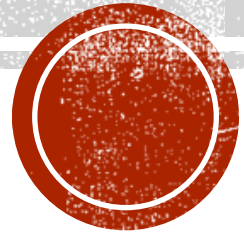
OTHER COMMON TESTS



THYROID FUNCTION TESTS

- Once released from the thyroid gland, thyroid hormone circulates in the bloodstream where free T4 and T3 are available to travel across the cell membrane. In the cytoplasm, T4 is deiodinated into T3, the active form of thyroid hormone. T3 combines with its nuclear receptor on thyroid hormone-responsive genes, leading to production of messenger RNA that, in turn, leads to production of proteins that influence metabolism and development.
- Effects include tissue growth, brain maturation, increased heat production, increased oxygen consumption, and an increased number of –adrenergic receptors.
- Clinically, individuals who have excess thyroid hormone (**thyrotoxicosis**) will have symptoms of increased metabolism such as tachycardia and tremor, while individuals with **hypothyroidism** note symptoms of lowered metabolism like edema and constipation

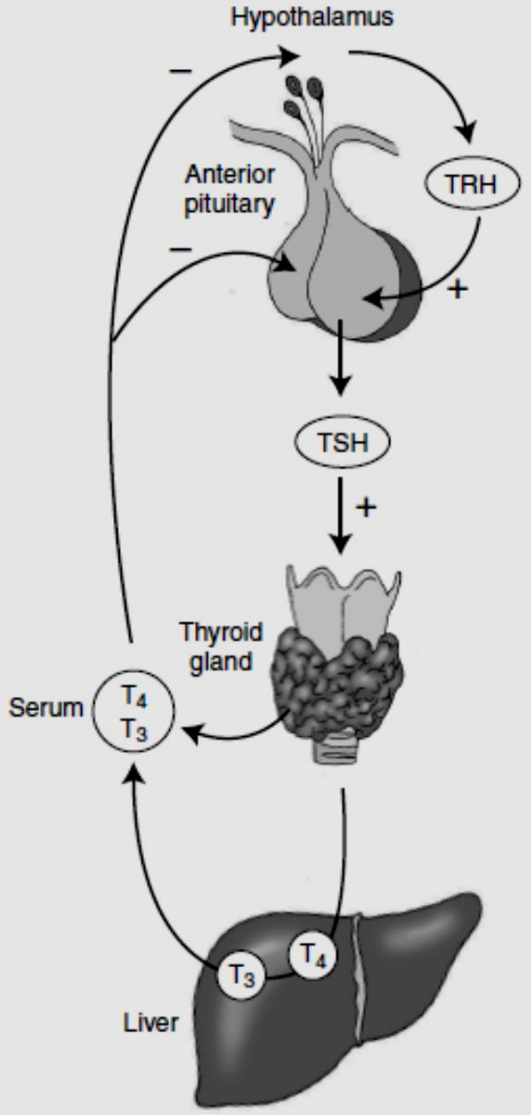


FIGURE 22-3. Hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) stimulates the production and release of thyrotropin (TSH). TSH stimulates the thyroid gland to synthesize and secrete thyroid hormone. T_4 that is released by the thyroid gland is mostly converted to T_3 by the liver and kidney. T_3 and T_4 feedback inhibit TSH release directly through action at the pituitary and indirectly by decreasing TRH release from the hypothalamus. (Adapted with permission from Surks MI, Sievert R. Drugs and thyroid function. N Engl J Med 1995;333:1688.)

THYROID FUNCTION TESTS

Thyroid function tests:

- **TSH**
- The most useful test for assessing thyroid function is the TSH.
- All the assays are capable of diagnosing primary hypothyroidism by low thyroid hormone production and elevated levels of TSH.
- Second-generation TSH immunometric assays, with detection limits of 0.1 mU/L, can effectively screen for hyperthyroidism, but third-generation TSH chemiluminometric assays, with detection limits of 0.01 mU/L, are less likely to give false-negative results and can more accurately distinguish between euthyroidism and hyperthyroidism.

TSH

- Second- and third-generation TSH assays are routinely used to monitor and adjust thyroid hormone replacement therapy as well as screen for both hyperthyroidism and hypothyroidism.

- The sensitivity of the third-generation TSH assays has led to the ability to detect subclinical disease-or a mild degree of thyroid dysfunction-due to the large reciprocal change in TSH levels seen for even small changes in free T4.

- In **subclinical hypothyroidism**, the TSH is minimally increased while the free T4 stays within the normal range. Likewise, in **subclinical hyperthyroidism**, the TSH is suppressed while the free T4 is normal.

T3 AND T4

- Serum total T4 and T3 levels are usually measured by radioimmunoassay (RIA), chemiluminometric assay, or similar immunometric technique. Because more than 99.9% of thyroid hormone is protein bound, alteration in thyroid hormone–binding proteins, unrelated to thyroid disease, frequently lead to total T4 and T3 levels outside of the normal range.
- Because of this, assays have been developed to measure **free T4 and T3**, the biologically active forms of thyroid hormone
- Currently available assay kits for measuring free T4 levels are not error proof, though, and can still be affected by some binding protein abnormalities. When this is suspected, measurement of free T4 levels is performed by dialysis.

THYROGLOBULIN

- Thyroglobulin is a protein synthesized and secreted exclusively by **thyroid follicular cells**. Its presences in the circulation is proof of the **presence of thyroid tissue**, either benign or malignant so its used as a tumor marker for thyroid cancer patients. Patients with well-differentiated thyroid cancer who have been treated successfully with surgery and radioactive iodine ablation should have undetectable thyroglobulin levels.
- Thyroglobulin is currently measured by double antibody RIA, enzyme-linked immunoassay (ELISA), immunoradiometric assay (IRMA), and immunochemiluminescent assay (ICMA) methods.
- The accuracy of the thyroglobulin assay is primarily dependent on the specificity of the antibody used and the absence of antithyroglobulin autoantibodies. Even with modern assays, antithyroglobulin autoantibodes interfere with measurements and lead to unreliable thyroglobulin results. Approximately 25% of patients with well-differentiated thyroid cancer will have antithyroglobulin autoantibodies. This is approximately twice as high as in the general population.
- If a patient with well-differentiated thyroid cancer and antithyroglobulin autoantibodies has been successfully treated with surgery and radioactive iodine ablation, autoantibodies should disappear over time

AUTOIMMUNE ANTIBODIES

- The most common cause of hyperthyroidism is an autoimmune disorder called
- **Graves' disease**: The antibody in this condition is directed at the TSH receptor and stimulates the receptor, leading to growth of the thyroid gland and production of excessive amounts of thyroid hormone. This condition can be diagnosed with tests that detect antibodies to the TSH receptor.
- Thyroid stimulating antibodies (TSAb) use a bioassay to determine presence of autoimmune hyperthyroidism. Tests for **TSH receptor antibodies** (TSHR-Ab) can detect antibodies directed against the TSH receptor whether they act to stimulate or block the TSH receptor. Both stimulating and blocking antibody assays will be positive in 70-100% of patients with Graves' disease.
- **Chronic lymphocytic thyroiditis** (**Hashimoto's thyroiditis**): is the most common cause of hypothyroidism in the developed world. In this condition, antibodies lead to decreased thyroid hormone production by the thyroid gland. The best test for this condition is the thyroid peroxidase (TPO) antibody, which is present in 10-15% of the general population and 80-99% of patients with autoimmune hypothyroidism

THYROID TESTS INTERPRETATION

TABLE 22-1 INTERPRETATION OF THYROID TESTS

	LOW FREE T_4	NORMAL FREE T_4	HIGH FREE T_4
Low TSH	Secondary hypothyroidism Severe nonthyroidal illness	Subclinical hyperthyroidism Nonthyroidal illness	Hyperthyroidism
Normal TSH	Secondary hypothyroidism Severe nonthyroidal illness	Normal	Artifact Pituitary hyperthyroidism Laboratory draw within 6 hours of thyroxine dose
High TSH	Primary hypothyroidism	Subclinical hypothyroidism	Test artifact Pituitary hyperthyroidism Thyroid hormone resistance

OTHER TOOLS FOR THYROID EVALUATION

- **Nuclear Medicine Evaluation:** Radioactive iodine is useful in assessing the metabolic activity of thyroid tissue and assisting in the evaluation and treatment of thyroid cancer. Radioactive iodine can also be useful in the evaluation of thyroid nodules in the presence of a low or undetectable TSH.

- **Thyroid Ultrasound:** used to assess thyroid anatomy and characterization of palpable thyroid abnormalities

- **Fine-Needle Aspiration (FNA)** biopsy is often the first step and most accurate tool in the evaluation of thyroid nodules, which allows prompt identification and treatment of thyroid malignancies and avoids unnecessary surgery in most individuals with benign thyroid lesions.

TUMOR MARKERS

- Cancer can be detected and monitored using biologic **tumor markers**, that are produced either directly by the tumor or as an effect of the tumor on healthy tissue.
- They can be used for **Screening, Diagnosis, and to test the effectiveness of the treatment**
- **Carcinoembryonic antigen (CEA)** is the most widely used tumor marker for colorectal cancer and is also frequently elevated in lung, breast, and gastrointestinal tumors. CEA can be used to aid in the diagnosis, prognosis, and therapy monitoring of colorectal cancer but not screening
- **Human Chorionic Gonadotropin (**hCG) is elevated in trophoblastic tumors, choriocarcinoma, and germ cell tumors of the ovary and testis.

TUMOR MARKERS

- **Prostate Specific Antigen (PSA):** detection of total PSA has been used in screening for and in monitoring of prostate cancer, evidence for the usefulness in detecting free PSA as a fraction of total has been identified. Patients with malignancy have a lower percentage of free PSA
- **α-Fetoprotein (AFP):** is an abundant serum protein normally synthesized by the fetal liver that is reexpressed in certain types of tumors. AFP is often elevated in patients with hepatocellular carcinoma (HCC) and germ cell tumors
- **Cancer Antigen 125 (CA-125):** It may be useful for detecting ovarian tumors at an early stage and for monitoring treatments without surgical restaging.

TABLE 31-4 ENDOCRINE TUMOR MARKERS

TUMOR MARKER	TUMOR TYPE	METHOD	SPECIMEN	CLINICAL UTILITY
Homovanillic acid (HVA)	Neuroblastoma, pheochromocytoma, paraganglionoma	HPLC	24-hr urine	Diagnosis of neuroblastoma[a]
Vanillylmandelic acid (VMA)	Pheochromocytoma, paraganglionoma, neuroblastoma	HPLC	24-hr urine	Diagnosis of neuroblastoma[a]
Metanephrines (fractionated)[b]	Pheochromocytoma, paraganglionoma, neuroblastoma	HPLC	24-hr urine or plasma	Screening and diagnosis of pheochromocytoma[c]
Catecholamines (fractionated)§[d]	Pheochromocytoma, paraganglionoma, neuroblastoma	HPLC, LC-MS/MS	24-hr urine	Screening and diagnosis of pheochromocytoma, paraganglionoma, neuroblastoma[c]
Hydroxyindoleacetic acid (5-HIAA)	Carcinoid tumors	HPLC	24-hr urine	Diagnosis of carcinoid tumors[e]
Serotonin	Carcinoid tumors	HPLC	Serum	Diagnosis of carcinoid tumors[e]
Calcitonin	MTC and neuroendocrine tumors	IA	Serum	Screening,[f] response to therapy, and monitoring recurrence of MTC
Parathyroid hormone (PTH)	Pituitary adenoma	IA	Serum	Diagnosis and postsurgical monitoring of 1′ hyperparathyroidism
Growth hormone (GH)	Pituitary adenoma, ectopic GH-secreting tumorsurgical	IA	Serum	Diagnosis and post monitoring of acromegaly
Prolactin (PRL)	Pituitary adenoma	IA	Serum	Diagnosis and postsurgical monitoring of prolactinoma
Adrenocorticotropic hormone (ACTH)	Pituitary adenoma, ectopic ACTH-producing tumor	IA	Serum	Diagnosis of ectopic ACTH-producing tumor
Cortisol	Adrenal tumors	IA	Serum or urine	Diagnosis of Cushing's syndrome, adrenal adenoma
Antidiuretic hormone (ADH)	Posterior pituitary tumors	IA	Serum	Diagnosis of SIADH
Chromogranin A	Pheochromocytoma, neuroblastoma, carcinoid tumors, small cell lung cancers	ELISA, RIA	Serum	Aid in diagnosis of carcinoid tumors, pheochromocytomas, and neuroblastomas
C-peptide	Insulin-secreting tumors	ELISA, IA	Serum	Diagnosis of insulinoma