Hypothyroidism: There is a clear increase in incidence of hypothyroidism with aging, with the incidence of overt hypothyroidism being 1-6% and that of subclinical hypothyroidism being >5-15%. The etiology is most often autoimmune thyroiditis (Hashimoto’s), but may less often be due to prior neck surgery, treatment with radioactive iodine or radiation therapy, or medications (amiodarone, lithium, interferon-α, interleukin-2). Overt disease presents with the same symptoms as in younger patients (weight gain, dry skin, cold intolerance, constipation, depression), but these symptoms are often attributed to aging, medications, or other illnesses. Overt hypothyroidism should always be treated, as this contributes to diminished quality of life, poor mental status, hyperlipidemia, and cardiac compromise.

Subclinical hypothyroidism refers to mild hypothyroidism with elevated TSH and T4 still in the low yet normal range. Of note, detailed review of the NHANES III data reveals a shift towards higher TSH levels in older patients even when those with positive TPO antibodies are excluded, with the 97.5 percentile for patients >80 being 7.5 mIU/L, making one question if older individuals should have a higher normal range. Symptoms are often mild and go unnoticed, but a past study suggests that 25-50% of patients feel improved after treatment. Furthermore, many patients will progress to overt disease, especially those who are older, have higher TSH, or positive antibodies. Data is inconsistent but largely suggests increased cardiac events in patients with TSH >10. Consensus recommendations tell us to treat patients with subclinical hypothyroidism if the TSH >10, but many treat if the TSH is persistently elevated with possible attributable symptoms.

Standard treatment for hypothyroidism is levothyroxine. In the elderly or those with underlying CAD, this should be started at a low dose (i.e. 25 µg) and titrated every 6-8 weeks until the TSH is in the (age-adjusted) normal range.

Hyperthyroidism: The incidence of hyperthyroidism is not clearly increased in the elderly, but the etiology is more often due to multinodular goiter, with single toxic nodules, Grave’s disease, and other causes being less common. Symptoms of hyperthyroidism tend to be masked in the elderly (apathetic hyperthyroidism), with classical presentations in older adults including weight loss, atrial fibrillation, proximal myopathy, and diminished bone mineral density. Overt hyperthyroidism should always be treated, as this contributes to diminished quality of life, cardiac dysfunction, and bone loss.

Subclinical hyperthyroidism refers to mild disease with suppression of TSH but T4 remaining in the upper normal range. This must be distinguished from suppressed TSH associated with non-thyroidal illness. The latter entity is defined by the clinical scenario and rise in TSH as the patient recovers from their illness. A study by Schouten and colleagues revealed that progression to frank hyperthyroidism was more common.
over 6 years in patients with an autonomous thyroid nodule than in those with Graves’ Disease; this was not confirmed in a larger study by Das and colleagues, who noted that progression was more common when the baseline TSH is <0.10 independent of age or etiology. Complications of subclinical hyperthyroidism are similar to those with overt disease, especially if the TSH is <0.10, so most would recommend treatment if the TSH remains suppressed to this level, if the patient is ≥65 years old, symptomatic (anxious, losing weight) or if there is osteoporosis or atrial fibrillation. If uncertain if symptoms are attributable, a trial course of anti-thyroid drugs can be tried.

Treatment can be accomplished with anti-thyroid drugs (methimazole preferred), radioactive iodine, or surgery. Many prefer treatment of multinodular goiters with RAI as there is a low incidence of subsequent hypothyroidism, there may be some associated gland shrinkage, and treatment is permanent.

**Thyroid Nodules and Goiter:** The prevalence of thyroid nodules increases with age, with up to 6% of older adults having palpable nodules on examination and >50% having thyroid nodules on ultrasound (many of these nodules are part of multinodular glands). Most of these nodules remain stable in size over time. The risk of autonomy may increase over time, with eventual development of hyperthyroidism. Further, the risk of thyroid cancer is increased in older patients, especially in men.

Most endocrinologists would first obtain TFT’s, and if these are consistent with hyperthyroidism, a radioactive iodine (RAI, I\textsuperscript{123}) scan should be obtained to evaluate for nodule functionality; hot nodules are virtually never malignant. In contrast, only ~5-15% of cold nodules are malignant. If TFT’s do not reveal hyperthyroidism, referral for fine needle aspiration biopsy to rule out malignancy is the next step. Ultrasound should be done to evaluate the number of nodules, nodule characteristics, and nodule size, and to guide fine needle aspiration. All “cold” nodules which are >1-2 cm, depending on ultrasound level of suspicion, should be biopsied to exclude cancer. TSH should be followed every 6-12 months to ensure that hyperthyroidism does not develop.

Benign, nontoxic nodules can be followed clinically. Thyroid hormone suppression therapy is not recommended as it has not been shown to decrease goiter size, and it increases the risk of hyperthyroidism. If compressive symptoms are present, surgery is the treatment of choice if the patient is a good surgical candidate. Otherwise, treatment with radioactive iodine will shrink the goiter an average of 40%.

**Late Onset Hypogonadism (LOH):** Late onset hypogonadism refers to the “clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels”. Many of the physiologic changes that occur with aging resemble those seen with hypogonadism, including loss of bone and muscle mass, increased fat mass, and impairment in physical and sexual function. Screening for low testosterone should only be done in men who have symptoms suggestive of testosterone deficiency, including diminished libido, erectile dysfunction, decreased morning erections, hot flashes, gynecomastia, or diminished bone mineral density or low trauma fracture, or in men with conditions associated with a high
prevalence of testosterone deficiency (sellar mass, treatment with steroids or long acting opioids). Benefits of testosterone replacement include improved libido, mood and motivation; improved muscle mass and bone mineral density; and decreased fat mass. These body composition changes which occur with testosterone replacement therapy are accompanied by improvement in insulin sensitivity (TH Jones. Journal of Diabetes. 2010; 2:146-56). Erectile dysfunction may or may not improve in men over age 50, and strength and function do not clearly improve. The Testosterone Trials also revealed increased hemoglobin in patients with anemia, and an increase in uncalcified coronary plaque although no increase in coronary events.

Testosterone replacement should be considered in men who have unequivocally low measured testosterone levels x2 as well as manifestations of testosterone deficiency. The treatment preparation chosen depends upon patient preference, but testosterone gel is often preferred, which provides constant testosterone levels without significant skin irritation. Testosterone levels are recommended to guide therapy. 2010 Endocrine Society Guidelines recommend aiming for a testosterone level in the mid-normal range for elderly men (300-450 ng/dl) rather than the mid-normal range for young men (400-700 ng/dl) as suggested in the 2018 guidelines. Additionally, one must monitor for adverse effects of treatment, including polycythemia, increased PSA (refer to urology if increase of >1.4 in first year, or to level of >4 in average man, >3 in high risk man), worsening hypertension or edema, symptoms of prostatism, and increased symptoms suggestive of obstructive sleep apnea. Some trials suggest increased risk of CV events in older men treated with testosterone replacement (Barsaria 2010, Vigen 2013), although this is not consistently found (Muraleedharan, 2014).

Hyperparathyroidism: Hyperparathyroidism (HPT) affects 1-2 per thousand individuals, occurring most often in post-menopausal women. The most common presentation today is asymptomatic hypercalcemia with an elevated or nonsuppressed PTH. Current consensus guidelines encourage repeat of the calcium level to ensure that it is elevated, as well as measurement of 25-hydroxy vitamin D, as hypovitaminosis D can cause secondary hyperparathyroidism (high PTH, but calcium is not elevated in the absence of primary HPT). Once vitamin D is replete, assessment of 24 hour urine calcium is also recommended, to exclude familial hypocalciuric hypocalcemia (FHH, expect urinary calcium clearance to be <0.01, whereas it is >0.02 in primary HPT). Surgery is recommended for patients who are symptomatic (renal stones, osteoporosis or fragility fracture), are <50 years old, have a calcium >1 mg/dl over the upper limit of normal, or who have an estimated GFR of <60 ml/min or hypercalciuria >400 mg/d. It is currently recommended that renal ultrasound to look for stones and spine imaging to look for unsuspected fracture be obtained. For patients who have surgical indications but refuse or are poor candidates, drug therapy can be considered. Cinacalcet is a an agonist of the calcium sensing receptor, making it more sensitive to extracellular calcium, and thereby decreasing the serum calcium level; it does not protect the bones. In contrast, alendronate enhances bone mineral density although it has minimal impact on the calcium. Estrogen and raloxifene also enhance bone mineral density, but not to the same extent seen with alendronate. Follow up for patients who do not warrant treatment
include yearly serum calcium, creatinine, and eGFR as well as evaluation of BMD every one to two years.
Hypo- and Hyperthyroidism:

1. Garber, JR, Cobin, RJ, Gharib, H, Hennessey, JV, Klein, I, Mechanick JI, Ressah-Pollack, R, Singer, PA, Woeber, KA. Clinical Practice Guidelines for Hypothyroidism in Adults. Endocrine Practice. 18(6):e1-e45, 2012. Nice review of subject, recommending case finding (in pts with other autoimmune diseases, FH of autoimmune thyroid disease, history of prior thyroid surgery or radiation, abnormal thyroid exam, or rx with amiodarone or lithium), screening for women planning pregnancy, and possible screening for all patients >60 yo, especially women. Rx is recommended for TSH > 10, and on an individualized basis with TSH 5-10, with treatment TSH goal modified based upon patient’s age (Guidelines for the Treatment of Hypothyroidism, Jonkaas et al, Thyroid. 2014. 24(12):1670-1750 is from the American Thyroid Association, and they recommend a TSH level of 4-6 in older adults who are treated with thyroid hormone replacement therapy).

2. Biondi, B, Cappola, AR, and Cooper, DS. Subclinical hypothyroidism: A Review. JAMA 2019. 322:153-60. Quick read indicating that subclinical hypothyroidism is most often due to Hashimoto’s thyroiditis, but reminds us that TSH levels do rise with age, so the upper limit of the normal range is likely 7.5, and subclinical thyroid disease is not as common as previously thought, w/ greater risk of progression in those with positive antibodies. Note treatment is indicated in younger individuals with symptoms and may want to treat older patients w/ TSH>10, w/ careful dose titration to avoid thyrotoxicosis.

3. Surks, MI, Ortiz, E, Daniels, GH, Sawin, CT, Col, NF, et al. Subclinical Thyroid Disease: Scientific Review and Guidelines for Diagnosis and Management. JAMA 2004; 291:228-238. Comprehensive summary of literature. Do not recommend routine screening for thyroid disease but do rec rx of hypothyroidism if TSH>10 (don’t rec checking Abs), or rx of hyperthyroidism if TSH<0.1 in the setting of Graves or MNG, as well as in presence of a. fib or low BMD.

4. Cooper DS and Biondi, B. Subclinical Thyroid Disease. The Lancet. 2012; 79:1142-54. Up-to-date summary of literature; not an easy read. Includes review of data showing both mildly low TSH being normal in many older patients, especially blacks, and slightly elevated TSH being normal in older adults as well. Risks of subclinical thyroid disease and recs for treatment are reviewed.

5. Ross et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyerthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 26:1343-1421, 2016. Comprehensive review of the topic noting that although Graves’ disease is the most common cause of hyperthyroidism, toxic nodular goiter (MNG) is more common as patients age. Recommend determination of etiology of thyrotoxicosis using thyroid uptake and scan, measurement of TRAb, or thyroidal blood flow on ultrasound; treatment with beta blockers in all patients with symptomatic thyrotoxicosis or tachycardia; and treatment with anti-thyroid drugs, radioactive iodine (RAI), or surgery. Note that subclinical hyperthyroidism progresses more often to overt disease when the TSH is <0.1, and CV mortality, CHF, atrial fibrillation and decreased bone density are increased in this group as
well. Treatment of subclinical hyperthyroidism is recommended if the TSH is <0.1, and should be considered w TSH 0.1-0.4 in patients >65 yo, or who have CV disease, osteoporosis, or symptoms of thyrotoxicosis. Similar recs in recent review by Tsai and Leung. Endocrine Practice, 2021.

Thyroid Nodules:

6- Burman, KD and L Wartofsky. Thyroid Nodules. N Engl J Med 2015; 373:2347-2356. Nice review, focusing mostly on approach/ eval of the nodule. Recommend baseline hx, PE, TSH, and thyroid ultrasound. If TSH is low, obtain radioiodine scan, as hot/fxnal nodule is benign. If TSH normal or high, bx (possibly under USG guidance) to determine need for surg. Molecular aspects that are discussed are more specialized than needed at the 1o care level.

7- Haugen, BR et al. 2015 Revised American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015, 26:1-140. Complete review of literature, with graded guidelines based upon the evidence. Glands with palpable thyroid nodules should be evaluated with USG for additional lesions, and all nontoxic nodules that are high or intermediate risk and >1 cm warrant fine needle aspiration bx; lesions that are lower risk may be considered for biopsy if they are >1.5 or 2 cm. Also would bx suspicious LN’s associated with subcentimeter lesions.

Thyroid Disease in the Elderly:


Late Onset Hypogonadism (Testosterone Deficiency Syndrome):


10- Bhasin, S, Brito, JP, Cunningham, GR, Hayes, FJ, Hodis HN et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018. 103:1715-44. Guideline recommendations with literature support on how to diagnose androgen deficiency (symptoms with low fasting AM testosterone x2); how to treat androgen deficiency (injections vs patches vs gel, depending on patient preference, aiming for age appropriate normal range); and how to monitor testosterone therapy (follow up of testosterone levels, PSA, DRE, hematocrit, progression of LUTS, BMD). Includes wonderful tables.

11-Handelsman, DL. Testosterone and Male Aging. Faltering Hope for Rejuvenation. JAMA. 2017 317(7): 699-701. Editorial that summarizes the results of the Testosterone Trials, a series of studies in 790 men who were >65 years of age with symptomatic hypogonadism. They found that testosterone gel titrated to a testosterone level in the mid-normal range for young healthy men: ↑’d libido and sexual function, but improved erectile function to a lesser degree than
phosphodiesterase inhibitors; did not improve physical function or vitality; did not improve cognition; ↑’d non-calcified coronary plaque with associated coronary luminal narrowing; ↑’d BMD and bone strength; and ↑’d hgb in men with anemia. Overall, they warn that the risks of testosterone rx may outweigh the benefits and warn us RE overuse.

Hyperparathyroidism:

12-Bilezikian, JP, Brandi ML, Eastell R et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014; 99:3561-9. Concisely reviews issues in diagnosis of primary hyperparathyroidism (PHPT), and guidelines for surgical and medical management and monitoring. All patients with symptoms require surgery, and asymptomatic patients with osteoporosis (low BMD or vertebral fractures), age <50, calcium >1 mg/dl over the upper limit of normal, eGFR<60 ml/min, and/or hypercalciuria, renal stones or nephrocalcinosis on imaging should be referred for surgery as well. Patients who would benefit from surgery but are poor surgical candidates or unwilling can be treated with alendronate to maintain bones and/or cinacalcet to help decrease the calcium. Patients who do not meet surgical criteria can have a yearly serum calcium, creatinine, EGFR, and follow up of BMD Q1-2 years.