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Hyperthyroidism

Pronunciations: (Hyperthyroidism)
Hyperthyroidism (overactive thyroid) is a condition where the thyroid gland synthesizes and secretes the thyroid hormones thyroxine (T4) and triiodothyronine (T3) in excess. The most common cause of primary hypothyroidism is an autoimmune disorder known as Grave's Disease which stimulates thyroid production.

Causes

Grave's Disease, also known as Basedow's Disease, is the most common cause of primary hyperthyroidism accounting for about 85% of all hyperthyroidism cases. In Grave's Disease, the presence of TSH-receptor-stimulating antibodies (TSAb) results in continuous stimulation of thyroid hormones and thyroid gland growth. Abnormal expression of the major histocompatibility complex class II antigens by follicular cells results in the CD4+ helper T cells entering the thyroid gland treating the TSH-receptor as an autoantigen, leading to stimulation of B cells to produce TSAb. Individuals with certain HLA-D and HLA-D subtypes, particularly HLA-B8 and HLA-D3, respectively, have an increased risk for Grave's Disease; however inheritance is polygenic and both environmental and genetic factors contribute to its onset. Choriocarcinoma and hydatidiform mole are also causes of primary hyperthyroidism because of increased production of human chorionic gonadotropin (hCG), a potent stimulator of thyroid hormone production. Gain-of-function mutations of TSH-R have been detected with solitary toxic ademomas and toxic multinodular goiter leading to continuous stimulation of the thyroid. Other causes of hyperthyroidism include accidental overdose of exogenous thyroid hormone (thyrotoxicosis factitia), struma ovarii, and thyroiditis leading to destruction of thyroid tissue and release of stored thyroid hormone. Excessive iodine ingestion has been shown to cause hyperthyroidism, although the exact mechanism behind this remains unclear. Excessive iodine may trigger Grave's Disease by providing iodine for thyroid hormone production and disrupting normal immune system functioning. Secondary causes of hyperthyroidism include a TSH-secreting anterior pituitary adenoma and pituitary resistance to thyroid hormone. An estimated 1.3% of Americans have hyperthyroidism. Grave's Disease is more prevalent in women, as is the case with most autoimmune diseases. Grave's disease is also associated with other autoimmune diseases such as Addison's Disease, diabetes mellitus, and several others.

Diagnosis

Symptoms:

Clinically, symptoms of hyperthyroidism can vary from dramatic to almost nothing. Obvious signs include enlarged goiter, Grave's ophthalmopathy, exophthalmos, and pretibial myxedema. Many symptoms are similar to an enhanced adrenergic response such as restlessness, weight loss, sweating, tachycardia, tremors, and nervousness. Thyroid storm, a life-threatening disorder, may also occur.

Other symptoms:

Frequent bowel movements (especially diarrhea)
Increased appetite
Nausea and vomiting
Insomnia
Moist skin
Hair loss

Interpretation of Laboratory Tests

The following methods are frequently used to help reach a diagnosis for hyperthyroidism. Selecting the type of test to order may depend on the severity of symptoms, confirming previously ordered tests, or availability of resources.
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LABORATORY TESTS		
Test Name	Normal values	Indicators
Serum TSH	0.2-4.7 mcU/ml Reference ranges vary between assays.	Low to undetectable is indicative of Grave's Disease. Elevated levels may indicate TSH-secreting pituitary adenoma or resistance.
Serum Free T4	0.8 – 2.0 ng/dl Reference ranges vary between assays.	Elevated levels with suppressed TSH indicates hyperthyroidism.
Serum T3	100 – 200 ng/dl Reference ranges vary between assays.	Elevated levels may be seen with this disorder, with levels being higher than T4.
Resin T3 Uptake (RT3U)	24% to 37%	Elevated levels are often associated with hyperthyroidism. This test can indirectly calculate Free T4.
TSI	< 130% of basal activity	Stimulation of adenylyl cyclase about 280% indicative of Grave's Disease. Test rarely needed.
Antithyroglobulin Antibody	Negative	Positive test may indicate Grave's Disease.
Antithyroid Peroxidase Antibodies	Negative	Positive test may indicate Grave's Disease.
OTHER TESTS		
Test Name	Normal values	Indicators
Vital Signs	Blood Pressure: 120/80 mm Hg Temp: 98.6 F	Vital signs and systolic blood pressure may be elevated with hyperthyroidism because of

	Pulse: 60 – 80 beats/minute Breathing: 12-18 respirations/minute	increased heart rate.

IMAGING TESTS	
Test Name	Indicators
Radioactive Iodine Uptake (RAIU)	100-200 µCi of ^{123}I is orally administered and radioactivity is measured on scintillation counter 6 to 24 hours after ingestion. RAIU will be elevated in hyperthyroidism.
Radioimaging	Reveals the shape and size of the thyroid gland and where iodine is distributed (hot vs cold nodules). The test requires ingestion of 200-300 µCi of ^{123}I sodium iodide. $^{99m}TcO_4^-$ pertechnetate is also used for radioimaging. ^{123}I will concentrate in functioning nodules ("hot").

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Prior to conducting thyroid assessment tests, it is very important to review the patient's clinical and medical history and conduct a thorough physical exam. The common diagnostic picture of Grave's Disease is low or undetectable TSH and elevated T4 and T3 levels. The first thyroid test should be serum TSH, which is usually very low or nearly suppressed. This test should next be followed by a serum FT4 test and then serum T3 if free T4 levels are normal. Elevated T3 concentrations with low to undetectable TSH and normal T4 levels may indicate early T3 toxicosis. Normal or elevated TSH concentrations with elevated T4 levels may be indicative of a pituitary-secreting adenoma or pituitary resistance to thyroid hormone. TSI is rarely needed to diagnose Grave's Disease, however tests for antithyroglobulin antibody and antithyroid peroxidase antibodies may help to confirm the diagnosis of Grave's Disease. The RAIU test is only needed when the exact cause of hyperthyroidism is not evident from the clinical results (i.e., multinodular goiter).

Common Current Treatments

Treatment of hyperthyroidism depends on the disease etiology. In the United States, the most common treatment of Grave's Disease and recurrent hyperthyroidism includes radioiodine ablation with radioactive sodium iodine (^{131}I). The exact dosage of ^{131}I is difficult to determine and is dependent on how the thyroid gland responds to treatment, antibody stimulus, and the dose given. Control of hyperthyroidism is usually achieved in 75% of all cases, however with repeated treatments and with high doses used to attain euthyroidism, permanent hypothyroidism usually ensues. Low dose therapy increases the risk for recurrent hyperthyroidism. Surgical removal of the thyroid gland (thyroidectomy) is an effective treatment of hyperthyroidism caused by Grave's Disease. Anti-thyroid medication (i.e., methimazole) and potassium iodide two weeks before surgery must be given prior to surgery to create euthyroidism and decrease the vascularity of the thyroid gland, respectively. The thyroid gland is almost completely removed to prevent recurrence, which is between 2 to 9%. The risk of hypothyroidism is very high in both treatment methods described above, which will require lifelong L-thyroxine treatment.

Medications

The following table lists some classes and examples of medications commonly used to treat hyperthyroidism. The two thionamides used in the US include propylthiouracil (PTU) and methimazole, whereas carbimazole (converted to methimazole *in vivo*) is mainly used in Asia and European countries. PTU and methimazole work by preventing the organification of iodine and the tyrosine coupling reaction. In addition, PTU impairs peripheral deiodination of T4 to T3. The initial dose is about 100-150 mg of oral PTU given every 8 hours, whereas methimazole may only be taken once daily in 15-30 mg doses orally. Once euthyroidism has been achieved, the lowest amount of thionamides should be given as a maintenance dose. Control is usually achieved after 3 months of drug therapy because stored thyroid hormone can continually be released. Drug therapy should be adjusted to keep T4 concentrations in normal range and as TSH concentrations increase, the maintenance dose may be lowered and eventually discontinued. The usual treatment regimen for anti-thyroid medications is 1-2 years with about a 50% success rate of remission. Remission is when therapy has been discontinued and euthyroidism is present without the drugs, however relapse is not uncommon. It is therefore very important to have adequate follow-up in all patients. An alternative is to give high enough dosages to create hypothyroidism and then treat with L-thyroxine, however results from this method are conflicting and do not guarantee successful remission. Thionamide therapy may result in lower T4 concentrations, with elevated T3 concentrations thus exacerbating hyperthyroidism. In this case scenario, drug dosage should not be lowered.

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THIONAMIDES		
Indication	Class/Examples	Notes
Hyperthyroidism (Grave's Disease) Thyroid Storm	Prevents organification of idodide and in high doses, peripheral deiodination: Propylthiouracil (PTU)	Vitamin K antagonist. Allergic reactions such as rash are common with this drug. 800-1200 mg/day are effective in treating thyroid strom.
Hyperthyroidism (Grave's Disease)	Methimazole Carbimazole	Vitamin K antagonist. Allergic reactions such as rash are common with this drug.
IODINE		
Indication	Class/Name	Notes
Thyroid Storm Surgery Preparation for thyroidectomy	Prevents iodide uptake in thyroid gland and decreases vascularization of gland: Potassium Iodide	If used for the treatment of thyroid storm, PTU must be given before iodide. Increases the risk of lithium toxicity. Skin rash and conjunctivitis are common reactions.
β-BLOCKERS		

Indication	Class/Name	Notes
Thyroid Storm Adrenergic excess Tachycardia	Propanolol	Important to monitor blood pressure and pulse. Several drugs (i.e., barbituates) may increase metabolism of the drug, while others (i.e., chlorpromazine) may delay metabolism and increase amount in the blood.
ANTI-INFLAMMATORY AGENTS		
Indication	Class/Name	Notes
Ophthalmopathy	NSAIDS Corticosteroids	

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Dietary Interventions

Osteoporosis is common in hyperthyroidism, especially in females. It is important that the patient receive adequate calcium and vitamin D intake to delay its onset. The current Recommended Dietary Allowance (RDA) for calcium is 1000 mg/day in adult male and females 19-50 years of age. Calcium intake should be increased to 1200 mg/day in those over 50. The current RDA for vitamin D is 5 µg/day in adult male and females 19 to 50 years of age. Vitamin D intake should be increased to 10 µg/day in those 50-70 years of age, and to 15 µg/day in those older than 70. Calcium needs can easily be met by the consumption of at least 3 servings of dairy products each day. Milk is fortified with vitamin D therefore 3 cups of milk per day will be adequate. If allergic reactions to milk or milk intolerance is present, calcium needs can be met by eating tofu, fortified soy products, nuts (i.e., almonds), and sesame seeds. Vegetables such as broccoli, bok choy, kale, and mustard greens are also good sources of calcium. Vitamin D is found in fish liver oils (i.e., cod liver oil), fortified cereals, and from the flesh of fatty fish. Supplementation of calcium is another option, however it must be noted that dairy products are best for protection against osteoporosis. Supplementation with 500 mg of calcium citrate malate and 200 I.U. of vitamin D in the morning and at night is effective. Once hyperthyroidism is corrected, weight gain will occur rapidly in patients who fail to lower caloric consumption. Exercise is an appropriate strategy to reduce weight gain and to improve overall health, however this should only be warranted if the patient does not present adrenergic excess. Exercise can be readily done with patients on β-blockers, yet blood pressure and heart rate should be monitored. Patients should avoid over-the-counter supplements and cold remedies that contain agents known to stimulate metabolism such as ephedrine, pseudoephedrine, and caffeine.

Orders

Once hyperthyroidism has been diagnosed, discussing treatment options with patients should be conducted immediately.

If thionamide therapy is decided upon, follow-up visits and thyroid tests to assess TSH, T4, and T3 should be conducted every 2-3 months after euthyroidism has been achieved.

It may take up to 3 months before clinical control is noted, however adrenergic symptoms may be controlled through the use of β-blockers. Patients with radioiodine ablation or thyroidectomy should have yearly follow-up visits. Monitoring for relapse or hypothyroidism is crucial.

What to Tell the Patient and Family

It is important to discuss the importance of compliance with medication if anti-thyroid therapy is chosen. Forgetting to take medications or medication cycling to maintain weight, are not uncommon and must be warned against. In addition, medications tend to cause a series of adverse reactions therefore the patient must be advised of such occurrences. Patients must be encouraged to have regular follow-up visits and to understand the severity of hyperthyroidism and risk of relapse without proper management. Lastly, weight management is an important concept to discuss with those who have been treated.

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