polyuria, one must confirm it by advising patients to maintain a home fluid intake and output record. A 24-hour urine output and creatinine measurements help confirm polyuria and adequacy of urine collection, respectively.

**Baseline Investigations**

Baseline investigation include plasma glucose, HbA1c, urea, creatinine, complete hemogram, thyroid function tests, sodium, potassium, calcium, potassium, plasma and urine osmolality, urine routine examination including specific gravity (normal 1.010–1.025; low in DI); and other tests as history and physical examination suggest.

**Paired Serum and Urine Osmolality**

Baseline paired serum and urine osmolality gives valuable information. The hallmark of DI is production of large volume of dilute urine. Urine osmolality less than 300 mOsm/kg with normal, or slightly elevated serum, osmolality suggests DI. To ascertain DI type; confirmatory tests like water deprivation test and hypertonic saline infusion test are required. The water deprivation test is labor intensive and both tests entail some risk in susceptible individuals. Fortunately, the water deprivation and hypertonic saline tests are not indicated in every patient with polyuria.

**Polyuria in Hypernatremic Patients**

Hypernatremic patients with polyuria, with urine osmolality less than 300 mosmol/kg, have DI and water deprivation test is not required as ADH is already stimulated to maximally concentrate urine. The next step is differentiation between NDI and CDI by evaluating response to desmopressin (Box 1).

Hypernatremic polyuric patients with urine osmolality more than 600 mosmol/kg have solute diuresis; however, mixed osmotic and water diuresis may be present. If on giving hypotonic fluids despite normalization of serum sodium, urine osmolality remains more than 600 mosmol/kg, diagnosis is solute diuresis. If on giving hypotonic fluids, urine osmolality falls to 300–600 mosmol/kg before sodium comes down to less than 145 mEq/L, diagnosis is mixed osmotic and water diuresis. If on giving hypotonic fluids, urine osmolality falls to less than 300 mosmol/kg before sodium comes down

**BOX 1 Assessing desmopressin response to differentiate between CDI, NDI, and PP**

- Desmopressin is given at a dose of 10 μg by nasal insufflation or 2–4 μg subcutaneously or intravenously. Urine osmolality is measured every 30 minutes for the next 2 hours.
- Complete NDI: Urine osmolality rises <15% to a value <300 mOsmol/kg
- Partial NDI: Urine osmolality rises 15–45% to a value <300 mOsmol/kg
- Complete CDI: Urine osmolality rises >100% to a value >300 mOsmol/kg
- Partial CDI: Urine osmolality rises to 15–100% to a value >300 mOsmol/kg
- Non-diagnostic: Minimal or no rise in urine osmolality to a value >300 mOsmol/kg. In most cases non-diagnostic results are seen in partial CDI and PP
- A baseline (without desmopressin) plasma copeptin >21.4 pmol/L suggest NDI
to less than 145 mEq/L, diagnosis is DI. Desmopressin response will determine DI type (Box 1).

Hypernatremic polyuric patients with urine osmolality 300–600 mosmol/kg may have solute or water diuresis. A total daily osmolar output (urinary osmolality × 24-hour urine output in litres) more than 1,000 mosmol indicates solute diuresis and less than 900 mosmol suggests water diuresis (DI). Desmopressin response will determine the DI type (Box 1).

Polyuria in Normonatremic Patients

Normonatremic patients with urine osmolality more than 600 mosmol/kg have osmotic diuresis. The diagnosis is frequently obvious from history and laboratory investigations.

Normonatremic patients with urine osmolality 300–600 mosmol/kg may have solute diuresis, DI, or PP. A total daily osmolar output more than 1,000 mosmol indicates solute diuresis and lesser suggest water diuresis.

Normonatremic patients with urine osmolality of less than 300 mosmol/kg suggest water diuresis.

Determining the Cause of Water Diuresis in Normonatremic Patients

The next step in water diuresis is to determine the cause namely CDI, NDI, and PP.

If history and investigations suggest NDI, for example, bilateral urinary tract obstruction, hypercalcemia, long-term lithium use, and presenting in infancy with family history of DI; water deprivation test may not be done. A baseline plasma copeptin level or desmopressin response may be directly evaluated to confirm NDI (Box 1).

In other cases of normonatremic polyuria [urine osmolality <300 mosmol/kg (and where NDI is not the obvious etiology) and total daily osmolar output <1,000 mosmol]]; water deprivation or thirsting test is done to raise the serum sodium more than 145 mEq/L and plasma osmolality more than 295 mosmol/kg to stimulate ADH to maximally concentrate urine.

The adequacy of ADH secretion and/or action can be assessed indirectly or directly. In indirect testing, at end water deprivation or hypertonic saline infusion, the urine osmolar response to exogenous AVP or desmopressin is assessed to classify the diuresis as CDI, NDI, and PP. In direct test, direct measurement of AVP or copeptin is done upon osmotic stimulation. Plasma AVP below, above, and at normal is diagnosed as CDI, NDI, and PP, respectively. However, AVP measurement provided a correct diagnosis in only 38% cases and was especially weak in differentiating partial CDI from PP. AVP limitations include its platelets binding, instability in isolated plasma even at –20°C and insensitivity of commercially available assays. Copeptin a 39-amino acid peptide is the C-terminal glycoprotein moiety of AVP prohormone pre-pro-vasopressin. It is cosecreted in equimolar amounts with AVP and neurophysin II. Copeptin is a surrogate marker for AVP secretion because of long half-life, insignificant diurnal variation, and absence of extraction step or pre-analytical procedures for testing.

Water Deprivation Test

Before subjecting patient to the test, moderate fluid restriction for few days re-establishes medullary hypertonicity, which might have been lost (medullary washout) due to excessive water intake in psychogenic causes. This could have led to persistent serum hypoosmolality with wash out of solutes from medulla; hindering ADH mediated water reabsorption.

All fluids are withheld during the test to induce dehydration to stimulate maximal ADH secretion. It is important to ensure patients have no access to drinking water during the test (to avoid surreptitious drinking); avoid cigarette and caffeine in preceding 24 hours; and are free from non-osmotic stimuli for ADH release (e.g., nausea and vomiting). In patients with severe symptoms (e.g., complete forms of DI), few hours of fluid restriction cause sufficient dehydration. Thus, the test can be started in the morning. In mild disorders (e.g., PP), it can take several hours for sufficient dehydration, the test may need to begin the previous night. Duration of fluid deprivation may range 4–18 hours.

At the beginning of test, patient is asked to void urine and initial body weight measured. Hourly monitoring of body weight, serum sodium, urine volume, and urine osmolality is done. The test is terminated when dehydration is sufficient enough determined by body weight reduction of 3%, serum sodium more than 145 mEq/L or no further increase in urine osmolality (three consecutive urine samples with osmolality <30 mOsm/kg variability). At test, termination plasma sodium, osmolality, and AVP/copeptin are measured. The patient is administered AVP or desmopressin and response
assessed. Giving exogenous AVP (or desmopressin) before serum sodium is more than 145 mEq/L cannot distinguish CDI from PP, since in both cases ADH levels are submaximal and will anyway respond to exogenous AVP or desmopressin. Therefore, maximum endogenous ADH secretion should be ensured by increasing serum sodium (>145 mEq/L) and osmolality (>295 mosmol/kg) before response to AVP or desmopressin is assessed.

**Hypertonic Saline Infusion Test**

Hypertonic saline infusion maybe used in place of water deprivation or may be used to supplement the water deprivation when it is insufficient to raise the serum osmolality to more than 295 mOsm/kg and serum sodium more than 145 mEq/L (often in primary polydipsia or partial DI). 3% NaCl is infused @ 0.1 mL/kg/minute for 1–2 hours till serum osmolality and sodium are more than 295 mOsm/kg and more than 145 mEq/L, respectively. Hypertonic saline infusion should be avoided in high-risk individuals.

**Interpretation**

- If at the end of water deprivation and/or hypertonic saline infusion test the urine osmolality more than 700 mosmol/kg, diagnosis is PP. If the urine osmolality less than 700 mosmol/kg it can be CDI, NDI, or PP.
- Assess desmopressin response, if urine osmolality of less than 700 mosmol/kg to differentiate CDI, NDI, or PP (Box 1).
- Plasma copeptin more than 4.9 pmol/L at end of the test (when serum sodium was >145 mEq/L) suggests PP and lower value suggests partial CDI.
- Therapeutic trial of desmopressin help differentiates PP from partial CDI. Desmopressin 10 μg/day is given intranasally for 3 days. Patients are advised to limit fluid intake to 1.5–2 liters/day. Thirst and polyuria are assessed; and urine osmolality and plasma sodium measured twice daily. In partial CDI, there is resolution of symptoms of thirst and polyuria; whereas persistent thirst, non-adherence to fluid restriction, and development of hyponatremia suggest PP.

**Polyuria in Hyponatremic Patients**

Hyponatremia, low urine osmolality (less than half of plasma osmolality) in polyuric patients, suggests water overload due to PP. Hyponatremia, polyuria, and high urine osmolality suggests osmotic (solute) diuresis.

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**Flowchart 1: A simplified approach to polyuria**

![Flowchart 1](image-url)
A Simplified Approach to Polyuria

Patients with polyuria should initially be classified as solute or water diuresis. In solute diuresis the cause is often obvious from history, physical examination, and baseline investigations. To further classify water diuresis, more tests are needed. Due to limitations of the indirect tests and increasing availability and reliability of copeptin measurements, a simplified approach to water diuresis is suggested (Flowchart 1).

Additional Testing

The polyuria type will determine additional testing. If history, physical examination, and laboratory evaluation suggest osmotic diuresis; the differential diagnosis are narrowed to diabetes mellitus, urea, saline/hypertonic saline, and mannitol. If evaluation suggests partial or central DI, MRI focusing on the hypothalamus and pituitary is required. It may show mass lesions; and loss of posterior pituitary bright spot in CDI. The bright spot results from T1-shortening effects of AVP stored in the neurosecretory granules. In PP the bright spot is usually seen. However, sometimes in NDI the bright spot may be absent due to prolonged stimulus for vasopressin release. If evaluation suggest NDI; offending drugs, anatomic lesions of kidney and other systemic illness should be looked for. In PP no further testing other than counseling is required.

Conclusion

The diagnosis of polyuria can be challenging and needs to be differentiated from increased urinary frequency. A systematic approach, including detailed history, physical examination, and appropriate laboratory testing, helps in diagnosis in most cases.

References

**Abstract**

Abnormalities in thyroid function test in a hospitalized patient are not always carried forward from the past; some do develop during the course of current systemic illness as well. Such abnormalities, where thyroid gland by itself is not at fault, are categorized under the heading, non-thyroidal illness syndrome. The commonest amongst such abnormalities is lowering of serum T3. Sometimes, serum T4 and TSH may also be reduced. These may develop because of alteration in synthesis, transportation, metabolism, or regulation of these hormones at different levels of hypothalamus-pituitary-thyroid axis. Most of these changes gradually return back to normal but the extent of correction and its exact course can’t yet been defined very well. Therapeutic interventions in these cases have been found to be largely futile in most cases though T3 supplementation has been shown to be of partial help in some cardiac patients.

**Introduction of the Clinical Case**

Abnormalities in thyroid hormone tests (TFT) are a frequent finding in patients admitted in ICU or wards because of various systemic illnesses. Many of them have had normal TFT in the past and some are found with normal TFT in follow-up as well. This poses a question upon the genesis of these abnormalities in patients suffering from systemic illnesses. Today, in this Postgraduate Clinic, we will discuss about a similar patient and will try to understand the disorder in a thorough manner.

A 63-year-old female was admitted in near ICU for altered sensorium and right hemiplegia, two days back. Her TFT revealed low serum T3, low normal serum T4 and mid normal serum TSH. Her family members informed that her TFT was absolutely within normal limits, just 2 months back.

**Question:** Given this scenario, how would you interpret current low T3?

**Answer:** Normal TFT, and also normal T3, 2 months back suggests that the lady was not carrying any thyroid disorder in the past. Low T3 observed during cerebrovascular event can therefore suggest that it might have been produced by the effect of systemic non-thyroidal illness (NTI) on the thyroid hormones (TH) rather than being produced because of any organic disorder of the thyroid gland itself. Such abnormalities in TFT, which arise after any NTI and are not produced by the disorder of thyroid gland itself, are called non-thyroidal illness syndrome (NTIS). Considering TFT to be normal before and after the NTI, such abnormalities in the past were also known as sick euthyroid syndrome. The nomenclature has now been discarded because normalcy cannot be assured in future, always.1,2

**Question:** Name some disorders which can make a person prone for NTIS.

**Answer:** NTIS can be observed in as high as 70% patients admitted in the ICU.3 Some common disorders associated with NTIS are as follows:
Severe critical illnesses: Such as pneumonia, septicemia, MI, CHF, respiratory failure, IBD, cirrhosis, CRF, DKA, and malignancies.

Trauma and major surgeries: Such as CABG

Deprivation of calories: Such as starvation and anorexia nervosa

Question: Does NTIS affect serum T3 only or it has any other clinical characteristics as well?

Answer: Clinical characteristics observed in NTIS are actually that of NTI and not because of abnormalities in TFT. Even total deficiency of TH may take as long as 2–3 weeks in producing its effects. So, even with the given abnormality of TFT, most patients appear to be clinically euthyroid. In the absence of any discernible clinical finding specific for the thyroid, NTIS is classified according to its laboratory characteristics only.

Low T3 syndrome—This is the commonest presentation of NTIS, which is seen in nearly 70% (40–100%) cases. It is often associated with elevated serum reverse T3 levels. Serum T4 and TSH levels are usually normal in the beginning.3–5

Low T4 syndrome—With the progression of systemic illness, serum T4 level also starts declining along with serum T3.1

Low TSH—Acute incident events such as major trauma, MI, or surgery are immediately associated with transient TSH elevation but progression of systemic illness may lead to fall in serum TSH levels in nearly 10% of such cases.1

Question: What could be the pathophysiology of abnormalities in TFTs in NTIS?

Answer: NTI may affect every aspect of TH including its secretion, peripheral metabolism, and action.

Low T3 syndrome (downregulation of T3 content in target tissues)—Low serum T3 is the initial feature of NTIS, which is associated with fall in tissue T3 concentration and its effects. It can be produced because of following factors.

Inhibition of conversion of T4 into T3—Approximately 80% of circulatory T3 is derived from the deionization of T4 by 5’-deiodinase type 1 (D1). NTIS leads to downregulation of D1 leading to reduced T4 to T3 conversion and therefore low serum T3.6

Inactivation of T3 and production of reverse T3—Another enzyme, 5’-deiodinase type 3 (D3), converts T4 into reverse T3. This is upregulated in NTIS leading to increased synthesis of reverse T3. In addition to converting T4 into T3, D1 is also responsible for metabolism of reverse T3. Downregulation of D1 in NTIS reduces its metabolism as well which is the main reason behind rise in reverse T3 in NTIS.7 T4 metabolism in NTIS, thus is diverted toward the formation of bio-inactive reverse T3 in place of bioactive T3.

Inhibition of TH uptake into the cell and binding of T3 with its nuclear receptor—Numerous cytokines can be produced during systemic illnesses such as IFN-gamma and Nonesterified fatty acids (NEFA). These may interfere with the entry of TH into the target cell and their interaction with TH receptor. It creates a situation of tissue hypothyroidism in NTIS.8

Low T4 syndrome (downregulation of T4 content in circulation)—Fall in serum T4 is an indicator of rising severity of NTIS. This can be produced because of two main reasons.

Increased metabolism of T4—Systemic illnesses are often associated with fall in tissue perfusion. This may be associated with expression of D3 which converts T4 into reverse T3.7 This leads to rise in serum reverse T3 level and fall in serum T4 level.

Inhibition of binding of T4 to TH binding proteins—Not only the metabolism, but the circulatory transportation of T4 is also affected in NTIS. As an acute phase reactant, serum albumin concentration falls in any acute illness. NEFA, which is otherwise bound to this albumin; therefore, increases in circulation. It displaces TH from TBG, which leads to fall in total T4 (and total T3) concentrations.5 Free T4 and T3 hormone concentrations largely remain unaffected.8,9

Low TSH (central downregulation of hypothalamic TRH and pituitary TSH release)—NTIS may be associated with reduction in sensitivity of thyrotrophs toward TRH leading to fall in TSH secretion. This too may arise out of two reasons.

Cytokines induced direct suppression of TSH—Cytokines, especially interleukins (mainly IL6), tumor necrosis factor (TNF alpha) and interferons (IFN beta), can directly suppress thyrotrophs to reduce TSH secretion.5

Reduced stimulation of TSH secretion—Thyrotrophs possesses a different set of enzyme, deiodinase type 2 (D2), which converts intra-pituitary T4 into T3. T3 thus produced within the thyrotrophs is responsible for negative feedback and suppression of TSH secretion. This D2 is up regulated in NTIS, leading to rise in intra-pituitary T3 and suppression of TSH secretion.5 NTIS,
thus is associated with exactly opposite effects on tissue T3 concentrations. Tissue T3 concentration falls in peripheral tissues but rises in thyrotrophs.

Reduced T3 concentration in target tissues and its reduced binding with TH receptors favors the hypothesis that NTIS is not merely an adaptive response to the systemic illness but is an actual state of “tissue hypothyroidism.” Initial changes could be the compensatory responses toward a systemic illness but prolongation of this adaptation definitely becomes harmful in the long term.8

**Question:** What are the differential diagnoses for various abnormalities found in TFT in NTIS?

**Answer:** In fact, abnormalities in TFT, seen in NTIS, may mimic any organic disorder of the thyroid gland.

Low or low normal serum T3, T4, and elevated serum TSH level, sometimes found in the initial course of the disease may mimic Hashimoto thyroiditis and subclinical or overt hypothyroidism.

Midnormal or low normal serum T3, T4, and low TSH level, often seen in advanced NTIS may mimic subclinical thyrotoxicosis or central hypothyroidism.

NTIS may not only produce new changes in TFT, which may mimic organic disorders of thyroid gland, but may also interfere with the detection of its preexisting organic disorders as well. Chronic severe NTIS and use of dopamine or glaucorticoid therapy may lead to marked suppression of TSH secretion. This may interfere with the diagnosis of untreated or partially treated thyroprivic hypothyroidism. Similarly, low serum T3 in NTIS will change the reflection of T3+T4 thyrotoxicosis into T4 toxicosis alone.1,8

Raised serum T3, low serum reverse T3, markedly disturbed serum TSH (>20 mIU/L or <0.1 mIU/L) and presence of antithyroid antibodies may be the indicators of organic thyroid disorders along with systemic illnesses.5,8

Above mentioned facts preclude the policy of routine screening of critically ill patients for thyroid dysfunctions. In fact, during any critical systemic illness, only those patients should be screened for thyroid dysfunctions in whom there is a high degree of clinical suspicion of any organic disorder of thyroid gland.

**Question:** Does NTIS carry any prognostic significance as well?

**Answer:** Serum T3 levels have been found to be inversely proportional to the severity of NTI. Low serum T3 levels observed during coronary angiography are not only associated with significant morbidities but have been found to carry 1.8× higher risk of total mortality and 2.5× higher risk of cardiac mortality as well.10

Low T4 level with NTI actually points toward a much grave prognosis. Serum T4 <4 mcg/dL may increase mortality by 50% and level <2 mcg/dL may increase it up to 80%.1,5,8,10-13

**Question:** If low T3, T4, and TSH are so clearly linked with poorer clinical outcomes then should these patients be offered TH supplementation?

**Answer:** NTIS was earlier thought to be just compensatory adaptation of acute systemic illnesses only but the view is gradually changing. Now we know that this adaptation is not always beneficial for the patient. Many clinical studies have been performed in recent past to look for the effects of TH supplementation in such cases.

**Intravenous T4 therapy**—Intravenous T4 therapy (1.5 mcg/kg/d IV) has been tried in some critically ill patients with low serum T4 concentration. Contrary to the presumptions, it could not reduce total mortality rate.14,15

Inability to normalize serum T3 level was opined to be the reason for its inefficacy.8

**T3 Therapy**—In an attempt to normalize serum T3 levels, T3 supplementation was also tried but this too could not reduce mortality.16

Till date, clinical benefits of TH supplementation have been observed in cardiac patients only.17 Its hypothesized that IV T3 supplementation should at least be tried in patients with NTIS in whom serum T4 level is less than 4 mcg/dL. With clinical recovery in NTI, it can be switched to oral T4 supplementation.8

**TRH therapy**—Knowing that the hypothalamic-pituitary set point is low in patients with NTIS, TRH therapy has also been tried in it. It could successfully normalize serum TSH, T4, T3, and reverse T3 levels. Considering the catabolic state of these ill patients, addition of growth hormone to TRH has been found to be more effective in raising anabolic activities in these patients.13,18

**Conclusion**

It can clearly be understood that systemic illnesses can affect TFT in variety of manners. Many of these affections have been recognized well and there pathogenesis have also been deciphered up to some extent. Yet, there are still many unseen facets of this disorder which are restricting us from offering any meaningful therapy to our patients.
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Abstract
The knowledge on practical management of thyroid disorders with precision is ever expanding as a huge number of cases are detected because of easy availability of investigation facility. However, all the cases with abnormal results of thyroid function do not require treatment immediately, or nor ever. In this chapter, brief analysis of relevant investigation and modalities of treatment on such entities of thyroid disorders is presented.

Introduction
For long time, the diagnosis of hypothyroidism was only clinical. It used to be suspected only after manifestation of myxedema (spotters in undergraduate examination) and hyperthyroidism on development of features of Graves or hypermetabolic state. Later indirect tests like effective thyroxine ratio was available, but not within reach. Hence, clinical parameters were only the guidance to manage the cases until availability of triiodo thyroxine (T3), tetraiodo thyroxine (T4), and thyroid stimulating hormone (TSH).1

Ever since direct hormone assay (T3, T4, TSH) is widely available for past three decades, there is great leap in detection of number of thyroid disorders and management precision. In the last decade, diagnosis of thyroid disorders clinically has become a rarity and physician is encountered with abnormal reports of thyroid function tests for opinion. This is because the thyroid function tests are done as routine in non-thyroid illness and sometimes on self motivation. Potentially misleading reports may result in mistakes of management. In such a scenario, physician is expected to guide the patient for further appropriate investigations, final diagnosis, plan of long-term treatment, and management. This article focuses on discussed issues of thyroid functional disorders to guide the physician approach.

Common Mistakes
- Proceeding further without recheck of the laboratory results
- Not ordering further investigations
- Starting on medicines on certain thyroid disorders, which spontaneously remit
- Use and abuse of iodine
- Under utilization of radioisotope scanning of thyroid
- Hurry to start on medicines in subclinical hypo- and hyperthyroidism
- Monitoring of treatment of hyperthyroidism by TSH levels
- Selection of modalities of treatment (anti-thyroid drugs, radioiodine ablation, surgery) in hyperthyroidism
- Pregnancy versus thyroid disorders
- Diet restriction
common Abnormalities in Thyroid function test (TFT)

- Increased TSH, normal/abnormal T3, T4
- Decreased TSH, normal/abnormal T3, T4
- Goiter or swelling of thyroid with normal TSH, T3, T4

Further investigations:
- Confirm the abnormality by repeating first line investigation TFT, since the treatment is prolonged and/or destructive
- Estimation of thyroid antibodies
  - Thyroid peroxidase antibodies (TPO)
  - Thyroglobulin antibodies (Tg-Ab)
  - TSH receptor antibodies (Tr-Ab), assay form of thyroid receptor stimulating immunoglobulin (TSI) used to predict neonatal thyrotoxicosis

The above antibodies tests are neither 100% sensitive nor specific. TPO assay is commonly done to assess the immune status of the disease, rest of the tests are not routinely done and expensive. TPO and Tg-Ab present in normal population, autoimmune hypothyroidism, Grave’s disease, multinodular goiter (MNG), transient thyroiditis. Where as Tr-Ab is absent in normal population, MNG, transient thyroiditis, and present in Grave, autoimmune hypothyroidism. Goiter and TPO-Ab are absent in secondary hypothyroidism.

- Ultrasound neck—it is done to know the size of thyroid, nodules in the thyroid gland, and for the presence of increased vascularity seen in Grave’s disease.
- Fine needle aspiration cytology (FNAC) usually ultrasound guided is done to differentiate benign and malignant lesions and also to note lymphocytic infiltration suggestive of autoimmune thyroiditis.
- Radioisotope scanning of thyroid—it is very specific investigation in differentiation of hyperthyroidism etiologically. Transient thyroiditis like sub-acute, viral, postpartum thyroiditis shows low uptake of tracer because of follicular damage. In Grave’s disease, gland is enlarged with homogenous increased uptake of tracer. Toxic adenoma shows focal areas of increased uptake of tracer and suppressed uptake in the remainder of the gland. Toxic multi-nodular gland is enlarged with increased and decreased uptake of tracer. Cold nodule (absence of uptake of tracer) suggestive of neoplastic lesion.

Disorders with Increased TSH, Normal/Abnormal T3, and T4

- Hashimoto’s/autoimmune thyroiditis, atrophic thyroiditis (end stage). It can present as hyper/hypothyroidism/normal. Investigations—TPO antibodies positive, Ultrasound, FNAC-lymphocytic infiltration suggestive of autoimmune thyroiditis.
- Iodine deficiency/endemic goiter—Not seen nowadays, diagnosed epidemiologically. Urine iodine levels are less than 50 ng/L. Treat by iodine supplementation. Iodine has complex effects on thyroid. Chronic administration of iodine causes hypothyroidism due to increased iodine content in thyroid. Paradoxically it can also precipitate thyrotoxicosis. Hence, there is hardly any necessity to recommend iodine for healthy persons.
- Goitrogens—Intake of cassava root, cabbage, cauliflower—due to presence of thiocyanate, causes hypothyroidism, diagnosed epidemiologically. Treat by thyroxine supplementation. There is no evidence based study to recommend routine restriction of cabbage, cauliflower, in all cases of hypothyroidism.
- Miscellaneous causes are—iatrogenic, infiltrative disorders like amyloidosis, sarcoidosis.

Disorders with Low/Undetectable TSH, Normal/Abnormal T3, and T4

- Subacute thyroiditis/De quervain’s—due to viral etiology. There is release of stored hormones due to inflammation. Spontaneous remission in 6 weeks. If thyroid antibodies are positive, suggests risk of ultimate progression to hypothyroidism. When prolonged abnormal levels of TFT, isotope scan—a low uptake confirms transient thyroiditis. Symptomatic treatment with NSAID/prednisolone.
- Grave’s disease—Autoimmune disorder. Monitoring for life long. Ultrasound—increased vascularity. Thyroid antibodies—TPO, Tr-Ab, Tg-Ab all are positive.
Isotope scanning—homogenous and diffuse high uptake confirms the diagnosis. Ideal management by anti-thyroid drugs, sometimes with remission after 12–18 months of treatment.2,4

- Toxic adenoma/solitary nodule—Ultrasound and FNAC to confirm the nodule. Isotope scan is the choice of investigation—focal uptake with hyper-functioning nodule and diminished uptake in the rest of the gland. Treatment of choice is radioiodine ablation.2,4
- Toxic multinodular goiter—Ultrasound and FNAC, isotope scanning ideal investigation—heterogenous uptake with multiple regions of increased and decreased uptake of tracer. Radioiodine ablation is the treatment of choice. Alternate treatment is surgical if compressive symptoms are present.

Goiter or Swelling of Thyroid with Normal TSH, T3, and T4

- Simple goiter—unknown stimulus
- Juvenile goiter—teenagers
- Non-toxic adenoma
- Non-toxic multinodular goiter

If ultrasound, FNAC, and thyroid antibodies are negative, these conditions require follow-up with monitoring of TFT periodically. No medical treatment is necessary. Surgical treatment if compressive signs develop.

Sick Euthyroidism or Non-thyroid Illness or Low T3 Syndrome

Thyroid gland is normal, Abnormal TFT (Low T3, Low or normal T4, Low or normal TSH) due to acute systemic illness, causing failure of peripheral conversation of T4 to T3. Needs to be re-evaluated after recovery from acute illness for thyroid disorder.3

Subclinical Thyroid Disease

Subclinical hypothyroidism with high TSH, normal T3, T4, and Subclinical hyperthyroidism with low TSH, normal T3, and T4 are milder forms of the disease. No universally accepted guidelines for treatment and case to be managed depending on symptoms, age, and comorbidities. Excessive treatment to be avoided.3,5

Monitoring of Therapy

Treatment of hypothyroidism is monitored based on the levels of TSH. Treatment of hyperthyroidism is monitored based on the levels of T4, since TSH levels take longer time to reach normal.

Pregnancy—Thyroid Disorders

There is altered metabolism of thyroid hormones and thyroid–pituitary axis stability. Hence trimester specific normal ranges of TSH, T3, and T4, to be followed.3,6

Case Reports—Author’s Own Experience

Case 1

Female 35 years; Engineer in Govt. Service
Incidental finding of low TSH, high T4, and normal T3
Ultra sound neck FNAC—Cystic colloid nodule
One month later—Persistent low TSH, TPO positive
Isotope scanning of thyroid showed normal uptake of tracer. Not started on any treatment because of normal uptake of tracer. Two months later repeat TFT showed raised TSH—26.02 µIU/mL.
Started on thyroxine. What started as hyperthyroidism turned to be autoimmune hypothyroidism over a period of 2 months.

Case 2

Male 40 years general check-up before leaving for Gulf.
Decrease TSH and increased T4 and T3.
Ultrasound neck diffuse enlargement of both lobes, increased vascularity. FNAC suggestive of autoimmune thyroid. TPO positive. Isotope scanning—Intense homogenous uptake of tracer 11.28% (normal is 0.5–4%).
Diagnosis—Graves disease under management with antithyroid drugs.

Case 3

Male 58 years presented with increased appetite, palpitations, tremors.
Decreased TSH and increased T4 and T3.
Ultrasound small colloid cyst left lobe of thyroid. Isotope scanning—diffuse increased tracer uptake—28.1%. Diagnosis Graves disease.
Clinically this case suggestive of hyperthyroidism, ultrasound showed colloid cyst but isotope scanning is in favor of Graves disease. For the above three cases of hyperthyroidism isotope scanning is the clinching investigation.
Conclusion

It is obvious TFT reports suggestive of hypothyroidism irrespective of etiology, the treatment is thyroxine replacement except in iodine deficiency hypothyroidism. Whereas TFT reports suggestive of hyperthyroidism, the treatment differs. Transient thyroiditis—No treatment, spontaneous recovery mostly.

Grave’s disease—Antithyroid drugs or Radioiodine ablation.

Transient thyroiditis—No treatment, spontaneous recovery mostly.

Grave’s disease—Antithyroid drugs or Radioiodine ablation.

Toxic adenoma/solitary nodule and Toxic multinodular goiter—Radioiodine ablation is the treatment of choice. To differentiate above disorders of hyperthyroidism, isotope scan is the investigation of choice.

References

CHAPTER 205
Glucocorticoids-induced Osteoporosis

Saurabh Jain

Abstract

Prolonged use of Glucocorticoids is associated with several adverse effects including Osteoporosis. High daily dose of GC (>7.5 mg), cumulative dose >5 gm both lead to increased risk of fractures. Vertebral fractures are most common. Often asymptomatic, these are found as incidental findings on routine chest X-rays. The fracture risk assessment tool – FRAX considers several risk factors for osteoporosis (including GC use) with the bone mineral density and gives us an estimate of the 10-year risk of major osteoporotic fracture and hip fracture in patients who are more than 40 years old. Prevention of GC-induced fractures requires identifying the high risk patient, and initiating them on preventive strategies like weight-bearing exercises, maintenance of normal weight, smoking cessation, and limitation of alcohol consumption. Bisphosphonates are considered as first-line agents for the management of Glucocorticoid induced osteoporosis. Treatment with an anabolic agent such as teriparatide or abaloparatide and Denosumab (human IgG2 monoclonal antibody specific to RANKL) should be followed by an antiresorptive agent. Patients experiencing treatment failure or having contraindications to conventional medications are considered of third line agents like raloxifene or with calcitonin. Raloxifene (a selective estrogen-receptor modulator) is approved by the FDA for the prevention and treatment of GC-induced osteoporosis in postmenopausal women. Pharmacologic treatment to prevent fractures are not recommended in pregnant ladies.

Introduction

Glucocorticoids (GC) are used in many inflammatory and autoimmune conditions. While being used to treat an underlying disease, GC are associated with appreciable risk of bone loss and increase the risk of fractures, which is actually more pronounced during the initial few months of use.

Epidemiology

The association of GC and osteoporosis was first described 80 years ago. The US data suggests that approximately 3% of adults older than 50 years and almost 1% of all adults receive GC either for allergic conditions or various inflammatory or neoplastic conditions. GC use over long term is associated with various adverse effects. Amongst them fracture is the most common preventable side effect which is often serious. Increase in the dose and duration of GC increases the risk of fracture.

Risk Factors for Fractures

Related to Glucocorticoid Use
- High daily dose of GC (e.g., >7.5 mg of prednisone daily)
- Cumulative dose of GC >5 g
- Current or recent (<3 month) use of GC
- GC-associated myopathy (increases the risk of falls)
- GC-induced hypogonadism
**Related to Underlying Condition**
Rheumatoid arthritis, ankylosing spondylitis, etc. are independent risk factors.

**Related to Risk of Osteoporosis**
Advance age; white race; female sex; menopause; smoking; alcohol use (>2 units per day); bone mineral density T-score less than −1.5; previous fracture.

Vertebral fractures are the most common GC induced fractures and are often asymptomatic. These are diagnosed as incidental finding on chest or abdominal radiograph. In patients who have asymptomatic vertebral fracture there is often no history of preceding trauma. The typical symptomatic patient presents with acute back pain after sudden bending, coughing, or lifting. The risk of vertebral fracture increases within 3 months of starting the treatment and is maximum at 12 months.\(^7,8\)

Studies, having a follow-up of 6 months to 10 years, have shown that with high dose of GC, risk of vertebral fractures is increased significantly. But, high doses if used intermittently (total cumulative dose of ≤1 g) had less fracture risk.\(^6\) High-dose inhaled GC (dose equivalent to ≥1 mg fluticasone) when used for more than 4 years showed a marginal increase in the risk of fracture.\(^9\)

Also worth remembering is that GC can cause avascular necrosis.

**Pathophysiology (Flowchart 1)**
Specifically related to bone, GC receptors are found on all cells except osteoclast. GC use sends negative feedback effect on the hypothalamus and pituitary gland. It acts as an exogenous cortisol, so elevated GC levels reduce the secretion of ACTH, along with FSH and LH. Reduction in ACTH results in reduced endogenous steroid hormone production from the adrenal glands including cortisol and androgens.

Low FSH and LH reduce production of androgens and estrogen from the gonads. Low androgens and estrogens increase the risk of osteoporosis.

**Flowchart 1:** Pathophysiology of glucocorticoid-induced osteoporosis
Bones contain three main types of cells. Osteocytes—the mature bone cells formed by osteoblasts, Osteoblasts—the bone building cells, and Osteoclasts—bone eating cells. And in our case, immature osteoclast termed pre-osteoclasts. GC stimulates osteocyte apoptosis, with long-term use. The predominant effect of GC on the skeleton is actually reduction in bone formation. The decline in bone formation is mediated by direct inhibition of osteoblast proliferation and differentiation, and by an increase in the apoptotic rate of mature osteoblasts and osteocytes. High GC levels stimulate RANKL synthesis by osteoblasts thus supporting osteoclast differentiation and net bone resorption. In normal condition there is this molecule called osteoprotegerin, which regulates this osteoblast-osteoclast interaction, by binding to the RANKL and preventing osteoclast stimulation. However, GC increases osteoclastic activity by suppressing synthesis of osteoprotegerin and also by increasing production of RANKL, which is required for osteoclastogenesis. So RANKL binds onto osteoclasts stimulating osteoclastic activity, it becomes active osteoclast, which will breakdown bone minerals and this is termed bone resorption. In addition GC increases bone resorption by decreasing secretion of androgens and estrogens. The net bone resorption by osteoclast reduces bone mineral density and bone remodeling, thereby increasing the risk of fractures. Bone resorption leads to an increase in serum calcium and phosphate levels due to the breakdown of bone minerals. Now when you have a high serum calcium the body does not want to keep it. High serum calcium reduces intestinal absorption of calcium and also increases urinary calcium excretion because you want to get rid of all the calcium in your body, now this will cause hypocalcemia. Hypocalcemia stimulates the parathyroid gland to release parathyroid hormone. Parathyroid hormone works by binding onto parathyroid hormone receptors on osteoblasts, which stimulates expression of RANKL, which will further promote osteoclastogenesis and so increase bone resorption further. Indirect GC effects that also predispose patients to an increased risk of fractures include reduced muscle mass and weakness, both leading to an increase in the risk of fall.

After discontinuation of GC treatment, the risk of fracture also downtrends. It was also reaffirmed in a prospective study where within 6 months after discontinuation of GC, lumbar spine showed significant recovery in bone mineral density.10

**Clinical Evaluation**

The fracture risk assessment tool—FRAX considers several risk factors for osteoporosis (including GC use) with the bone mineral density and gives us an estimate of the 10-year risk of major osteoporotic fracture and hip fracture in patients who are more than 40 years old.11

One of the limitation of the FRAX score calculation is that it uses bone mineral density at the hip joint, which can give false values as GC have the greatest detrimental effect on the vertebrae. Also in patients, receiving very high doses of prednisone may underestimate the risk of fracture.

**Treatment**

Prevention of GC-induced fractures requires identifying the high-risk patient, and initiating them on preventive strategies.

**Nonpharmacologic Options**

- Weight-bearing exercise
- Maintenance of normal weight
- Smoking cessation
- Limitation of alcohol consumption
- Assessment and management of fall risks
- Minimizing GC use

**Calcium and Vitamin D**

Because GC increases the excretion of urinary calcium, dietary intake of calcium (1,000 mg per day) and vitamin D (600–800 IU) is commonly suggested to patients receiving GC.

A Cochrane meta-analysis suggested that the bone mineral density at the lumbar spine was significantly better in patients receiving calcium and vitamin D supplementation in comparison with the placebo group.12

**Pharmacologic Treatment**

**Bisphosphonates**

Multiple randomized trials have suggested that in patients receiving GC, the use of bisphosphonates is associated with an increase in the bone mineral density.13 A 2016 Cochrane review involving 12 RCTs showed that in the group receiving bisphosphonates the risk of new vertebral fractures was lower by 43% in comparison to those who received either calcium or vitamin D, or both. In patients
receiving bisphosphonate treatment over a period of 3–5 years, there was less incidence of serious adverse events (like osteonecrosis of the jaw and atypical femoral fractures). Due to their good safety profile and affordable cost, oral bisphosphonates are recommended as first-line agents to prevent GC induced fractures unless they are contraindicated or have undesirable adverse effects.

Patients who are not able to tolerate the oral formulation, or who for some reasons are not adherent to oral bisphosphonate regime, are offered intravenous bisphosphonates.

Other Recommended Agents
Teriparatide and abaloparatide are anabolic molecules and increases bone formation. In a study of 428 patients on GC, receiving either teriparatide or alendronate were followed for 36 months. Patients receiving teriparatide showed better improvement in bone mineral density at the spine, than alendronate. They also had lesser rate of radiographic vertebral fractures. However, no significant difference was noted in the rates of nonvertebral fracture in the two groups. In the teriparatide group, 21% of patients had hypercalcemia, as compared to 7% in the alendronate group. In a smaller study, effects of teriparatide and risdonate were noted on middle-aged men receiving GC. Teriparatide group showed higher bone mineral density and lower rate of fractures. However, after discontinuation of teriparatide, bone loss and fractures occurred at a rapid rate. Hence, after discontinuation of teriparatide, it is prudent to initiate an antiresorptive agent such as teriparatide or abaloparatide should be followed by an antiresorptive agent.

Denosumab is human IgG2 monoclonal antibody specific to RANKL. By binding to RANKL, it suppresses the development of osteoclasts. In a trial involving patients on GC, denosumab was compared with risdonate. Denosumab group showed superiority with respect to increase in spinal bone mineral density at 12 months and noninferiority in terms of rates of fracture. Few studies have reported higher risk of infection with denosumab in comparison to bisphosphonates which may be attributed to its immunomodulatory effects. Hence in patients on immunosuppressive medicines or biologicals, denosumab is generally not recommended. Denosumab, in dosages that is used to treat osteoporosis, is associated with minimal risk of osteonecrosis of the jaw and atypical fractures. However, similar to anabolic agents, after its discontinuation there is a rapid increase in the rates of vertebral fracture, especially in patients with a previous history of vertebral fracture. Here also an alternative antiresorptive therapy should be initiated after its discontinuation.

Third-line Agents
Patients experiencing treatment failure or having contraindications to conventional medications are considered of third-line agents like raloxifene or with calcitonin. Raloxifene (a selective estrogen-receptor modulator) is approved by the FDA for the prevention and treatment of GC-induced osteoporosis in postmenopausal women. A study done in postmenopausal women receiving GC showed that raloxifene significantly increased absolute bone mineral density at the lumbar spine by 1.3%, in comparison to Calcium and Vit D supplementation. However, no difference in bone mineral density was noted at the femoral neck between the treatment groups. Studies have shown that raloxifene use is associated with decreased risk of estrogen-receptor–positive breast cancer; however, it can cause serious complications like venous thromboembolism, and fatal stroke.

Calcitonin-Salmon is a man-made form of the hormone. A meta-analysis of nine trials with 500 patients on GC, compared the effects of calcitonin with calcium and Vit D supplementation, concluded that calcitonin improved the bone mineral density at the lumbar spine (but not hip); however, there was no difference in the risk of vertebral fracture in both the groups. Calcitonin is available as injectables which can be administered subcutaneously and also as a nasal spray. Hypocalcemia and Vit D deficiency must be corrected before initiating the treatment. In clinical trials among calcitonin treated patients, overall incidence of malignancies are reported to be higher in comparison with placebo.

Treatment in Women of Childbearing Age
Pharmacologic treatment to prevent fractures is not recommended in pregnant ladies. A summary of case study involving 65 women receiving bisphosphonate
before or in the first trimester of pregnancy showed no clinically significant adverse effects in the fetus. However, there is a reluctance to treat women in childbearing age with bisphosphonates as it may cause long-term retention of these agents in bone and may have affect on the fetal skeleton later when these ladies conceive. If treatment has to be offered owing to their risks, agents having a shorter half-life and lesser retention in bone are generally recommended such as risedronate and teriparatide. Animal’s studies have shown that denosumab has teratogenic effects and should be used with caution in women of childbearing age.

Guidelines/Recommendations

The 2017 Guidelines of the American College of Rheumatology recommend the following:

Which patient requires intervention?
- All adults taking ≥2.5 mg of prednisone daily for >3 months

Whom to test and monitor for changes in BMD?
- All adults ≥40 years of age and adults <40 years with a history of fragility fracture or other risk factors;
- Test within 6 months after initiation of GC;
- Repeat testing every 2–3 years and every 1–3 years in adults ≥40 years receiving GC without treatment for osteoporosis.

Correction used with the FRAX tool to adjust risk estimate for prednisone dose >7.5 mg:
- Risk of major osteoporotic fracture is increased by 15% and risk of hip fracture is increased by 20%

Calcium and Vit D supplementation:
- 800–1,000 mg of calcium daily and 600–800 IU of vitamin D daily

Threshold for pharmacologic treatment:
- All adults with a previous fragility fracture
- Adults ≥40 years with BMD T score of −2.5 or less or FRAX risk ≥20% for major osteoporotic fracture or ≥3% for hip fracture
- Consider in adults ≥40 years with FRAX risk 10–19% for major osteoporotic fracture or >1–2.9% for hip fracture
- Adults <40 years with BMD T score below −3 and >7.5 mg of prednisone daily
- Adults with >10%/year bone loss at hip or spine
- Adults ≥30 years taking very-high-dose GC (≥30 mg daily)
- High cumulative use (>5 g in 1 year)

Pharmacologic interventions:
- First-line therapy: oral bisphosphonates
- Second-line therapies (in order of preference): intravenous bisphosphonates, teriparatide, denosumab, raloxifene (only in postmenopausal women when other listed second-line medications are not appropriate)

Duration of pharmacologic intervention:
- If continuing to receive GC >5 years, continue treatment if having moderate to high risk
- If GC is discontinued before 5 years, continue treatment for osteoporosis for 5 years if moderate to high risk
- Discontinue treatment for osteoporosis when GC are discontinued if low risk.

Conclusion

Long-term use of Glucocorticoids is known to cause many adverse effects and it is essential to identify the high-risk individuals. After lifestyle change and correction of calcium and vitamin D, initiation of appropriate anti-resorptive medicines can prevent long-term debilitation and morbidity associated with osteoporosis.

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