Paparella: Volume I: Basic Sciences and Related Disciplines

Section 2: Physiology

Part 2: Head and Neck

Chapter 17: Physiology of the Thyroid and Parathyroid Glands

Dean M. Toriumi, Jack D. Kerth

Thyroid Gland

The thyroid gland was first described by Galen in the second century A.D. He thought the function of the gland was to lubricate and moisten the larynx. In 1656, Wharton reported the thyroid gland warmed the trachea, lubricated the larynx, aided the function of the recurrent laryngeal nerve, and contributed to the beauty of the neck. Eventually, clinical observations defined the true function of the thyroid gland. In 1842, Graves described the clinical presentation of hyperthyroidism, which included sweating, tremor, and tachycardia. In search of a substance secreted by the thyroid gland, Kendall isolated thyroid hormone in 1914 and proposed the name "thyroxin".

The two main functions of the thyroid gland are production of thyroid hormones and calcitonin. The thyroid follicle is composed of cuboidal cells arranged about a lumen filled with colloid. Thyroxine (T4) and triiodothyronine (T3) are synthesized within these follicles, and secreted by the gland.

The thyroid gland is the major source of calcitonin, which is synthesized in the parafollicular C-cells. These cells are a part of the neuroendocrine system and actually arise from the ultimobranchial body of the embryo. Calcitonin is instrumental in the control of calcium metabolism and the prevention of hypercalcemia.

Thyroid Hormone

Iodine Metabolism

Iodine is essential for thyroid hormone synthesis and the normal function of the gland. An average daily intake of 0.1 mg of iodine is needed to replace iodine lost primarily in the urine. Most of the iodine in the body is in the thyroid gland, the thyroid-serum iodine ratio being about 25:1 in normal individuals. About two thirds of iodine in plasma is lost in renal excretion, and approximately one third is used in thyroid metabolism. The main dietary sources of iodine are seafood, eggs, and milk. Increased quantities of iodine in table salt and bread have decreased the incidence of iodine deficiency in the United States.

Elemental iodine is converted to iodide in the stomach and upper small bowel. Then iodide is transported to the thyroid gland via the blood and is actively transported into the thyroid follicular cells. There, iodide is rapidly oxidized. This step is catalyzed by thyroid peroxidase.

Synthesis of Thyroid Hormone

Tyrosine residues combine with iodine in the thyroglobulin molecule at the periphery of the thyroid follicle, resulting in the formation of iodinated tyrosine residues, or monoiodotyrosine and diiodotyrosine. T3 is formed by the coupling of monoiodotyrosine and diiodotyrosine, whereas T4 is formed by combining two diiodotyrosine molecules. Both T3 and T4 are bound to thyroglobulin, which is synthesized by the follicular cells. The thyroglobulin, which is synthesized by the follicular cells. The thyroglobulin protein molecule acts as a substrate for iodination and iodothyronine formation as well as a storage site for iodine. When thyroglobulin is resorbed into thyroid cells and hydrolyzed, T3 and T4 are released into the circulation.

Action of Thyroid Hormone

The exact mechanism of action of thyroid hormone is not clearly understood. The metabolic effects of thyroid hormone on peripheral tissue are widespread and involve an increase in oxygen consumption and calorigenesis. The absence of T4 results in a 40 per cent reduction in the basal metabolic rate. Thyroid hormone also influences protein synthesis and carbohydrate and fat metabolism.

Thyroid hormone stimulates protein synthesis and regulates all aspects of carbohydrate metabolism. The changes in protein synthesis are related to increased incorporation of amino acids into mitochondrial protein and to accelerated activity of some mitochondrial enzymes. Thyroid hormone regulates the glycogenolytic and hyperglycemic effects of epinephrine and potentiates the effects of insulin on glycogen synthesis and glucose metabolism. Lipid metabolism is influenced by T4, as demonstrated by the fact that serum cholesterol and phospholipid vary inversely with thyroid activity. In general, thyroid hormone increases oxidative phosphorylation.

It is well accepted that thyroid hormone has a significant effect on growth and development. In thyroidectomized tadpoles, maturation and growth are delayed. They do not transform into frogs until thyroid hormone is administered. Thyroid hormone is important in normal human development, as noted in cretinism, in which the hormone is lacking.

Thyroid Hormone Homeostasis

The thyroid gland is regulated by the level of thyroid-stimulating hormone (TSH) secreted by the basophilic cells of the anterior pituitary gland. The release of TSH is controlled by negative feedback of T3 and T4 serum levels and by thyrotropin-releasing hormone (TRH). TRH is secreted by the hypothalamus and reaches the pituitary via the hypothalamic portal system. In response to TSH, the thyroid gland (via changes in the concentration of cyclic adenosine monophosphate (cAMP)) increases the rate of synthesis and release of thyroid hormones. Long-acting thyroid stimulator, a gamma globulin, can be extracted from cultured lymphocytes of some patients with Graves' disease. Clinically, long-acting thyroid stimulator seems to play a part in the pathogenesis of pretibial myxedema and is chemically distinct from TSH.

The two biologically active thyroid hormones are T4 and T3. T3 is much more potent, but the concentration of serum T4 is about three times as great as serum T3. Some T3 is produced by the thyroid gland, but most of it is formed by the monodeiodination of T4 in the peripheral tissues. The half-life of T4 is about 6 to 7 days, whereas T3 has a half-life of about 24 hours. These time intervals can vary depending on the thyroid status of the individual.

Another product of monodeiodination of T4 is 3',5',3-triiodo-L-thyronine, or reverse T3 (rT3), which is biologically inert. Approximately 85 per cent of T4 metabolized daily is deiodinated, slightly more to rT3 than to T3 (the active form). About 75 per cent of T3 and all of rT3 are produced by extrathyroidal T4 deiodination.

Thyroid hormone exists in both the free and protein-bound forms. Three plasma proteins can bind to iodothyronines: thyroxine-binding globulin (TBG), thyroxine-binding prealbumin, and albumin; the first two are specific iodothyronine-binding proteins. Total serum concentrations of T3 and T4 are routinely measured. These values are significantly affected by alterations in serum iodothyronine-binding capacity. Ninety-nine per cent of thyroid hormone is bound to serum proteins, so the total serum concentration of hormone is directly related to the amount of binding protein available in the serum. The unbound free thyroid hormone fraction is the physiologically active form but comprises only about 1 per cent of the total serum concentration.

Evaluation of Thyroid Function

Thyroid function is evaluated by determining the level of hormone production and the serum concentration of the thyroid-binding proteins. Alterations in thyroid function are a result of changes in the binding proteins nearly as frequently as actual abnormalities in thyroid hormone production. Thyroid function correlates most accurately with thee free or unbound hormone concentration in the serum rather than the total serum concentration.

Serum concentrations of T3, T4, rT3, and TSH are determined by radioimmunoassay. A major problem is that T3 and T4 determinations are influenced by thyroid-binding proteins. Since free and bound hormones are in equilibrium, changes in binding proteins are reflected by changes in total concentrations measured by radioimmunoassay. Free hormone is determined by dialysis techniques, but these are too time consuming for clinical laboratory use. To avoid diagnostic error in determining thyroid hormone levels, the serum thyroid hormone-binding capacity must be evaluated. In cases of altered levels of thyroid hormone-binding proteins, the T3 resin uptake (RT3U) test can be used to ascertain the corrected total T3 and T4 serum concentrations. Using the total serum T4 concentration and RT3U, which indirectly measures serum levels of unsaturated thyroxine-binding globulin (UTBG), the free T4 index (FT4I) and free T3 index (FT3I) can be calculated as follows:

FT4I (or FT3I) = T4 (or T3) x (RT3 of patient / RT3 of control).

The RT3U test does not depend on the concentration of T3 in the serum to any significant extent. The RT3U depends primarily on the serum T4 and the UTBG. Table 1 demonstrates some clinical situations in which the RT3U test is critical in making the correct diagnosis.

Table 1. Triiodothyronine Uptake Test (RT3U Test) and some Clinical Examples

TBG	Resin Uptake (RT3U Test Result)	Clinical Condition	"Free" Thyroxine
Normal	> 14.6%	Hyperthyroid	High$
Normal	10.0-14.6%	Euthyroid	Normal$$
Normal	< 10.0%	Hypothyroid	Low$$$
Elevated	< 10.0%	Pregnancy	Normal$$$$

$ TBG is normal and T4 is elevated, leaving little unsaturated thyroid-binding globulin (UTBG) to compete for 125I-T3 in the RT3U test; therefore, RT3U value is elevated. The TGB/T4 ratio is low, resulting in excess "free" T4.

$$ TBG and T4 are normal; therefore, the RT3U test and "free" T4 are normal.

$$$ TBG is normal and T4 is low, leaving excess UTBG to compete for 125I-T3 in the RT3U test; therefore, RT3U is low. The TBG/T4 ratio is high, resulting in a low "free" T4.

$$$$ TBG and T4 are elevated with a large UTBG. The competition between UTBG and resin in the RT3U test favors UTBG, and therefore, the RT3U value will be low. The TBG/T4 ratio is normal; therefore, the "free" T4 remains normal.&

The RT3U test involves the addition of a known amount of T3 labeled with I131 to the patient's serum. The serum is absorbed on a resin sponge that competes for free T3 with any free thyroid-binding protein in the serum. With complete binding of the protein by endogenous thyroid hormone (as in hyperthyroid states), little opportunity exists for exogenous radioactive T3 to bind to protein. The added T3 thus remains free in the serum to be absorbed by the resin sponge. This results in a high level of RT3U, which indicates hyperthyroidism. In the serum of hypothyroid patients, RT3U is low because most of the exogenous radioactive iodine-labeled T3 attaches to the large quantity of available serum thyroid-binding protein. A smaller amount of labeled T3, therefore, remains in the serum to be absorbed by the resin sponge.

Pregnancy and progestational hormones increase the levels of thyroid-binding proteins, causing elevated total hormone concentrations and low levels of RT3U in the absence of either hyperthyroidism or hypothyroidism. Conversely, total serum hormone levels are decreased and RT3U is increased when thyroid-binding proteins are low, as in patients receiving anabolic steroids, in patients with nephrotic syndromes, or those with genetic defects limiting production of thyroid-binding globulin. Most common causes of altered levels of thyroid-binding globulin are listed in Table 2.

Table 2. Factors That Influence Binding Protein Levels

Binding	Increased	Decreased
TBG$	Oral contraceptive or other source	Anabolic steroids

	of estrogen	Prednisone therapy
	Pregnancy	Androgens
	Newborn state	Glucocorticoids
	Hepatitis	Marked hypoproteinemia
	Biliary cirrhosis	Chronic liver disease
	Acute intermittent porphyria	Acromegaly
	Genetically determined	Asparaginase
	Prolonged perphenazine therapy	Genetically determined
		Nephrotic syndromes
		Dilantin$$$
TBPA$$	None reported	Thyrotoxicosis
		Severe illness
		Surgery
		Chronic liver disease
		Parturition
		High-dose salicylates$$$

$ TBG, Thyroxine-binding globulin.
$$ TBPA, Thyroxine-binding prealbumin.
$$$ These agents affect binding capacity by displacing thyroxine from binding proteins, whereas the other factors result in changes in TBG and TBPA levels.&

Radioactive iodine uptake is another method of evaluating thyroid function. A trace (5 to 10 microC) of I131 is given orally. For a smaller radiation dose, I123 or pertechnetate (technetium-99m) can be used. The amount of radioactive iodine taken up by the gland is measured by a gamma counter placed over the gland. In patients with hyperthyroidism, both peak uptake and the rate of uptake are greater than those in euthyroid patients. The optimal time for measurement is from 2 to 6 hours.

Radioactive iodine uptake increases with iodine deficiency and decreases if iodine levels are increased with a large dietary iodine intake, iodine-containing drugs, or x-ray contrast media. Other causes of decreased radioiodine uptake include hypothyroidism, exogenous thyroid hormone, TSH deficiency due to pituitary or hypothalamic disease, and medications that inhibit the metabolism of iodine. Such medications include tolbutamide, reserpine, phenylbutazone, para-aminosalicylic acid, and antithyroid drugs. Other than hyperthyroidism, elevated radioactive iodine uptake may be due to iodine deficiency caused by dietary insufficiency or potent diuretic agents.

The suppression of radioactive iodine uptake by exogenous thyroid hormone in euthyroid patients is the basis of the radioactive iodine suppression test. This test differentiates patients with hyperthyroidism from those with "high normal" radioactive iodine uptake levels. A radioactive uptake test is first performed. Thyroid hormone is administered orally for varying periods of time, and the radioactive iodine uptake of the thyroid repeated. In a normal patient, TSH secretion is suppressed by the exogenous hormone, thyroid activity is thereby diminished, and the radioiodine uptake is decreased. In patients with primary hyperthyroidism, this response is not observed since thyroid activity is independent of TSH secretion.

Evaluation of the thyroid-pituitary axis may be helpful in differentiating intrinsic thyroid abnormalities from those due to abnormalities in the secretion of TSH. In addition, appropriate responses to injection of exogenous TRH and TSH may be helpful to define the cause of abnormal serum concentrations of thyroid hormone. The TRH stimulation test is widely used to document the presence of thyrotoxicosis in equivocal cases. Patients with thyrotoxicosis have low basal TSH levels because pituitary release is inhibited by high circulating levels of thyroid hormone. Patients who appear to be thyrotoxic but who have measured hormone levels at the upper limit of normal, or those who appear to be euthyroid but with high plasma concentrations of T4, are given 500 microg of TRH, and serum TSH is measured at baseline, 20, and 30 minutes. A normal response is a rise in serum TSH to greater than 7 microunits/mL. Failure of the serum TSH to rise above this level supports the diagnosis of thyrotoxicosis.

Serum TSH is measured by radioimmunoassay and is the most sensitive method to detect thyroid gland hypofunction. Primary (thyroidal) and secondary (hypothalamic-pituitary) hypothyroidism can be differentiated, because TSH concentrations are high in primary disease and low in the secondary form. Primary hypothyroidism is also differentiated from secondary disease by determining radioactive iodine uptake before and after 3 days of TSH administration, since uptake will increase in those with secondary hypothyroidism.

Determinations of serum thyroid antibody levels may also be helpful. Patients with nontoxic goiters have absent or low levels of antibodies to thyroglobulin and thyroid microsomes, whereas in Hashimoto's disease, the levels of these substances are high.

For initial evaluation, when hyperthyroidism is suspected, tests for T3, T4, and RT3U are recommended. Serum T3 levels are included because some hyperthyroid patients present only with elevations of T3. If hypothyroidism is suspected, T4, RT3U, and serum TSH levels are obtained. Serum TSH is an extremely sensitive indicator of hypothyroidism and often is clearly elevated, even when the T4 level is only minimally depressed.

Antithyroid Drugs

Antithyroid drugs act during the different stages of iodine metabolism. Potassium perchlorate blocks the uptake of iodine by the thyroid gland. Propylthiouracil, methylthiouracil, and carbimazole block iodide oxidation to elemental iodine by competitive inhibition of thyroid peroxidase. These three drugs also interfere with iodination of tyrosine and with the coupling reaction. Propylthiouracil interferes with the peripheral conversion of T4 to T3. High concentrations of iodide (greater than 35 microg/100 mL) act to block the oxidation of iodide and the synthesis of T3 and T4. A high concentration of iodide in the follicular cells also inhibits the release of previously formed hormone. These antithyroid effects are seen in hypophysectomized animals and are independent of TSH. The follicular cells act to autoregulate their function based on their intracellular iodine content. This autoregulatory mechanism recalibrates itself and adapts ("escapes") to the high iodide concentration in 10 to 14 days, demonstrating the short-term antithyroid effects of high-dose iodine therapy.

Disorders of Thyroid Function

Cretinism, exemplified by stunted growth, low basal metabolic rate, delay in the appearance of ossification centers and the eruption of teeth, and mental retardation, develops in thyroid-deficient children. These patients are treated with thyroid replacement to accelerate growth patterns, but the mental retardation is irreversible.

Hypothyroidism in adults is exhibited by lack of energy, intolerance to cold, dryness of skin and hair, weight gain, constipation, a typical facial appearance, hoarseness, and prolongation of the relaxation phase of tendon reflexes. Long-term problems include myxedema, electrolyte abnormalities, and myocardial dysfunction. The diagnosis is confirmed by thyroid function testing. Patients with this condition often respond well to thyroid supplements (T3 or T4) or desiccated thyroid. Table 3 lists the average daily oral maintenance dose for commonly used thyroid preparations.

Table 3. Average Daily Maintenance Dose of Commonly Used Thyroid Preparations

Thyroid Hormone Preparation	Average Daily Oral Maintenance Dose
Levothyroxine	150 microg
Thyroid extract, USP	100-200 mg
Liothyronine	50 microg
Liotrix	2 units.&

Graves' disease is a systemic autoimmune condition that is exhibited by hyperthyroidism, exophthalmus, and pretibial myxedema. Patients with this condition have a high basal metabolic rate, heat intolerance, weight loss, and tachycardia. These patients are treated with antithyroid drugs, radioactive iodine, or surgery.

Parathyroid Glands

The parathyroid glands synthesize and secrete parathyroid hormone (PTH), the primary calcium-regulating hormone. Usually, a pair of glands are located superiorly and another pair inferiorly on the thyroid. On occasion, one finds variable numbers of these glands in different locations in the mediastinum. The parathyroid glands are composed of chief cells, oxyphil cells, and water-clear cells. The chief cells are the main source of PTH. The oxyphil and water-clear cells are derived from chief cells and are capable of secreting PTH.

Calcium Metabolism

The average daily dietary intake of calcium is 0.5 to 1.0 gram. The urinary calcium output varies with diet but is approximately 150 to 200 mg/day. The kidneys resorb 99 per cent of the filtered calcium, even in the presence of hypercalcemia. Calcium absorption is an active process that takes place primarily in the duodenum and upper jejunum, and requires vitamin D metabolites. Of the 1000 grams of calcium in the body, 11 grams is intracellular, 1 gram is in the extracellular fluid, and the remainder is stable in the bone. In plasma, 47 per cent of the calcium is protein bound, 47 per cent is ionized, and the remainder is bound to

organic anions. The extracellular calcium exchanges with the intracellular fluid, exchangeable bone, and the glomerular filtrate, with minimal net movement.

Ionized calcium is crucial in the excitability of nerve function and the contractility of cardiac and skeletal muscle. Calcium is also important in the structure and function of cellular organelles and cell membranes as well as metabolic processes. Calcium is thought to be required to carry out the actions of cyclic adenosine monophosphate (cAMP) and bone formation.

Severe hypercalcemia results in cardiac and renal complications as well as mental depression. Hypocalcemia can result in tetany, convulsions, and death. For these reasons, control of serum calcium concentration is crucial to survival.

Normal total serum calcium concentration ranges from 8.5 to 10.1 mg/100 mL. Ideally, one would measure the serum ionized calcium concentration, but this is difficult. Total serum calcium concentration correlates well with serum ionized calcium concentration as long as serum protein concentrations are normal. When serum protein (especially albumin) levels are abnormal, total calcium levels must be considered in relation to protein levels. For each gram of alteration of the total protein above or below 6.5 g/100 mL, protein-bound calcium as well as total serum calcium increases or decreases 0.8 to 1.0 mg/100 mL.

Calcium homeostasis requires the controlled interaction between parathyroid hormone, specific vitamin D metabolites, and calcitonin. We will present each of these components separately and then discuss how they interact to control serum calcium concentration.

PTH

In 1970, Niall and associates isolated and determined the amino acid sequence of bovine PTH. PTH is a straight-chain peptide with a molecular weight of approximately 9500 and contains 84 amino acid residues. The biologically active portion of the peptide is in the first 34 amino acids at the amino-terminal end of the molecule.

Synthesis of PTH

PTH is synthesized within the parathyroid gland as a larger molecule that has 115 amino acids and is called preproparathyroid hormone (prepro PTH). This molecule is cleaved, removing 25 amino acids from the amino-terminal (N-terminal) end of the molecule. Then an intermediate precursor called proparathyroid hormone, which consists of 90 amino acids, is formed. Most PTH is secreted in this form and is cleaved in the reticuloendothelial cells of the liver, primarily into amino- and carboxy-terminal fragments. The amino-terminal fragment contains the biologically active portion of the PTH molecule.

Action of PTH

PTH acts to correct hypocalcemia by its actions on bone, intestinal absorption of calcium, and renal tubular resorption of calcium. The complexity of its actions requires a precise feedback control mechanism.

The administration of PTH to animal models or human subjects produces hypercalcemia, hypophosphatemia, and phosphaturia. This results from three mechanisms: (1) increased bone resorption, (2) increased calcium absorption from the intestines, and (3) increased tubular resorption of calcium and decreased tubular resorption of phosphate by the kidney. PTH secretion also increases the renal excretion of bicarbonate, potassium, and amino acids while decreasing the excretion of ammonia, magnesium, and titratable acid.

PTH acts on kidney and bone through the adenyl cyclase system. PTH stimulates adenyl cyclase activity and raises cyclic 3',5'-AMP levels in kidney and bone. These mechanisms are triggered by the binding of PTH to receptors in the kidneys and bone.

Evaluation of Parathyroid Function

Parathyroid hormone is an 84-amino acid structure that has an amino-terminal fragment and a carboxy-terminal fragment. The biologically active amino-terminal fragment has a half-life of several minutes, whereas the carboxy-terminal fragment has a half-life of several hours. Radioimmunoassay to measure the carboxy-terminal (C-terminal) fragments of the PTH molecule is the most accurate test for the diagnosis of hyperparathyroidism. In itself, the presence of an elevated PTH level does not confirm a diagnosis of hyperparathyroidism. An increased plasma PTH indicates hyperparathyroidism only in conjunction with an elevated calcium level.

Measurement of the tubular reabsorption of phosphate has been used to help diagnose hyperparathyroidism. The tubular reabsorption of phosphate is normally greater than 85 per cent. In patients with hyperparathyroidism, phosphate reabsorption is usually less than 30 per cent, but this value varies significantly, and therefore, the test is not as accurate as measuring PTH and calcium levels.

Specific PTH receptors in the kidney tubule activate adenylate cyclase with a resultant increase in intracellular cAMP. Some of the cAMP leaks into the tubular fluid, resulting in increased concentrations in the urine of patients with hyperparathyroidism. One can calculate the nephrogenous cAMP, which is determined as a function of the creatinine clearance. In 90 per cent of patients with hyperparathyroidism, the urinary level of cAMP is increased. For the diagnosis of hyperparathyroidism, measuring urinary cAMP is not as accurate as measurement of PTH by radioimmunoassay.

When routine calcium determination reveals abnormally elevated levels, the PTH level should be checked. If the PTH level is elevated, a computed tomography or a magnetic resonance scan should be obtained to identify parathyroid pathology. When parathyroid enlargement is noted on physical examination, calcium and PTH levels must be obtained. Hyperparathyroidism may require surgical intervention.

Disorders of Parathyroid Function

Hyperparathyroidism is characterized by hypercalcemia, which can result in nephrolithiasis, nephrocalcinosis, depression, fatigue, muscle weakness, peptic ulcer, constipation, eye changes, ectopic calcification, and hypercalcemic crisis. Hyperparathyroidism can also produce increased urinary calcium (polydipsia, polyuria), hypomagnesemia

(paresthesia, hyperreflexia), and renal damage (hypertension, renal stones). The effects of PTH on bone can result in demineralization of the bony skeleton with bone pain, cysts, and fractures. Symptoms of hyperparathyroidism can be very subtle, or can become manifest as multisystem failure.

Hyperparathyroidism can be primary, secondary, or tertiary. Primary hyperparathyroidism is usually caused by an adenoma of the parathyroid or parathyroid gland hyperplasia. In secondary hyperparathyroidism, an underlying cause, such as chronic renal failure, results in hypocalcemia and an elevated PTH level. In some cases, renal failure comes first, leading to secondary hyperparathyroidism and finally to tertiary hyperparathyroidism that becomes manifest by hypercalcemia.

Hypercalcemia is frequently diagnosed on routine blood analysis in asymptomatic patients. Symptomatic patients usually have a greater elevation in their serum calcium level and often have other physical findings or radiologic changes, such as the typical "moth-eaten" ground-glass skull or subperiosteal bone resorption in the middle and terminal phalanges of the fingers.

If renal complications and bone lesions progress, then surgical treatment is indicated. In a patient with an adenoma and three normal parathyroid glands, only the abnormal gland is removed (Table 4). In parathyroid hyperplasia, 30 mg of viable parathyroid tissue is preserved on an intact vascular pedicle and the remaining glands are excised and cryopreserved. If only three normal glands are found, the thyroid lobe on the side of the missing gland is removed and serially sectioned. With secondary hyperparathyroidism, all four glands are excised and 60 to 90 mg of excised tissue is autotransplanted into the forearm.

Table 4. Extent of Surgical Resection for Hyperparathyroidism

Primary Hyperparathyroidism

Single Adenoma$
- Resect single enlarged gland
- Spare three other normal glands

Hyperplasia
- Spare 30 mg of parathyroid tissue on an intact vascular pedicle
- Resect the remainder of the parathyroid tissue
- Cryopreserve the resected parathyroid tissue

Two Adenomas
- Resect both enlarged glands
- Spare the other two normal glands

Secondary Hyperparathyroidism

Four Enlarged Glands
- Resect all four enlarged parathyroid glands
- Immediately autotransplant 60-90 mg of fresh parathyroid tissue

Cryopreserve the remainder of the parathyroid tissue.

$ If only three normal glands are found, then the thyroid lobe on the side of the missing gland is resected.
$ If one gland is enlarged, two are normal, and exploration of the superior mediastinum is negative, no thyroid tissue is resected.&

Hypoparathyroidism is almost exclusively noted as a postoperative problem following extensive thyroid, laryngeal, or mediastinal surgery and should be suspected when patients complain of perioral numbness or twitching, muscle spasm, and carpopedal spasm. Chvostek's sign is elicited by gentle tapping over the distribution of the facial nerve, resulting in unilateral facial spasm. A positive Chvostek's sign demonstrates general neuromuscular irritability and latent tetany. Serum calcium levels are low with a low PTH level. These patients need aggressive calcium supplementation with vitamin D. The serum calcium concentration must be monitored closely to ensure that treatment is effective.

Vitamin D

The natural form of vitamin D is known as cholecalciferol, or vitamin D3, and is produced by the irradiation of 7-dihydrocholesterol in the skin. To become metabolically active, cholecalciferol is hydroxylated in the liver to 25-hydroxycholecalciferol (25-OH D3), then it is further hydroxylated in the kidney to 1,25-dihydroxy-cholecalciferol (1,25-(OH)2 D3). The final metabolite, 1,25-dihydroxy-cholecalciferol, is the active form, which is crucial to mobilizing calcium and phosphorus from bone as well as increasing intestinal absorption of these substances.

Action of Vitamin D3

In the presence of parathyroid hormone, when serum calcium and phosphorus levels are low, synthesis of 1,25-(OH)2 D3 increases. The additional 1,25-(OH)2 D3 is needed for the action of PTH on the gut and bone. This process mobilizes calcium and phosphorus from bone and intestines, and serum calcium levels return to normal.

Calcitonin

Synthesis of Calcitonin

Calcitonin was initially described in 1962 by Copp and associates as a calcium-lowering polypeptide. Calcitonin is produced in the mitochondria-rick parafollicular C-cells, which come from the neural crest and are part of the amine-precursor uptake and decarboxylation system of peptide- or amine-secreting cells. Medullary carcinomas of the thyroid are C-cell, calcitonin-secreting tumors.

Calcitonin in humans is made up of 32 amino acids and has a molecular weight of 3500, with an amino acid sequence that differs from other species. The radioimmunoassay system for detecting human calcitonin is crucial in the diagnosis and follow-up of patients with medullary carcinoma of the thyroid gland.

Action of Calcitonin

Calcitonin acts to lower serum calcium concentration by inhibiting calcium release from bone. Calcitonin acts swiftly. In tissue culture, it produces change in osteoclasts of mouse calvariae within 15 minutes of administration. Calcitonin prevents hypercalcemia and works against PTH through this antiosteolytic effect on bone. The hormone activates adenylate cyclase with resultant increases in the concentration of intracellular cAMP. Marx and colleagues discovered actual receptors for calcitonin located in kidney and bone.

Calcitonin depress appetite, inhibit gastric secretion and ulcer formation, and act as a diuretic and a potent analgesic. Continued research on calcitonin may find receptors for this molecule in many different organ systems.

Clinical Application

Calcitonin is secreted by the parafollicular C-cells of medullary carcinoma of the thyroid gland, and is used as a tumor marker. Medullary thyroid carcinoma is a component of multiple endocrine neoplasia, type 2A, or Sipple's syndrome. The complete syndrome consists of medullary thyroid carcinoma, pheochromocytoma, and in about half of the reported cases, parathyroid hyperplasia. The other subtype multiple endocrine neoplasia, type 2B, includes medullary thyroid carcinoma; pheochromocytoma; Marfan-like habitus; mucosal neuromas of the lips, tongue, or conjunctivae; and ganglioneuromas but without hyperparathyroidism. Detection of calcitonin levels is particularly useful in screening families with multiple endocrine neoplasia type 2 syndrome and for follow-up after thyroidectomy of patients with medullary carcinoma of the thyroid.

Because of its effective antiosteolytic activity, calcitonin is used to treat Paget's disease and for controlling hypercalcemia due to hyperparathyroidism and bone malignancy.

Calcium Homeostasis

The regulation of serum calcium concentration is performed primarily by the parathyroid glands via a negative feedback system. A low serum calcium concentration acts to stimulate the secretion of PTH, which, in turn, raises serum calcium concentration to normal levels. The stimulated secretion of PTH is independent of the nervous system or the pituitary gland. Sherwood and co-workers showed that the secretion rate of PTH is directly proportional to the fall in the serum calcium concentration. In addition, hypocalcemia results in the increased synthesis of 1,25-(OH)2 D3, which is needed for the action of PTH on the gut and bone.

Hypercalcemia results in the decreased secretion of PTH and the decreased synthesis of 1,25-(OH)2 D3. Both of these factors decrease serum calcium concentration. The secretion of calcitonin increases linearly, with elevation of serum calcium concentration acting in a negative feedback system. Calcitonin decreases serum calcium and serum phosphorus concentration by inhibiting bone resorption and producing an antiosteolytic effect on bone that antagonizes PTH.

Calcium metabolism is controlled by a feedback system that incorporates the actions of PTH, calcitonin, and 1,25-(OH)2 D3. A defect in any one of these components can result in life-threatening changes in serum calcium concentrations.

An understanding of thyroid and parathyroid physiology can help the head and neck surgeon in the diagnosis and management of disease in these closely related endocrine organs. Extensive biochemical and clinical research continues to define the mechanism of action of thyroid hormone, parathyroid hormone, and calcitonin. New developments may change diagnostic modalities and treatment philosophy. Thus, the clinician must be knowledgeable in the physiology of the thyroid and parathyroid glands.