BLI Class 4

Thyroid

Hypothalamus – anterior pituitary (AP) – thyroid gland (endocrine axis)

TRH (thyrotropin releasing hormone) – stimulates AP to release **TSH = thyrotropin** (thyroid stimulating hormone) – TSH will stimulate thyroid gland to produce and release – T3 (triiodothyronine) and T4 (tetraiodothyronine, thyroxine)

To make T3 and T 4 need to have iodine in the diet and tyrosine (amino acid). Tyrosine + 3 or 4 iodine's will create T3 or T4.

1. What protein holds T3 and T4 in thyroid gland until it is released in blood? – Thyroglobulin (TG)
2. What is the protein that carries most of T3 and T4 in blood – thyroxin binding globulin (TBG)

Proteins that can bind and carry T3 and T4 – TBG, albumin, thyroxin binding parvalbumin.

Most of the T3 and T4 is bound to proteins in blood.

How much of free T3 and T4 is in blood – 0.3% free T3 and **0.03% of free T4**

The most of the metabolic activity/most active is T3.

What is the main thyroid circulating hormone? – T4

What is the T3 reservoir in the body? T4

Where is TBG and albumin made in the body? Liver

TRH – TSH – T3 and T4. What mechanism regulates this endocrine axis? Negative feedback system.

If T3 and T4 levels in blood go down that will stimulate release of **TSH**, when T3 and T4 increase there will suppression of **TSH** release

Hyperthyroidism or hypothyroidism, normal – euthyroid

Thyroid panel (Thyroid functional tests – TFTs)

1. Total T4, **Free T4** (not bound to the protein and is free to enter the cells) (FRT4)
2. Free T4 index – calculated value of available T4
3. **Total T3**, Free T3 (FRT3)
4. **TSH**
5. TRH
    a. Low in central (Tertiary) hypothyroidism – idiopathic or hypothalamic disease like cancer, mini stroke
6. TRH stimulation test
7. TSH stimulation test
8. Thyroglobulin (TG)
9. Antibody tests
10. TBG (Thyroxine binding globulin)
    a. Increased in pregnancy, estrogen replacement therapy, infectious hepatitis, estrogen producing tumors
    b. Decreased in protein losing enteropathy, protein losing nephropathy, malabsorption, testosterone producing tumors, ovarian failure, major stress
11. T3RU – T3 resin uptake – measures binding capacity of TBG
    a. Taken in conjunction with the total T4, the T3RU offers insight into the cause of any given deviation of T4 concentration.
12. RAIU – radioactive iodine uptake
    a. The thyroid's avidity for iodide and the ease of measuring it externally give the clinician another indirect measurement of T4 production, fractional thyroid accumulation of an oral dose of (131)I can be measured.

Primary, secondary, or tertiary hyper or hypothyroidism

Patient present to your clinic with complains of unexplained weight gain, fatigue, cold intolerance, constipation, dry skin. Order thyroid blood panel.

Scenario 1

1. **TSH – high**
2. **Free T4 – low**
3. T3 – low
4. T4 is low

Hypothyroidism. – thyroid gland is not responding to high TSH. = Primary hypothyroidism. The most common reason for primary hypothyroidism is Hashimoto's disease. Next best test to confirm that is to look for autoantibodies against TSH receptors. These antibodies that are detected in patient are against what antigen in the body? TSH receptor on thyroid cell and block these receptors from TSH and themselves do not stimulate these receptors = hypothyroidism

In a patient with elevated TSH and low FT4 would indicate which one of these conditions – primary hypothyroidism

Patient present to your clinic with complains of unexplained weight gain, fatigue, cold intolerance, constipation, dry skin. Order thyroid blood panel.

Scenario 2, patient brings blood work

1. **TSH -low**
2. **Free T4 – low**
3. T3 – low
4. T4 – low

Hypothyroidism. Secondary hypothyroidism = pituitary dysfunction = CT scan of the head – pituitary adenoma. Pituitary is not making TSH and thyroid is correctly responding by not making T3 and T4 In this case thyroid gland would be normal

Scenario 2A

Patient from scenario 2 there was no pituitary adenoma. What else can be ordered. – TRH

1. **Low TRH**
2. **Low TSH**
3. **Low FT4**

4. Low T3
5. Low T4

Tertiary hypothyroidism – hypothalamus problem – mini stroke

Female patient presents to your office – unexplained weight loss, palpitation, fatigue, muscle weakness, increased appetite, **anxiety ,** tremors, irritability, heat intolerance, diarrhea

Scenario 3, this patient brings back blood work

1. TSH low
2. FT4 high
3. T3 high
4. T4 high

Hyperthyroidism. Primary hyperthyroidism (Low TSH and high T3, T4) Most common reason – Graves disease. Next test – antibody test – these TSH receptor stimulating antibodies

Scenario 4, same patient different blood work:

1. TSH high
2. T4 high
3. T3 high
4. FT4 high

Secondary hyperthyroidism – rule out active TSH producing pituitary adenoma, normal thyroid gland responds by making more T3 and T4

T3 is useful test for hyperthyroidism, but not that useful in detection of hypothyroidism

Total T4 is not as good as Free T4. Abnormalities in protein levels can have significant effect on total T4 levels

1. Pregnancy and hormone replacement therapy can increase TBG and may cause total T4 falsely elevated

2. Patient with massive proteinuria – decreased TBG, total T4 is less, if you look at free T4 the value is normal

Interfering factors

1. Aspirin, propranolol – increases free T4

Ultrasensitive (third-generation) thyrotropin (TSH) assays remain the best screening test for thyroid disorders.

Subnormal or suppressed thyrotropin levels are seen in most patients with thyrotoxicosis (Highly elevated T3, T4 levels)

Free T4 levels or the free T4 index is usually elevated, as is the free T3 level or free T3 index. Subclinical hyperthyroidism, defined as a free T4 or free T3 level within the reference range with suppressed thyrotropin, also can be seen.

On occasion, only the free T3 level is elevated, a syndrome known as T3 toxicosis. This may be associated with toxic nodular goiter or the ingestion of T3. Elevated T3 levels are often seen in early phase Graves' disease as well.

Assays for thyrotropin-receptor antibodies (particularly TSIs) almost always are positive in Graves disease. Detection of TSIs is diagnostic for Graves disease.

The presence of TSIs is particularly useful in reaching the diagnosis in pregnant women, in whom the use of radioisotopes is contraindicated.

What condition can develop in a newborn that does not produce proper amount of thyroid hormones – cretinism – short and mentally retarder

Blood arthritis panel

1. ESR – erythrocyte sedimentation rate
2. **C-reactive protein** – produced by the liver and elevation can indicate inflammation process in the body – Rheumatoid Arthritis, infection, obesity
3. **ANA** – antinuclear antibody – the most common screening test for systemic rheumatic disease
    a. Elevated look for – (RA/rheumatoid arthritis, scleroderma, Sjogren's syndrome, mixed connective tissue disease, SLE)

b. Patient presents with subcutaneous nodes, morning stiffness with joint pain and swelling in both hands symmetrically for last 8 month. Blood work shows elevated ANA and C-reactive protein – RA

4. Rheumatoid factor (RF) – about 70-90% of people with high RF have RA
   a. People who do not have RA can have elevated RF
5. Anti-CCP (Anti-cyclic citrullinated peptide) – looks for antibody in diagnosis of RA. This test can catch the RA in early stages. If this test is positive there is 97% chance that the patient has RA
   a. Anti-CCP and RF are positive
6. Uric acid – elevated in Gout and kidney disease
   a. Waste, made mostly in liver, excreted by kidney, from purine and pyrimidine metabolism
7. HLA-B27 - if this marker is present in blood it could indicate (increases the risk) of development of **ankylosing spondylitis**
8. Lyme disease – ELISA screening and confirm by immunoblot

Pregnancy test

1. hCG – human chorionic gonadotropin – in norm it is produced by placenta in pregnant woman
   a. Early in pregnancy the level of hCG increased in blood and eliminated in urine
   b. Pregnancy test – tests hCG in urine
   c. Blood test for hCG – conform, monitor, screen for fetal abnormalities, tumor marker, ectopic pregnancy
   d. There should be steady increase of hCG until 10^{th} week of pregnancy, reaches peak and then slowly starts to decrease and is not detectable few weeks after delivery.
   e. Pregnant patient presents with lower-than-expected increase of hCG. What that would that indicate – Ectopic pregnancy
   f. Abnormal levels of hCG also can indicate possible fetal chromosomal abnormalities (Down's syndrome) – can be used as screening tool between 11 and 20 weeks of gestation.
   g. Normal pregnancy – but higher than expected hCG levels – multiple pregnancy

h. What chemical maintains pregnancy until placenta develops and starts producing hCG – progesterone

2. Pregnancy associated plasma protein A (PAPP-A)
   a. Produced by trophoblasts
   b. Low levels at 8-14 weeks of gestation are associated with growth restriction, trisomy 21, trisomy 18, neural tube defect, preeclampsia, premature delivery and stillbirth

Progesterone assay

1. Progesterone main effect is to induce the development of the **secretory phase** of the endometrium in anticipation for fertilized egg. Secreted by corpus luteum after ovulation. Increased in luteal phase of the ovulatory cycle.
2. Can detect ovulation and its time
3. During pregnancy corpus luteum produces progesterone for few weeks until placenta takes over (around 12 weeks)
4. Increased: ovulation, pregnancy, luteal cyst, choriocarcinoma of the ovary, hydatidiform mole of the uterus
5. Decreased: preeclampsia, toxemia of pregnancy, threatened abortion, placental failure, fetal death, ovarian neoplasm, amenorrhea, ovarian hypofunction

Estrogen

1. Group of steroids that are responsible for the development and function of the reproductive system organs and formation of secondary sexual characteristics in women
2. Blood estrogens – estrone (E1), estradiol (E2), estriol (E3)
   a. E1 – directly can be made from androstenedione and other androgens. Also can be produced in ovaries, placenta, testicles and adipose tissue. E1 – is the primary estrogen in men and postmenopausal woman
   b. E2 – primarily produced in ovaries and is under FSH and LH regulation. Premenopausal women. Male testes also can make E2. It is the most potent estrogen. It is a good marker for ovarian function

c. E3 – produced in placenta. Part of second trimester screening to evaluate risk for chromosomal abnormalities

Prostate specific antigen (PSA)

1. Low 0-2.5 ng/ml, slightly elevated 2.6-10 ng/ml, moderately elevated 10-19.9 ng/ml, significantly elevated >20 ng/ml
2. Elevated in prostate cancer, inflammation and hyperplasia
3. 80% of the tests are false positive
4. Free PSA is more accurate and **p2PSA** isoform is more specific for cancer
5. Prostate cancer specific biomarkers
   a. Prostate cancer gene 3 (PCA3), GOLPH2, SPINK1
6. My prostate score (MiPS) – PSA + PCA3 + TMPRSS2-ERG in the urine
7. Benign prostatic hyperplasia - Moderately elevated PSA in 30-50% of BPH
8. Elevated in 25 to 92% of patients with prostate cancer
9. **PSA elevated what is the best test to determine if there is cancer of prostate** – biopsy
10. Male patient with high risk of prostate cancer there will lower cutoff of PSA than in general population
11. Screening of prostate cancer – digital rectal exam and PSA

Antibodies

1. Acetylcholine receptor antibody (AChR Ab)
   a. Myasthenia gravis (MG)
2. Anticardiolipin antibodies
   a. Systemic lupus erythematosus
3. Anticentromer antibodies
   a. Scleroderma with CREST syndrome (Calcinosis, Reynaud's phenomenon, esophageal disfunction, sclerodactyly and telangiectasia
4. Anti-DNA antibody
   a. SLE
   b. RA, Chronic hepatitis
5. Antiglomerular basement membrane antibody
   a. Goodpasture syndrome, Lupus nephritis
6. Antineutrophil cytoplasmic antibody (ANCA)

    a. Positive Wegener granulomatosis
7. Antinuclear antibody (ANA)
    a. Used to diagnose and screen autoimmune diseases
    b. Many types ANAs
    c. SLE, Drug induced lupus
    d. Sjogren's syndrome
    e. RA
    f. Rheumatic disease
    g. Chronic active hepatitis
    h. Infectious mononucleosis
8. Anti-parietal cell antibody (APCA)
    a. Atrophic gastritis, Pernicious anemia, Juvenile diabetes, Hashimoto's thyroiditis
9. Antiscleroderma antibody (Scl-70)
10. Platelet antibody
    a. Increased in ITP (Idiopathic thrombocytopenic purpura)
11. Antithyroid microsomal antibody
    a. Hashimoto d, RA, Pernicious anemia, Thyrotoxicosis
12. Antithyroglobulin antibody
    a. Hashimoto, RA, Pernicious anemia, Thyrotoxicosis
13. Anti-SS-A, Anti-SS-B, Anti-SS-C
    a. Sjogren syndrome
14. Antispermatozoal antibody