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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Goitre (British English), or **goiter** (American English), is a swelling in the neck resulting from an enlarged thyroid gland. A goitre can be associated with a thyroid that is not functioning properly.

Worldwide, over 90% of goitre cases are caused by iodine deficiency. The term is from the Latin *gutturia*, meaning throat. Most goitres are not cancerous (i.e., benign), though they may be potentially harmful.

A goitre can present as a palpable or visible enlargement of the thyroid gland at the base of the neck. A goitre, if associated with hypothyroidism or hyperthyroidism, may be present with symptoms of the underlying disorder. For hyperthyroidism, the most common symptoms are associated with adrenergic stimulation: tachycardia (increased heart rate), palpitations, nervousness, tremor, increased blood pressure and heat intolerance. Clinical manifestations are often related to hypermetabolism (increased metabolism), excessive thyroid hormone, an increase in oxygen consumption, metabolic changes in protein metabolism, immunologic stimulation of diffuse goitre, and ocular changes (exophthalmos). Hypothyroid people commonly have poor appetite, cold intolerance, constipation, lethargy and may undergo weight gain. However, these symptoms are often non-specific and make diagnosis difficult.

"DISEASE DIGNOSIS" segment talks about Thyroid enlargement also known as Goitre.

"INTERPRETATION" highlights Thyroid Markers while **"TROUBLESHOOTING"** discusses problems faced in FIA systems.

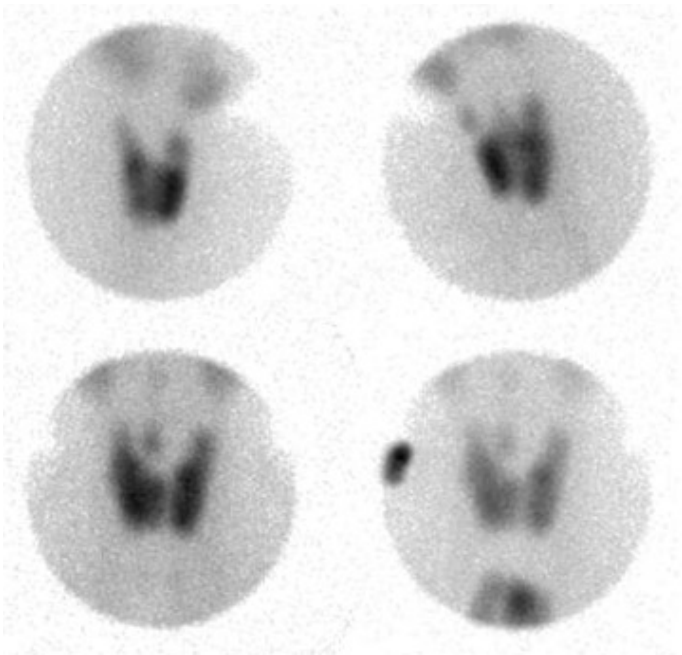
BOUQUET has not been ignored.

DISEASE DIAGNOSIS

GOITER

Practice Essentials

A goiter is an enlarged thyroid gland, and it may be diffuse or nodular. A goiter may extend into the retrosternal space, with or without substantial anterior enlargement. Because of the anatomic relationship of the thyroid gland to the trachea, larynx, superior and inferior laryngeal nerves, and esophagus, abnormal growth may cause a variety of compressive syndromes. Thyroid function may be normal (nontoxic goiter), overactive (toxic goiter), or underactive (hypothyroid goiter). Initial screening for goiters should include thyroid-stimulating hormone (TSH). In 1656, Thomas Wharton described the distinct nature of what he termed the thyroid gland, distinguishing it from the larynx, as this structure had been considered a laryngeal gland from the time of Andreas Vesalius in the 16th century. It was nearly 200 more years before the function of the thyroid was elucidated. The normal adult thyroid gland weighs 10-25 g and has 2 lobes connected by an isthmus. Nearly 50% of thyroid glands exhibit a pyramidal lobe arising from the center of the isthmus. Longitudinal dimensions of the lobes of the thyroid range up to 5 cm, as shown in the image below.



Thyroid nuclear scan of a patient with a euthyroid goiter showing different projections.

Signs and symptoms of goiters

A goiter may present in various ways, including the following:

- Incidentally, as a swelling in the neck discovered by the patient or on routine physical examination
- A finding on imaging studies performed for a related or unrelated medical evaluation
- Local compression causing dysphagia, dyspnea, stridor, plethora, or hoarseness
- Pain due to hemorrhage, inflammation, necrosis, or malignant transformation
- Signs and symptoms of hyperthyroidism or hypothyroidism
- Thyroid cancer with or without metastases

Diagnosis of goiters

Initial screening should include TSH. Given the sensitive third-generation assays, in the absence of symptoms of hyperthyroidism or hypothyroidism, further testing is not required. An assessment of free thyroxine index or direct measurement of free thyroxine would be the next step in the evaluation. Further laboratory testing is based on presentation and results of screening studies and may include thyroid antibodies (antithyroid peroxidase; formerly, the antimicrosomal antibodies and antithyroglobulin), thyroglobulin, sedimentation rate, and calcitonin in an individual at high risk for medullary carcinoma of the thyroid. Ultrasonography can be used to establish and follow goiter size, consistency, and nodularity. It can also be employed to localize nodules for ultrasonographically guided biopsy. Computed tomography (CT) scanning is useful in determining the effect of the thyroid gland on nearby structures. It also may be helpful in the follow-up of patients with thyroid cancer that shows evidence of recurrence. Magnetic resonance imaging (MRI) has the same indications as CT scanning. Fine-needle aspiration biopsy is employed for cytologic diagnosis. Fine-needle aspiration of the thyroid is used to determine the cause of an enlarged gland. In general, the procedure is not used in the workup of autonomously functioning nodules. Core biopsy, or large-needle biopsy, of the thyroid uses a larger-gauge needle, providing a fragment of tissue. This procedure also carries with it a higher morbidity than fine-needle aspiration biopsy. Core biopsy has the advantage of more complete sampling.

Management of goiters

Small benign euthyroid goiters do not require treatment. The effectiveness of medical treatment using thyroid hormone for benign goiters is controversial. The size of a benign euthyroid goiter may be reduced with levothyroxine suppressive therapy. Moreover, treatment of hypothyroidism or hyperthyroidism often reduces the size of a goiter. Goiters with primary thyroid malignancy require levothyroxine replacement after surgery and radioactive iodine ablation. Metastatic lesions to the thyroid gland require treatment of the primary malignancy. Granulomatous and infectious etiologies for goiter require specific treatment depending on the underlying cause.

Surgery is reserved for the following situations:

- Large goiters with compression
- Malignancy
- When other forms of therapy are not practical or are ineffective

If it is practical, treat endemic goiters in iodine-deficient regions with iodine supplementation in the diet and avoidance of goitrogens. Treatment with iodine supplementation or levothyroxine may reduce goiter size.

Pathophysiology

The thyroid gland is controlled by thyroid-stimulating hormone (TSH; also known as thyrotropin), secreted from the pituitary gland, which in turn is influenced by the thyrotropin-releasing hormone (TRH) from the hypothalamus. TSH permits growth, cellular differentiation, and thyroid hormone production and secretion by the thyroid gland. Thyrotropin acts on TSH receptors located on the thyroid gland. Thyroid hormones are synthesized from iodination of tyrosine. The iodine is transported from plasma into the thyroid cell via a sodium-iodide symporter. This is an active process resulting in an intracellular iodine level exceeding 20 times the plasma iodine level. This iodine transport activity is controlled by TSH. Serum thyroid hormones levothyroxine and triiodothyronine feed back to the pituitary, regulating TSH production. Interference with this TRH-TSH thyroid hormone axis causes changes in the function and structure of the thyroid gland. Stimulation of the TSH receptors of the

thyroid by TSH, TSH-receptor antibodies, or TSH receptor agonists, such as chorionic gonadotropin, may result in a diffuse goiter. When a small group of thyroid cells, inflammatory cells, or malignant cells metastatic to the thyroid is involved, a thyroid nodule may develop. A deficiency in thyroid hormone synthesis or intake leads to increased TSH production. Increased TSH causes increased cellularity and hyperplasia of the thyroid gland in an attempt to normalize thyroid hormone levels. If this process is sustained, a goiter is established. Causes of thyroid hormone deficiency include inborn errors of thyroid hormone synthesis, iodine deficiency, and goitrogens. A goiter may result from a number of TSH receptor agonists. TSH receptor stimulators include TSH receptor antibodies, pituitary resistance to thyroid hormone, adenomas of the hypothalamus or pituitary gland, and tumors producing human chorionic gonadotropin.

Epidemiology

Frequency

Worldwide, the most common cause of goiter is iodine deficiency. It is estimated that goiters affect as many as 200 million of the 800 million people who have a diet deficient in iodine. In the Wickham study from the United Kingdom, 16% of the population had a goiter. In a German study, 635 people underwent ultrasonographic thyroid screening, as well as basal TSH measurement, during a preventive-health checkup. Thyroid nodules were detected in 432 (68%) of the persons screened; in a previous German study, ultrasonographic screening of more than 90,000 people detected thyroid nodules in 33% of the normal population. The authors of the latter report attributed this difference to the fact that patients in their study were screened using 13 MHz ultrasonographic scanners, which were more sensitive than the 7.5 MHz scanners used in the previous study. According to the investigators, their results indicated that the question of routine iodine supplementation requires renewed attention. The incidence of thyroid cancer has been rising worldwide. The reasons are unclear, but this trend may be related to better detection and diagnostic methods.

Mortality/Morbidity

Most goiters are benign, causing only cosmetic disfigurement. Morbidity or mortality may result from compression of surrounding structures, thyroid cancer, hyperthyroidism, or hypothyroidism.

Race

No racial predilection exists.

Sex

The female-to-male ratio is 4:1.

- In the Wickham study, 26% of women had a goiter, compared to 7% of men.
- Thyroid nodules are less frequent in men than in women, but when found, they are more likely to be malignant.

Age

The frequency of goiters decreases with advancing age. The decrease in frequency differs from the incidence of thyroid nodules, which increases with advancing age.

Prognosis

Benign goiters have a good prognosis. However, all goiters should be monitored by examination and biopsy for possible malignant transformation, which may be signaled by a sudden change in size, pain, or consistency. Fortunately, the risk of this is low. In patients exposed to low levels of radiation the risk rises. Based on the Wickham study, a few of the goiters increased in size. A small percentage of multinodular goiters do cause hyperthyroidism. Lifelong surveillance is necessary. Patients with chronic lymphocytic thyroiditis generally have glands that become atrophic. A study by Sorensen et al found that patients with symptomatic benign nodular goiter who underwent thyroidectomy experienced improvements in tracheal anatomy, inspiratory flow, and health-related quality of life. The investigators found a median 26% improvement in tracheal narrowing and 33% diminishment in tracheal deviation, at 6 months postsurgery. The study also reported a 1% improvement in tracheal narrowing for each 10% reduction in goiter volume. In addition, forced inspiratory flow at 50% of forced vital capacity showed a small improvement. With regard to quality of life, the Impaired Daily Life scale from the Thyroid-Specific Patient-Reported Outcome Measure (ThyPRO) improved by 0.33-points for every 1% reduction in tracheal narrowing. A study by Chaves et al using the ThyPRO questionnaire indicated that multiple aspects of health-related quality of life improve following surgery in patients with benign non-toxic goiter. Particular improvement was found with regard to overall quality of life, goiter symptoms, and tiredness.

Patient Education

Educate a patient about potential etiologies, eg, adequate dietary iodine intake, avoidance of goitrogens, regular personal neck examination, and physician examination. For patients on medical therapy, reinforce the need to take medications on a regular basis. Review symptoms of hyperthyroidism.

CLINICAL PRESENTATION

History

A goiter may present in various ways, including the following:

- Incidentally, as a swelling in the neck discovered by the patient or on routine physical examination
- A finding on imaging studies performed for a related or unrelated medical evaluation
- Local compression causing dysphagia, dyspnea, stridor, plethora, or hoarseness
- Pain due to hemorrhage, inflammation, necrosis, or malignant transformation
- Signs and symptoms of hyperthyroidism or hypothyroidism
- Thyroid cancer with or without metastases.

Physical

The general examination for hyperthyroidism, hypothyroidism, and autoimmune stigmata is followed by systematic examination of the goiter. A retrosternal goiter may not be evident on physical examination. Examination of the goiter is best performed with the patient upright, sitting or standing. Inspection from the side may better outline the thyroid profile, as shown below. Asking the patient to take a sip of water facilitates inspection. The thyroid should move upon swallowing. See the image below.

Patient with a goiter. Prominent side-view outline.

Palpation of the goiter is performed either facing the patient or from behind the patient, with the neck relaxed and not hyperextended. Palpation of the goiter rules out a pseudogoiter, which is a prominent thyroid seen in individuals who are thin. Each lobe is palpated for size, consistency, nodules, and tenderness. Cervical lymph nodes are then palpated. The oropharynx is visualized for the presence of lingular thyroid tissue. The size of each lobe is measured in 2 dimensions using a tape measure. Some examiners make tracings on a sheet of paper, which is placed in the patient's chart. Suitable landmarks are used and documented to ensure consistent measurement of the thyroid gland. The pyramidal lobe often is enlarged in Graves disease. A firm rubbery thyroid gland suggests Hashimoto thyroiditis, and a hard thyroid gland suggests malignancy or Riedel struma. Multiple nodules may suggest a multinodular goiter or Hashimoto thyroiditis. A solitary hard nodule suggests malignancy, whereas a solitary firm nodule may be a thyroid cyst. Diffuse thyroid tenderness suggests subacute thyroiditis, and local thyroid tenderness suggests intranodal hemorrhage or necrosis. Cervical lymph glands are palpated for signs of metastatic thyroid cancer. Auscultation of a soft bruit over the inferior thyroidal artery may be appreciated in a toxic goiter. Palpation of a toxic goiter may reveal a thrill in the profoundly hyperthyroid patient.

Goiters are described in a variety of ways, including the following:

- Toxic goiter: A goiter that is associated with hyperthyroidism is described as a toxic goiter. Examples of toxic goiters include diffuse toxic goiter (Graves disease), toxic multinodular goiter, and toxic adenoma (Plummer disease).
- Nontoxic goiter: A goiter without hyperthyroidism or hypothyroidism is described as a nontoxic goiter. It may be diffuse or multinodular, but a diffuse goiter often evolves into a nodular goiter. Examination of the thyroid may not reveal small or posterior nodules. Examples of nontoxic goiters include chronic lymphocytic thyroiditis (Hashimoto disease), goiter identified in early Graves disease, endemic goiter, sporadic goiter, congenital goiter, and physiologic goiter that occurs during puberty.

Autonomously functioning nodules may present with inability to palpate the contralateral lobe. Unilobar agenesis may also present like a single thyroid nodule with hyperplasia of the remaining lobe. The Pemberton maneuver raises a goiter into the thoracic inlet when the patient elevates the arms. This may cause shortness of breath, stridor, or distention of neck veins.

Causes

The different etiologic mechanisms that can cause a goiter include the following:

- Iodine deficiency
- Autoimmune thyroiditis - Hashimoto or postpartum thyroiditis
- Excess iodine (Wolff-Chaikoff effect) or lithium ingestion, which decrease release of thyroid hormone
- Goitrogens
- Stimulation of TSH receptors by TSH from pituitary tumors, pituitary thyroid hormone resistance, gonadotropins, and/or thyroid-stimulating immunoglobulins
- Inborn errors of metabolism causing defects in biosynthesis of thyroid hormones
- Exposure to radiation
- Deposition diseases/infiltrative disease
- Thyroid hormone resistance (pituitary thyroid hormone resistance with resultant elevated TSH)
- Subacute thyroiditis (de Quervain thyroiditis)
- Silent thyroiditis
- Riedel thyroiditis
- Infectious agents
  - Acute suppurative - Bacterial
  - Chronic - Mycobacteria, fungal, and parasitic
- Granulomatous disease
- Thyroid malignancy
- Low selenium levels: This may be associated with goiter prevalence.

Differential Diagnoses

- Anaplastic Thyroid Carcinoma
- Branchial Cleft Cyst
- Carotid Artery Aneurysm
- Lymphatic Malformation (Cystic Hygroma)
- Fibroma
- Granulomatous Disease of the Thyroid
- Infectious Thyroiditis
- Lipomas
- Lymphadenopathy
- Medullary Thyroid Carcinoma
- Papillary Thyroid Carcinoma
- Parathyroid Adenoma
- Parathyroid Cyst
- Pseudogoiter
- Sarcoma
- Subacute Thyroiditis
- Thyroglossal Duct Cyst
- Thyroid Abscess
- Thyroid Lymphoma
- Thyroid Nodule

Laboratory Studies

Initial screening should include TSH. Given the sensitive third-generation assays, in the absence of symptoms of hyperthyroidism or hypothyroidism, further testing is not required. An assessment of free thyroxine index or direct measurement of free thyroxine would be the next step in the evaluation. Further laboratory testing is based on presentation and results of screening studies and may include thyroid antibodies (antithyroid peroxidase; formerly, the antimicrosomal antibodies and antithyroglobulin), thyroglobulin, sedimentation rate, and calcitonin in an individual at high risk for medullary carcinoma of the thyroid.

Imaging Studies

Ultrasonography

Ultrasonography can be used to establish and follow goiter size, consistency, and nodularity. It can also be employed to localize nodules for ultrasonographically guided biopsy. A study by Kelly et al indicated that in some patients with multinodular goiter, the risk of neoplasia can be effectively assessed with ultrasonography rather than with fine-needle aspiration biopsy. The investigators reported that in study patients with no suspicious features on ultrasonography, the average risk of neoplasia in multinodular goiters was 0.0339, although this risk rose significantly when one or more suspicious features were present.

Roentgenography

Roentgenography is used to assess extent of a goiter and presence of calcification. Ultrasonography has replaced this modality. Roentgenography is used to visualize calcifications within a goiter and regional lymph glands.

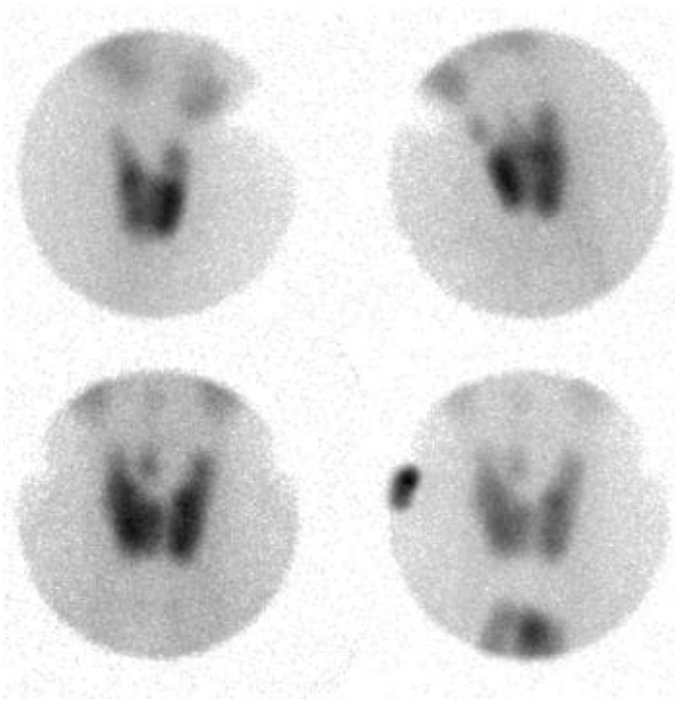
Computed tomography (CT) scanning

CT scanning is more precise than roentgenography. CT scanning can be used to delineate size and goiter extent. Due to the superficial placement of the thyroid gland, ultrasonography is more useful in following size. CT

scanning does a much better job of determining the effect of the thyroid gland on nearby structures. It also may be useful in the follow-up of patients with thyroid cancer that shows evidence of recurrence. CT scanning can be used to guide biopsy of the thyroid.

MRI

Magnetic resonance imaging has the same indications as CT scanning (see above). Radionuclide uptake and radionuclide scanning are used to assess thyroid function and anatomy in hyperthyroidism, as shown below. Additionally, thyroid scanning may be useful in the patient with neck or superior mediastinal masses. Radionuclide scanning allows determination of the function of a nodule. Function of a thyroid nodule has value both diagnostically and therapeutically. See the image below.



Thyroid nuclear scan of a patient with a euthyroid goiter showing different projections.

Other

Barium swallow is used to assess esophageal obstruction. Spirometry: The flow-volume loop is useful in determining the functional significance of compressive goiters. Perchlorate discharge test is used in individuals with inborn errors of thyroid hormone synthesis. It is used rarely today to determine the ability to trap and organify iodine.

Procedures

Fine-needle aspiration biopsy is used for cytologic diagnosis. Fine-needle aspiration of the thyroid is used to determine the cause of an enlarged gland. In general, the procedure is not used in the workup of autonomously functioning nodules. The procedure has little morbidity and can be tailored to the situation. Core biopsy, or large-needle biopsy, of the thyroid uses a larger-gauge needle, providing a fragment of tissue. This procedure also carries with it a higher morbidity. Core biopsy has the advantage of more complete sampling. Partial thyroidectomy may be used as a first-line procedure for patients with a high probability of cancer. It is reserved mostly if the result of a fine-needle aspiration is suspicious or if the patient/physician prefers it. Total thyroidectomy is performed for malignant goiters.

Histologic Findings

Simple nontoxic goiters show hyperplasia, colloid accumulation, and nodularity. Nodular hyperplasia is commonly seen in multinodular goiter. Cytologic findings include benign appearing follicular cells, abundant colloid, macrophages, and, sometimes, Hürthle cells. Inflammatory disorders of the thyroid, such as chronic lymphocytic (Hashimoto) thyroiditis, contain a mixed population of lymphocytes mixed with benign appearing follicular cells. Malignant nodules may be follicular cell in origin, ie, papillary (most common), follicular, Hürthle cell, or anaplastic. They also may be from parafollicular cells, medullary carcinoma or lymphoma, or other categories.

Medical Care

Small benign euthyroid goiters do not require treatment. The effectiveness of medical treatment using thyroid hormone for benign goiters is controversial. Large and complicated goiters may require medical and surgical treatment. Malignant goiters require medical and surgical treatment.

- The size of a benign euthyroid goiter may be reduced with levothyroxine suppressive therapy. The patient is monitored to keep serum TSH in a low but detectable range to avoid hyperthyroidism, cardiac arrhythmias, and osteoporosis. The patient has to be compliant with monitoring. Some authorities suggest suppressive treatment for a definite time period instead of indefinite therapy. Patients with Hashimoto thyroiditis respond better.
- Treatment of hypothyroidism or hyperthyroidism often reduces the size of a goiter.
- Thyroid hormone replacement is often required following surgical and radiation treatment of a goiter. Use of radioactive iodine for the therapy of nontoxic goiter has been disappointing and is controversial.
- Medical therapy of autonomous nodules with thyroid hormone is not indicated.
- Ethanol infusion into benign thyroid nodules has not been approved in the United States, but it is used elsewhere.

Goiters with primary thyroid malignancy require levothyroxine replacement after surgery and radioactive iodine ablation. Metastatic lesions to the thyroid gland require treatment of the primary malignancy. Granulomatous and infectious etiologies for goiter require specific treatment depending on the underlying cause.

Surgical Care

Surgery is reserved for the following situations:

- Large goiters with compression
- Malignancy
- When other forms of therapy are not practical or are ineffective

Preoperatively, establish euthyroid state prior to surgical treatment. Evaluation must include the stability of the airway. This must be secured immediately if ventilatory status appears tenuous. Emergency surgical treatment of a goiter in a patient with hypothyroidism requires intravenous levothyroxine and glucocorticoids at stress doses. Emergency surgical treatment of a goiter in a thyrotoxic patient requires antithyroid medications, beta blockers, and glucocorticoids at stress doses. Suppressive doses of iodine are helpful. Intraoperative and postoperative management includes hemodynamic monitoring, which is important in patients with preoperative hyperthyroidism or hypothyroidism. Postoperative management also includes monitoring of serum calcium. A literature review by Li et al indicated that total thyroidectomy is a safe procedure for the treatment of bilateral multinodular nontoxic goiter, demonstrating a lower recurrence rate than

bilateral subtotal thyroidectomy. However, total thyroidectomy was also found to carry a significantly higher risk of postoperative transient hypoparathyroidism than did the other procedure. A study by Finnerty et al indicated that in patients with multinodular goiter who undergo total thyroidectomy, a higher score on the 5-factor modified frailty index is more predictive of thyroidectomy-specific complications, including hematoma and recurrent laryngeal nerve palsy, than is older age. A retrospective study by Frank et al indicated that in patients with hyperthyroidism who undergo total thyroidectomy, the complication rate, including with regard to transient hypocalcemia, temporary dysphonia, and postoperative hematoma, does not differ significantly from that for the procedure in patients with benign euthyroid or malignant thyroid disease. The investigators also found that among the patients with hyperthyroidism, the complication rates were similar between those with Graves disease and patients with toxic multinodular goiter. A study by Khan et al indicated that in patients with retrosternal goiter, a transcervical surgical approach is preferable to a transthoracic procedure. The study, which employed the National Surgical Quality Improvement Program (NSQIP) database, found that various postoperative morbidities, including those involving transfusions and unplanned intubations, were higher with the transthoracic approach. The data suggested that overall mortality might be increased as well with this procedure. A literature review by Khan et al estimated that in thyroidectomy for retrosternal goiter (defined in this study as one that extends below the sternal notch), 6.12% of surgeries take an extracervical approach. Extracervical approaches include sternotomy, posterolateral thoracotomy, and video- or robotically assisted thoracoscopic surgery. A study by Bove et al indicated that in patients with retrosternal goiter, recurrence and extension of the goiter beyond the carina are preoperative risk factors for postoperative complications following total thyroidectomy. The study also found evidence that, compared with total thyroidectomy for cervical goiter, the risk for transient hypocalcemia and transient recurrent laryngeal nerve palsy is greater following the same procedure for retrosternal goiter. Similarly, a study by Cappellacci et al found differing outcomes in total thyroidectomies as carried out on patients with retrosternal goiters and those with classic cervical goiters. The rates of transient postoperative hypoparathyroidism in the two groups were 19.9% vs 9.4%, respectively, while the rates of permanent postoperative hypoparathyroidism were 3.3% vs 1.6%, respectively. With regard to recurrent laryngeal nerve injury (RLNI) in total thyroidectomy, the rate of permanent injury was again higher for retrosternal goiters than for classic cervical goiters (1.4% vs 0.4%, respectively). However, no difference was found in rates of transient RLNI.

INTERPRETATION

THYROID MARKERS

Interpreting thyroid markers involves looking at TSH, Free T4 (Ft4), and Free T3 (FT3) together: **High TSH + Low FT4/FT3 = Hypothyroidism (underactive)**; **Low TSH + High FT4/FT3 = Hyperthyroidism (overactive)**; while normal levels usually mean a healthy thyroid, abnormal patterns can point to pituitary issues or autoimmune diseases, needing a doctor's review to understand your specific thyroid health.

Key Markers & What They Mean

- **TSH (Thyroid-Stimulating Hormone):** Produced by the pituitary, it tells the thyroid to make hormones.
  - **High TSH:** Pituitary working overtime to stimulate an underactive thyroid (hypothyroidism).
  - **Low TSH:** Pituitary calming down a thyroid that's making too much hormone (hyperthyroidism).
- **Free T4 (FT4) & Free T3 (Ft3):** The actual active thyroid hormones.
  - **Low FT4/FT3:** Thyroid isn't producing enough.
  - **High FT4/FT3:** Thyroid is producing too much.

Common Patterns (Primary Thyroid Issues)

- **Hypothyroidism (Underactive):** High TSH, Low FT4/FT3.
- **Hyperthyroidism (Overactive):** Low TSH, High FT4/FT3.

Other Important Markers

- **Thyroid Antibodies:** High levels (like TSI) suggest autoimmune conditions such as Hashimoto's (hypo) or Graves' disease (hyper).
- **Calcitonin:** High levels can indicate thyroid cancer or kidney issues.

Important Considerations

- **Reference Ranges Vary:** Lab ranges differ; always check the specific lab's range.
- **Clinical Picture:** Results must be interpreted with your symptoms and overall health by a doctor.
- **Subclinical Issues:** Mild thyroid failure might show up with only one abnormal marker, like borderline TSH.

  In essence, TSH acts like a thermostat: If T4/T3 are low, TSH goes up; if T4/T3 are high, TSH goes down. Your doctor uses these patterns, plus antibody tests if needed, to pinpoint the problem.
- Thyroid Test Results Explained: TSH, T3, and T4 Levels
  28 Feb 2025 — Understanding thyroid test results can seem hard, but it's easier when you break it down. By looking at TSH, T3, and T4.
- Normal Thyroid Hormone Levels - UCLA Health
  A high TSH level indicates that the thyroid gland is not making enough thyroid hormone (primary hypothyroidism).

Thyroid Levels in Different Disease Conditions

Disease	*T3*	*T4*	*TSH*	*FT3*	*FT4*	*T-Uptake*	*Tg*	*Anti-TPO*	*TRH*	*TBG*
Primary Hypothyroidism	↓	↓	↑	↓	↓	↓			R	
Hyperthyroidism	↑	↑	↓	↑	↑	↑	↑			
Pituitary insuffiency, tertiary hypothroidism		↓	↓		↓	↓			R*	
T3, thyrotoxicosis				↑	↓				R	
Subacute thyroiditis		↑	↓		↑	↑[a], ↓[b]	↑			
Nontoxic nodular goiter					↑		↑			
Graves disease				↑	↑			↑		
Hashimoto thyroiditis				↑		↑[d], ↓[e]		↑		
Lymphadenoid goiter								↑		
Iatrogenic hyperthyroidoidism					↑					
Myxedema			↑		↓					
Estrogen therapy, oral contraceptives, pregnancy		↑	↓[c]			↓				↑
Androgen therapy, steroid, hypoproteinemia (nephrosis, cirrhosis)		↓				↑				
Hypothyroidism treated with thyroxine					↓					
Hypothyroidism treated with hypoproteinemia thyroidism					↑					
Anti-thyroid drug for thyrotoxicosis		↓, N	↓			↓				
Benign adenoma							↑			
Untreated and metastatic carcinoma of thyroid							↑			
Acute psychiatric illness, acute medical illness, hepatic disease, malnutrition, addisons disease, acromegaly					↓					

a–recovery stage, b- active stage, c- 1st trimester, d- early, e-late, R- respose, R*- delayed response, ↓-decrease, ↑ increase

TROUBLESHOOTING

IMMUNOFLUORESCENCE TROUBLESHOOTING

Identify the problem with your immunofluorescence staining from the options below:

Weak or No Staining
High Background
Non-specific Staining

WEAK OR NO STAINING

Incorrect light source/filter set:

- Ensure your microscope is equipped with the correct light source and filter set for the fluorophore you have chosen.

Gain/exposure is too low:

- Turn up the gain and/or increase the exposure time to ensure you are capturing any signal present.

Fluorescent tag bleached:

- Avoid over exposure of the slide to light sources for extended periods. Always store slides in the dark.

Cell/tissues are over fixed:

- Reduced the duration of fixation.
- Perform antigen retrieval to unmask the epitope.

Cells were not permeabilized:

- Methanol and acetone fixation will permeabilize cells.
- If using formaldehyde, permeabilize cells with 0.2% Triton X-100.

Tissue/cells dried out:

- Samples must be kept covered in liquid throughout the staining process.

Not enough primary antibody:

- Use a higher concentration of antibody.
- Incubate longer.

The primary and secondary antibodies are incompatible:

- The secondary antibody should be raised against the host of the primary antibody. For example, if the primary antibody is a Mouse Anti-HSP70, use an Anti-Mouse secondary antibody (ie. Goat Anti-Mouse).
- Isotypes should also be compatible.

Suitability of the primary antibody:

- Confirm that the antibody has been validated in IHC, and specifically what type- formalin fixed, paraffin-embedded, fresh frozen, etc.
- Test the antibody in a western blot to make sure it hasn't been damaged.

Slide storage issues:

- Samples should be imaged shortly after processing as the signal decreases over time. Store slides at 4^{o}C in the dark if needed.

Antibody Storage issues:

- Freeze/thaw cycles are detrimental and can cause degradation. It is best to create aliquots of smaller amounts as soon as the product arrives at your location.
- Antibody was not stored as recommended. Unfortunately this might require a new vial to be used instead.
- If the secondary was not stored in the dark (when using immunofluorescence), a new vial will need to be used instead.

The protein is not present in the tissues being tested:

- Run a positive control.
- If the protein is present, but not abundantly, use an amplification step to maximize the signal.

Incubation time is too short:

- Increase the duration of incubation of the primary antibody with the sample.

HIGH BACKGROUND

Autofluorescence:

- Check to see if there is any fluorescence in an unstained section of the processed tissue. If there is, then this is autofluorescence in the tissue.
- Avoid glutaraldehyde fixative or wash with 0.1% sodium borohydride in PBS to remove free aldehyde groups.
- May be due to endogenous molecules (FAD, FMN, NADH, lipofuscin), and will require pre-photobleaching, treatment with sudan black, or cupric sulfate.

Tissue is too thick:

- Consider using thinner tissue sections.

Antibody Concentration is too high:

- Reduce the concentration of the primary and/or secondary antibody used.

Secondary is binding non-specifically:

- Run a secondary control without the primary. If there is staining, then change the secondary.

Blocking is insufficient:

- Increase the blocking incubation period and consider changing the blocking agent.

Amplification:

- Reduce amplification incubation time and dilute the secondary antibody.

Insufficient washing:

- Proper washing of the tissue between steps is critical. Ensure you are following the protocol guidelines for wash steps.

NON-SPECIFIC STAINING

Spectral overlap:

- If imaging more than one fluorescent probe, the fluorophores may have excitation and emission spectra that overlap. Adjust your light sources and filters to pick up only one signal at a time. If this is not possible, choose new fluorophores that do not have spectral overlap.

Antibody Concentrations too high:

- Try reducing the concentration, and the incubation period.

The primary is raised again the same species as the tissues stained (eg. Mouse on mouse):

- Try using a primary that is raised against a different species. Otherwise try to block the endogenous IgG with serum from the same species as the secondary. You can also try to incubate sections with 1% Triton to clean the tissues. Or Use TBS-Tween 20 as a washing buffer, rather than using PBS-Tween 20.

Aggregates:

- Spin down secondary antibodies in a microcentrifuge to move aggregates to the bottom of the tube. Take from the top.

BOUQUET

Two boys were arguing when the teacher entered the room.

The teacher says, "Why are you arguing?"

One boy answers, "We found a ten dollor bill and decided to give it to whoever tells the biggest lie."

"You should be ashamed of yourselves," said the teacher, "When I was your age I didn't even know what a lie was."

The boys gave the ten dollars to the teacher.

In Lighter Vein

Customer: Excuse me, but I saw your thumb in my soup when you were carrying it.
Waitress: Oh, that's okay. The soup isn't hot.

Teacher: "Nick, what is the past participle of the verb to ring?"
Nick: "What do you think it is, Sir?"
Teacher: "I don't think, I KNOW!"
Nick: "I don't think I know either, Sir!"

Wisdom Whispers

Don't raise your voice, improve your argument.

Anger is one letter short of danger.

Listen to what people don't say.

If it makes you HAPPY, no one else's **OPINION** should MATTER.

Brain Teasers

1. **A swollen thyroid gland is known as:**
   (a) Adenoma
   (b) Goitre
   (c) Nodule
   (d) Cyst

2. **Which condition is characterized by an overactive thyroid gland (hyperthyroidism) with symptoms like weight loss and protruding eyeballs (exophthalmos)?**
   (a) Myxedema
   (b) Cretinism
   (c) Grave's Disease
   (d) Hashimoto's Thyroiditis

3. **What condition results from severe iodine deficiency in infants/children, causing intellectual and developmental delays?**
   (a) Acromegaly
   (b) Myxoedema
   (c) Cretinism
   (d) Graves' disease

4. **The hormones primarily produced by the thyroid gland are:**
   (a) Insulin and Glucagon
   (b) T3 (Triiodothyronine) and T4 (Thyroxine)
   (c) ADH and Oxytocin
   (d) Cortisol and Aldosterone

ANSWER: 1-B, 2-C, 3-C, 4-B

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