Thyroid Disease and Cancer

Amy E. Baker, PA-C
Clinical Medicine

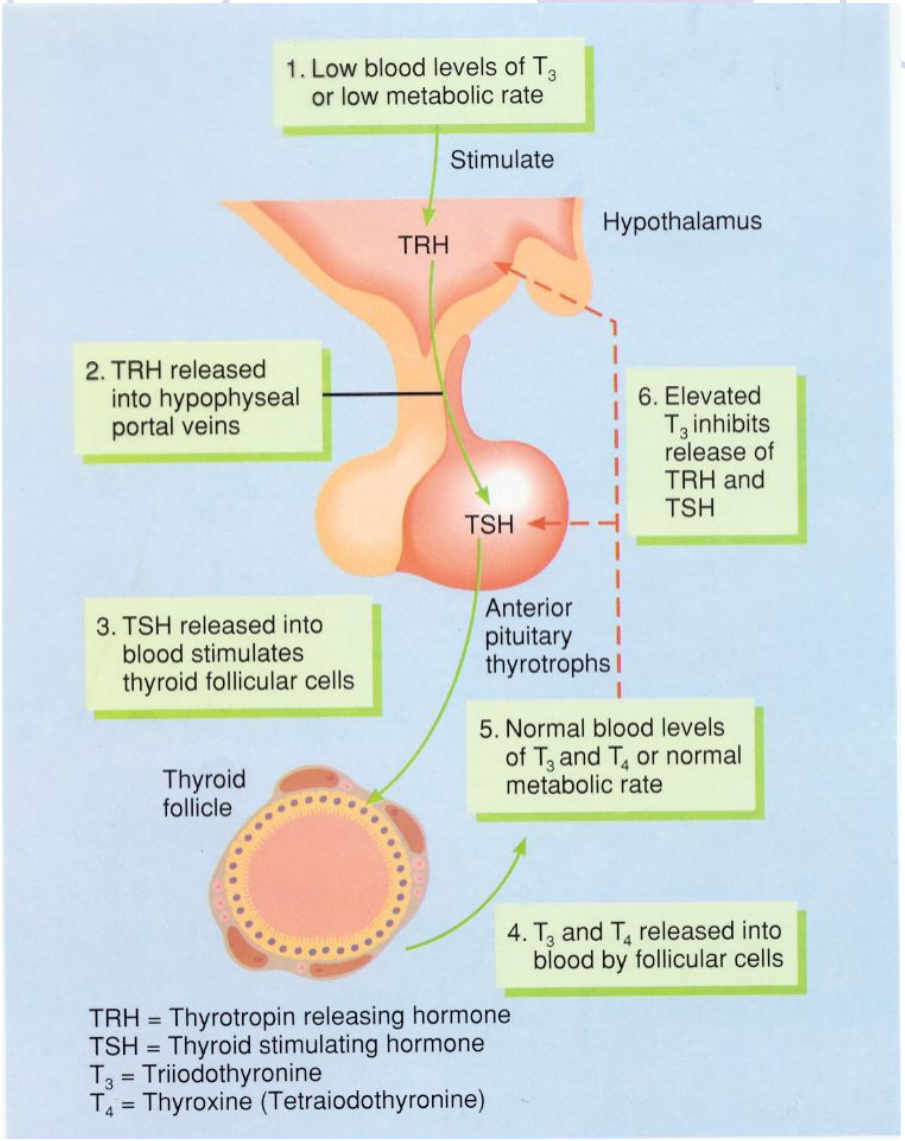
Review: Thyroid

- Gland comprised of two lobes spanning the trachea
- Produces thyroxine (T4) and triiodothyronine (T3)
- T4 is produced only in the thyroid
- 20-25% of T3 is secreted by the thyroid, the rest is formed by deiodination of T4

Role of Thyroid Hormones

- Stimulate neural and skeletal development during fetal life
- Stimulate oxygen consumption at rest and bone turnover
- Increase GI motility
- Increase heart rate and contractility
- Maintain basal body temperature
- Increase production of RBC's
- Control respiratory drive
- Increase metabolism

Thyroid Hormone Secretion



Thyroid Hormone Secretion

- Regulated by a feedback system involving the hypothalamus, pituitary gland, and thyroid gland
- TRH (thyrotropin-releasing hormone) is secreted by the hypothalamus
- This stimulates the synthesis and release of TSH from the anterior pituitary

Thyroid Hormone Secretion

- TSH stimulates the thyroid gland to produce T3 and T4
- T3 and T4 directly inhibit the pituitary TSH secretion
- Negative feedback will increase free thyroid hormones that cause a decrease in TSH secretion and vice versa
- Becomes very useful in evaluating signs and symptoms of thyroid disease

Hypothyroidism aka Myxedema

- Deficiency of thyroid hormone secretion causing a generalized slowing of metabolism
- Primary disease of the thyroid, secondary disease of lack of pituitary TSH, or tertiary disease resulting in failure of hypothalamus to secrete TRH

Hypothyroidism

- Most common cause- Hashimoto's Thyroiditis (aka Chronic Lymphocytic Thyroiditis)
- Also caused by iodine deficiency, thyroid ablation, radiation, medications, adenomas, pituitary destruction, sarcoidosis
- Amiodarone (due to high concentration of iodine in the drug)
- Hepatitis C patients (due to administration of interferon during treatment)

Hypothyroidism: Signs and Symptoms

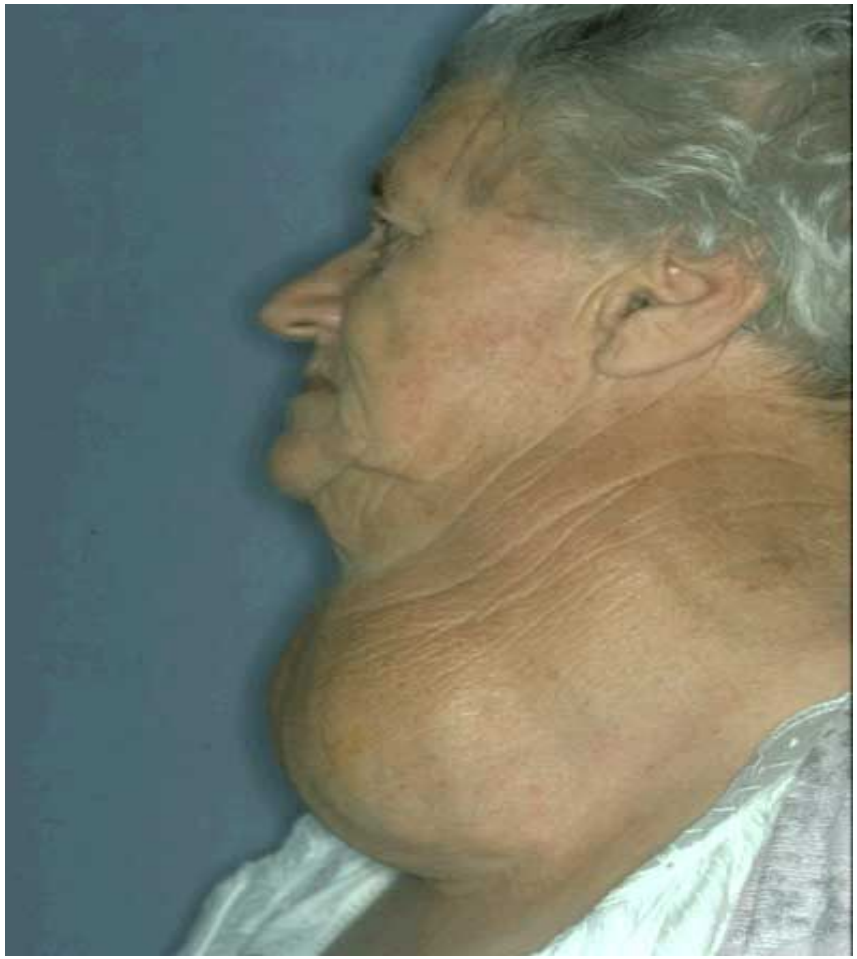
- Early S/S
  - Lethargy
  - Weakness
  - Cold intolerance
  - Constipation
  - Dry Skin
  - Menorrhagia
  - Depression
  - Mild weight gain
- Late S/S
  - Slowed speech
  - Lack of sweating
  - Peripheral edema
  - Hoarseness
  - Decreased sense of taste and smell
  - Increased weight gain

Hypothyroidism: Physical Exam Findings

- Early PE
  - Thin brittle nails
  - Thinning of hair
  - Pallor
  - Delayed deep tendon reflexes
  - Bradycardia
- Late PE
  - Goiter
  - Puffiness of face and eyelids
  - Carotenemic skin color
  - Hard pitting edema
  - Pleural, peritoneal, and pericardial effusions

Goiter

- Diffuse enlargement of the thyroid
- Associated with hypothyroidism caused by Hashimoto's, iodine deficiency, genetic thyroid enzyme defects, or drugs
- Hypothyroid phase that occurs in subacute viral thyroiditis



Hashimoto's Thyroiditis

- Presents with enlarged tender thyroid gland
- Positive thyroid antibodies
- Increased TSH
- Can resolve on its own, but mostly treated with synthetic thyroxine

Hypothyroidism: Differential Diagnosis

- Any other condition causing unexplained menstrual abnormalities, myalgias, constipation, weight changes, hyperlipidemia, or anemia
- Myxedema added into DDX of unexplained CHF without relief from traditional medical therapy
- Unexplained ascites
- Depression and psychosis
- Pituitary adenomas

Primary Hypothyroidism: Labs

- **Increased TSH** (normal 0.4-5.5)
- Overt: TSH increased, free T4 low: treat
- Subclinical: TSH increased: free T4 normal: subclinical, treat if symptomatic or TSH over 10, controversial
- Antibody titers of thyroperoxidase and thyroglobulin increased in Hashimoto's
- May also see increased cholesterol
- Nonspecific findings such as increased LFT's, anemia, hyponatremia, hypoglycemia, increased creatine kinase

Hypothyroidism: Treatment

- **Treatment of choice is levothyroxine**
  - Dosing is typically calculated at 1.6mcg/kg/day
  - Starting doses vary depending on age, pregnancy, and other comorbidities, usually start with 50-100 mcg
  - Start low, go slow with elderly (25 mcg)
- Early treatment has a very good outcome
  - Overt: TSH increased, free T4 low: treat
  - Subclinical: TSH increased: free T4 normal: subclinical, treat if symptomatic or TSH over 10, controversial
- Patients taking same daily dose demonstrate a significant increase in serum T4 levels within 1-2 weeks and near peak in 3-4 weeks

Hypothyroidism: Treatment

- Monitor labs after 1 month, then 3 months, then every 6 months to evaluate efficacy of maintenance dose and need for dose adjustment
- Relapse can occur if treatment is interrupted
- Maintenance dose varies between 75-250mcg

Hypothyroidism: Complications

- Mostly cardiac in nature secondary to overzealous thyroid replacement
- Increased susceptibility to infection
- Psychosis
- Miscarriage in pregnancy
- TSH secreting tumors
- Myxedema Coma

Myxedema Coma

- Associated with severe hypothyroidism
- Induced by underlying infection (cardiac, pulmonary, or CNS), cold exposure, or drug use
- Caused by interstitial accumulation of mucopolysaccharides and inappropriate secretion of ADH leading to lymphedema
- Hyponatremia results from impaired renal tubular sodium reabsorption

Myxedema Coma

- Sx- hypothermia, hypoventilation, hyponatremia, hypoxia, hypercapnia, hypotension, convulsions, and CNS signs
- Mostly seen in elderly women
- High mortality rate, medical emergency

Myxedema Coma: Treatment

- Levothyroxine sodium 400 mcg IV as loading dose, then 100 mcg IV daily
- Treat hypothermia with warming blankets
- Treat hypercapnia with intubation and ventilation
- Treat any underlying infection
- Assess for and treat patients with adrenal insufficiency with hydrocortisone

Hypothyroidism and Pregnancy

- Critical to treat mother early on as fetus depends on T4 from mother for CNS development
- Maternal hypothyroidism in 1st Trimester has shown to cause some developmental delays
- Follow mother with TSH levels every 4-6 weeks
- Tight control with narrower window in pregnancy

Hypothyroidism and Pregnancy

- Dosing of levothyroxine is variable
- Women who are already hypothyroid before pregnancy typically need a dose increase of 30% once pregnancy is confirmed
- Typically return to their original dose post-partum

Congenital Hypothyroidism: Cretinism

- Common cause of preventable mental retardation
- Affects 1:5000 infants
- Evident in 1st several months
- Can be due to congenital lack of thyroid or abnormal biosynthesis
- TH is essential for normal brain development and growth
- Neonatal screenings have been implemented to detect early
- If treated properly, risk of mental retardation in nonexistent
- Treatment of choice: levothyroxine lifelong

Cretinism

Parents will report:

- Feeding problems
- Somnolence
- Jaundice
- Flaccidity
- Constipation
- Developmental delays

Child will present with:

- Broad flat nose
- Protruding tongue
- Protruding abdomen
- Development of goiter
- Umbilical hernia
- Delayed growth, short stature
- Developmental delays

Children with cretinism

Hyperthyroidism

Hyperthyroidism aka Thyrotoxicosis

- Involves an increase of thyroid hormone
- Increased rate of metabolism
- Most common cause is Grave's Disease
  - Autoimmune
  - Gland is usually enlarged
  - Mostly women (8:1 ratio to men)
  - Onset between 20-40 years of age
  - Familial tendency

Hyperthyroidism

- Commonly associated with DM, myasthenia gravis, and pernicious anemia
- Grave's patients are at an increased risk of developing Addison's disease, alopecia areata, celiac disease, DM I, myasthenia gravis, cardiomyopathy, and hypokalemic periodic paralysis

Hyperthyroidism Grave's disease

- Accompanied by infiltrative ophthalmopathy (exophthalmus) and pretibial myxedema
- Grave's demonstrates positive antibodies on thyroid panel

Other Causes of Hyperthyroidism

- **Most common cause-Grave's Disease**
- Toxic adenomas
- Subacute thyroiditis
- Thyrotoxicosis factitia
- Medications, especially amiodarone
- Also pituitary tumor, pregnancy, thyroid cancer

Hyperthyroidism: Signs and Symptoms

- Symptoms
  - Nervousness
  - Restlessness
  - Heat intolerance
  - Muscle cramps
  - Frequent bowel movements
  - Weight changes (mostly loss)
  - Palpitations
  - Angina
  - Menstrual irregularities
- Physical Exam Findings
  - Stare
  - Lid lag
  - Fine resting tremor
  - Moist warm skin
  - Hyperreflexia
  - Fine hair
  - A-fib
  - Ophthalmopathy

Hyperthyroidism: Differential Diagnosis

- Anxiety or mania
- Anemia, leukemia, polycythemia
- Pheochromocytoma
- Acromegaly
- True cardiac arrythmias
- Myasthenia gravis

Primary Hyperthyroidism: Labs

- **Decreased TSH, usually less than 0.1**
- Increased T3, T4, thyroid resin uptake, Free T4
- Increased RAI uptake in Grave's

Hyperthyroidism: Treatment

- Often treated by endocrinology upon initial diagnosis
- Varies according to age and severity
- Propanolol
  - Symptomatic relief of tremor, tachycardia, diaphoresis, and anxiety
  - Used until hyperthyroidism definitively treated
  - Also treatment of choice for thyroid storm

Hyperthyroidism: Treatment

- Thiourea Drugs
  - Methimazole or Propylthiouracil (PTU)
  - Used for young adults or patients with mild hyperthyroidism, small goiters, or those who do not want isotope therapy
  - Can be administered long term
  - Lower occurrence of post-treatment hypothyroid than with surgery or RAI
  - PTU is drug of choice during lactation and pregnancy

Hyperthyroidism: Treatment

- Iodinated contrast agents
  - Effective for temporary relief
  - Iopanoic acid or ipodate sodium
  - Effective with severely symptomatic patients

Hyperthyroidism: Treatment

- Radioactive Iodine
  - Excellent method of destroying overactive thyroid tissue by damaging the cells that concentrate it
  - No increased risk of malignancy following treatment
  - Contraindicated during pregnancy
  - Usually given with propanolol
  - Higher failure rate if given to Grave's patients also on methimazole or PTU

Hyperthyroidism: Treatment

- Radioactive Iodine complications
  - Exophthalmus/Grave's ophthalmopathy can worsen afterwards in 15% of patients (incidence is higher in smokers)
  - Lifelong follow-up with labs
  - Higher incidence of rebound hypothyroidism

Hyperthyroidism: Treatment

- Thyroid Surgery
  - Surgical removal of all or part of gland
  - Good option for women who are pregnant or have small children
  - Risk of hypoparathyroidism and laryngeal nerve palsy

Hyperthyroidism: Complications

- Grave's Ophthalmopathy
- Subacute Thyroiditis
- Cardiac Complications
  - A-fib
  - Sinus tach
  - Heart failure

Hyperthyroidism: Complications

- Thyroid Crisis or Storm
  - Occurs with stressful illness, thyroid surgery, or RAI administration
  - S/S: marked delerium, severe tachycardia, n/v/d, dehydration, very high fever
  - Very high mortality rate
  - Propanolol is the drug of choice

Hyperthyroidism: Complications

- Pretibial myxedema
- Thyrotoxic hypokalemia
  - Periodic paralysis
  - Suspect in Asian/Native American men with sudden symmetric flaccid paralysis, hypokalemia, and hypophosphatemia

Hyperthyroidism and Pregnancy

- Very rare
- Diagnosis may be delayed because many s/s are similar to what is considered “normal pregnancy”
- Increased risk of thyroid storm
- Fetal retardation of growth
- Premature delivery

Subclinical Hyperthyroidism

- Asymptomatic individuals with decreased TSH and normal T3 and Free T4
- Usually does not progress to overt thyrotoxicosis
- Can be at increased risk of bone loss
- Chance of developing complications is low

Prognosis of Hyperthyroidism

- Rarely subsides spontaneously
- Variety of options for treatment
- Complications can persist after treatment
- Recurrence even after treatment is common
- Post-treatment hypothyroidism is common
- Women are at an increased risk of death from thyroid disease

Thyroid Nodules and Multinodular Goiter

General Information

- Diffuse or nodular palpable enlargement
- 4% of North American adults
- Incidence greater in iodine deficient areas
- Most patients are euthyroid, but still have an increased incidence of hyper/hypothyroidism
- Most nodules are benign (70%)

Diffuse Multinodular Goiter

- Usually benign
- Causes
  - Benign multinodular goiter
  - Iodine deficiency
  - Pregnancy
  - Grave's disease
  - Hashimoto's thyroiditis
  - Subacute thyroiditis
  - Infection

Solitary Thyroid Nodule

- Mostly benign adenoma
- Colloid nodule
- Cysts
- Sometimes primary thyroid malignancy or metastatic neoplasm

Solitary Thyroid Nodule

- Incidence of malignancy increases in patients with a history of head/neck radiation, family history of thyroid cancer, or history of other malignancies
- Increased risk of malignancy in nodules that are large, adherent to the trachea or strap muscles, or those associated with lymphadenopathy

Solitary Thyroid Nodule

- Nodules or goiter can be large enough to be cosmetically embarrassing, cause discomfort, hoarseness, or dysphagia
- Retrosternal large multinodular goiters can cause dyspnea or SVC syndrome

Evaluation and Treatment of Nodules

- Ultrasound first- can also aid with biopsy or aspiration
- Biopsy indicated if nodules are growing as being monitored, appear malignant, or if over 1 cm
- Follow-up ultrasound in 3 months to 1 year if findings are non-invasive for stability

Evaluation and Treatment of Nodules

- Radioactive Iodine (RAI) uptake scan-radioactive iodine (I^{131} or I^{123} injection to evaluated hot (hyperfunctioning) vs. cold (hypofunctioning) has limited use
- Oncology referral and radiation if indicated
- Toxic Solitary Nodules treated with surgery or RAI
- Toxic Multinodular Goiter treated with propanolol, RAI more so than surgery, and methimazole

Thyroid Cancer

Thyroid Cancer

- Female:Male ratio 3:1
- 26,000 people in U.S. are diagnosed with thyroid cancer yearly and 1/250 people eventually receive this diagnosis
- About 13% of people at time of autopsy are found to have thyroid cancer

Types of Thyroid Cancer

- Papillary
- Follicular
- Medullary
- Anaplastic

Thyroid Cancer: Papillary

- **Most common, least aggressive**
- 81% of all thyroid cancers
- Usually presents as a single thyroid nodule
- Caused by genetic mutations or translocations
- Radiation exposure can cause it to be more aggressive

Thyroid Cancer: Papillary

- Tumor spreads via lymphatics becoming multifocal in 60% of patients, and involving both lobes in 30%
- 80% have microscopic mets in cervical lymph nodes
- Even with palpable mets, mortality rate does not increase, but risk of local occurrence increases
- Chronic low grade papillary cancer can sometimes undergo late anaplastic transformation into aggressive cancer

Thyroid Cancer: Follicular

- Results from gene mutations or translocations
- 14% of all thyroid cancers, more aggressive than papillary
- Some secrete enough T4 to cause thyrotoxicosis if tumor load becomes significant

Thyroid Cancer: Follicular

- Mets- neck, bone, lung
- Most absorb iodine to make diagnostic imaging possible
- Poorly differentiated and oncocytic cell variants are associated with high risk of mets and recurrence

Thyroid Cancer: Medullary

- Caused by germline mutations
- 3% of all thyroid cancers (1/3 familial, 1/3 sporadic, 1/3 MEN Type 2)
- Genetic analysis needed for diagnosis
- Arises from parafollicular thyroid cells that can secrete calcitonin, prostaglandins, serotonin, ACTH, and other peptides
- Can cause symptoms and be used as tumor markers

Thyroid Cancer: Medullary

- Early mets usually present adjacent to muscle and trachea and mediastinal lymph nodes
- Late mets to bone, lung, adrenals, liver
- Does not concentrate iodine
- Symptoms are flushing and diarrhea

Thyroid Cancer: Anaplastic

- **Least common, most aggressive**
- Caused by gene mutations
- 2% of thyroid cancers
- Older patients present as a rapidly enlarging goiter or mass
- Mets early to surrounding nodes and distant sites
- Local pressure symptoms of dysphagia, hoarseness, vocal cord paralysis
- Does not concentrate iodine

Other Thyroid Malignancies

- 3% of all thyroid cancers
- Lymphomas
  - Older women
  - Rapidly forming enlarged painful mass arising out of multinodular goiter and affected by autoimmune thyroiditis
  - Mostly B-cell or MALT
  - Metastatic cancer from bronchogenic, breast, or renal cancers, or malignant melanoma

Thyroid Cancer: Labs and Studies

- Labs usually normal with the exception of hormone secreting tumors
- RAI entire body scan- used after thyroidectomy for surveillance and to look for mets
- U/S-evaluate nodule or goiter/aid in guidance for biopsy
- CT/MRI-search for mets
- PET Scan-search for bone mets

Thyroid Cancer: Treatment

- Surgery (treatment of choice)
- Need for thyroid hormone replacement for life s/p surgery
- Monitor TSH
- Thyroid cancer is resistant to chemo
- RAI therapy
- Radiation

Thyroid Cancer: Prognosis

- Papillary
  - Very good especially in adults <45yo
  - Five year survival rate between 80-99%
  - Worse for older patients, mets, or lack of iodine reuptake
- Follicular
  - Mortality rate 3-4 times higher than in papillary
  - <1cm nodule with only partial thyroidectomy has higher mortality
  - Risk of recurrence is 2-fold in men as compared to women, as well as in multifocal v. unifocal

Thyroid Cancer: Prognosis

- Medullary
  - 10 year survival rate
    - 90% confined to thyroid
    - 70% in cervical nodes
    - 20% in distant mets
    - Women <40 yo have a better prognosis in general
- Anaplastic
  - 1 year survival rate of 10% and 5 year survival rate of 5% of patients
  - Fully localized tumors have better prognosis

Questions?