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Endocrinology (508 ch)

for biochemistry diploma students

Lecture 6, 7 & 8

Thyroid Stimulating Hormone (TSH)

A- Hormones of the anterior lobe:

1- Thyroid stimulating hormone (TSH): (lecture 6)

It, therefore, regulates thyroid function i.e. regulates the secretion of tri-iodothyronine (T3) and thyroxin (T4) in blood. In turn, TSH reflects the levels of the latter hormones in blood. In general, the increase of T4 depresses the TSH and vice versa.

❖ **Absence of TSH is accompanied by:**

Involution or damage of thyroid gland, **d**ecrease of thyroid uptake of iodine, decrease of transformation of di-iodo-tyrosine to thyroxin and finally, inhibition of the release of thyroid hormones from the gland.

The TSH test doesn't require any special preparation. However, it's important to tell your doctor if you're taking medications that might interfere with the accuracy of the TSH measurement. Some medications that could interfere with a TSH test are:

- amiodarone
- dopamine
- lithium
- prednisone
- potassium iodide

You may need to avoid using these drugs before the test. However, don't stop taking your medications unless your doctor tells you to do so.

What do the Results of a Thyroid-Stimulating Hormone Test Mean?

The normal range of TSH levels is 0.4 to 4.0 milli-international units per liter. If you're already being treated for a thyroid disorder, the normal range is 0.5 to 3.0 milli-international units per liter.

A value above the normal range usually indicates that the thyroid is underactive. This indicates hypothyroidism. When the thyroid isn't producing enough hormones, the pituitary gland releases more TSH to try to stimulate it.

A value below the normal range means that the thyroid is overactive. This indicates hyperthyroidism. When the thyroid is producing too many hormones, the pituitary gland releases less TSH.

Depending on the results, your doctor may want to perform additional tests to confirm the diagnosis.

It's important to understand the meaning and possible causes of both high thyroid stimulating hormone (TSH) and low TSH, whether you have been living with thyroid disease for a long time or are only having the test to screen for a thyroid disorder. A high TSH level can mean a new diagnosis of hypothyroidism or inadequate thyroid replacement. A low TSH might mean hyperthyroidism or overtreatment of hypothyroidism. That said, there are exceptions to these interpretations, as well as what a "normal" level may be for you.

How TSH Levels Change?

TSH levels are confusing and not necessarily intuitive. For example, many people question why high TSH levels can mean the thyroid is underactive and low TSH levels can mean it's overactive. Understanding exactly how the thyroid gland works can help.

Your thyroid gland produces thyroid hormone. When it functions properly, your thyroid is part of a feedback loop with your pituitary gland that involves several key steps:

1. First, your pituitary gland senses the level of thyroid hormone that is released into the bloodstream.

2. Your pituitary releases the special messenger hormone TSH, which stimulates the thyroid to release more thyroid hormone.
3. When your thyroid, for whatever reason—illness, stress, surgery, or obstruction, for example—doesn't or can't produce enough thyroid hormone, your pituitary detects the reduced levels of thyroid hormone and moves into action by making more TSH, which then triggers your thyroid to make more thyroid hormone. This is the pituitary's effort to raise the levels of thyroid hormone and return the system to normal.
4. If your thyroid is overactive and producing too much thyroid hormone—due to disease or taking too high a dose of thyroid hormone replacement drugs—your pituitary senses that there is too much of the hormone circulating and slows or shuts down TSH production. This drop in TSH is an attempt to return circulating thyroid hormone levels to normal.

Interpreting TSH Levels

Once you understand these thyroid basics, it's easier to understand what a low TSH and a high TSH reveal about your thyroid's function.

The normal range for TSH is between 0.5 mU/l and 5.0 mU/l.[1]

- **A high TSH** suggests your thyroid is underactive (hypothyroid) and not doing its job of producing enough thyroid hormone.
- **A low TSH** suggests your thyroid is overactive (hyperthyroid) and producing excess thyroid hormone.

As with most medical conditions and tests, however, there are exceptions to this rule. It's also important to note that normal thyroid levels may be abnormal for *you*. For example, a TSH greater than 3.0 mU/l is abnormal in pregnancy.

Controversy Over Optimal TSH

While most laboratories define a normal TSH as between roughly 0.5 mU/l and 5.0 mU/l, some experts argue that the upper limit of a normal TSH should be lower (around 2.5 mIU/L) due to the fact that the vast majority of young adults without thyroid disease have a TSH value between 0.4 and 2.5 mIU/L. In addition, some physicians believe older patients should have a higher TSH (for example, greater than 4.0 mU/l or 5.0 mU/l) since TSH normally increases with age.[1]

Some of this controversy can be averted by doctors simply looking at each person as an individual. For example, a person who still has significant symptoms of hypothyroidism at a TSH of 4.0 mU/l (especially someone who is young or middle-aged) may do better with a goal TSH of around 1.0 mU/l. In contrast, someone who has health risks (such as heart disease or osteoporosis) may benefit from having a goal TSH that is higher (perhaps 5.0 mU/l or 6.0 mU/l).

In pregnancy, TSH should not be allowed to rise above 3.0 mU/l for the health of both the baby and mother.[2]

Causes of High TSH

A high TSH means different things depending on whether a person has known thyroid disease or not.

In People Without Thyroid Disease

A high TSH in people who are not undergoing thyroid disease treatment usually indicates the presence of primary hypothyroidism. This is by far the most common form of hypothyroidism and occurs because the thyroid gland produces an inadequate amount of thyroid hormones.[3] The pituitary gland will sense these low levels and increase production of TSH. An elevated TSH may also occur with normal thyroid function due to the presence of antibodies and more.

In People Being Treated for Thyroid Disease

A high TSH may be found in people being treated for either hypo- or hyperthyroidism. With hypothyroidism, a high TSH usually means that the dose of thyroid hormone needs to be increased. In some cases, however, the dose is optimal, but the medication is not fully absorbed. (Many foods and medications can affect levothyroxine, and it's important to learn how to properly take thyroid hormones.)[4] With hyperthyroidism, a high TSH usually means that the treatment (whether surgery, radioactive iodine, or medications) was effective in turning off the overproduction of thyroid hormone, and that a person has now become hypothyroid.

Causes of Low TSH Results

A low TSH often, but not always, means that a person has an elevated level of thyroid hormones. **In People Without Known Thyroid Disease.** While often associated with hyperthyroidism, a low TSH could also be a sign of central hypothyroidism.

- Hyperthyroidism: Hyperthyroidism can be transient and permanent and due to a number of causes ranging from autoimmune disease, to toxic nodules or goiters, to pregnancy-related thyroiditis.[5]
- Central hypothyroidism: Less commonly, a lack of TSH produced by the pituitary gland (due to its dysfunction) can lead to low thyroid levels in the blood. While this is an exception to the general rule that hypothyroidism is associated with a high TSH, central hypothyroidism is uncommon and usually associated with a deficiency of other pituitary hormones (and subsequently, a number of other symptoms).

In People With Thyroid Disease

In people being treated for hypothyroidism, a low TSH level may mean:

- Overmedication with thyroid hormone replacement

- An optimal dose of medication, but interactions that cause increased absorption or activity
- Central hypothyroidism

In people being treated for hyperthyroidism, a low TSH level usually means that further treatment is needed to reduce thyroid hormone levels or that a person must continue to be monitored to make sure thyroid hormone levels return to normal (such as in cases of transient thyroiditis related to pregnancy or chemotherapy treatment).[6]

Factors That May Affect Your TSH Results

There are a number of variations and factors that can affect TSH levels. It's important to be aware of these, as treatment that is dictated solely by lab values (as opposed to also considering an individual's symptoms) can result in an ineffective plan.

Antibodies

Antibodies are thought to interfere with accurate thyroid testing in roughly 1 percent of people.[7] In a 2018 review, it was estimated that in people who have these antibodies, the interference with TSH testing caused either misdiagnosis or inappropriate treatment in more than 50 percent of cases:

- **Heterophile antibodies:** Heterophile antibodies are antibodies that may occur when a person is exposed to animal-derived pharmaceuticals and antibody therapies. Their presence is more common in people who have had certain vaccinations, blood transfusions, or have been exposed to some animals (not household pets). The estimated incidence of these antibodies varies widely, but when present, they can interfere with TSH levels. There is no easy way to know if you have these antibodies, but a discrepancy between TSH levels and free T4 (the hallmark of heterophile antibodies), or between TSH levels and how you feel, should raise the question.

- **Thyroid antibodies**: Thyroid autoantibodies, present in some people with or without a thyroid condition, may also affect TSH levels. Again, a discrepancy between lab values and how you feel should raise the question of whether or not the test is accurate.
- **Other antibodies:** Other antibodies important in TSH testing interference include anti-ruthenium antibodies and anti-streptavidin antibodies.

Other Factors

A number of other factors can affect TSH test results either through having an effect on actual levels of thyroid hormones or interacting with testing measures. Some of these include:

- The time of day that the test is done: TSH levels are higher if you're tested after fasting (for example, in the morning after not having eaten since the night before) as compared to after eating later in the day.[8]
- Illness
- Pregnancy
- Some medications that are used for heart disease and in cancer treatment
- Foods or supplements rich in/derived from iodine or kelp
- Biotin supplements
- Non-steroidal anti-inflammatory medications such as Advil (ibuprofen)
- Changes in sleep habits

In order to get the most accurate results, it's important to be consistent. For example, always having your test done at the same time of day.

When TSH Alone is Not Enough?

During diagnosis, most doctors use the TSH test to evaluate thyroid function and determine the optimal course of treatment. There are times, however, when a TSH is or may be insufficient.

For instance, free T4 in addition to TSH is usually tested if a doctor suspects thyroid dysfunction arising from disease of the pituitary gland or hypothalamus.[1] Likewise, if the TSH is normal, but a person still has symptoms of being hyperthyroid or hypothyroid, free T4 may be checked.

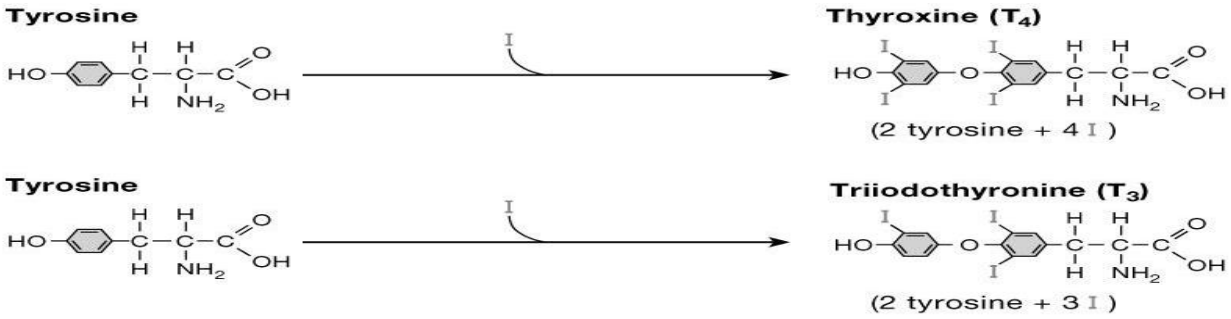
TSH is also not necessarily sufficient to monitor hypothyroidism during pregnancy, and a T4 and free T4 are often recommended. Depending on the clinical situation, other thyroid tests that may be evaluated include triiodothyronine (T3), free T3, reverse T3, and thyroid antibody tests.

➢ Thyroid Hormones: (lecture 7)

There are two biologically active thyroid hormones (derived from modification of tyrosine):

1- Tetraiodothyronine (T4; usually called thyroxine).

2- Triiodothyronine (T3).



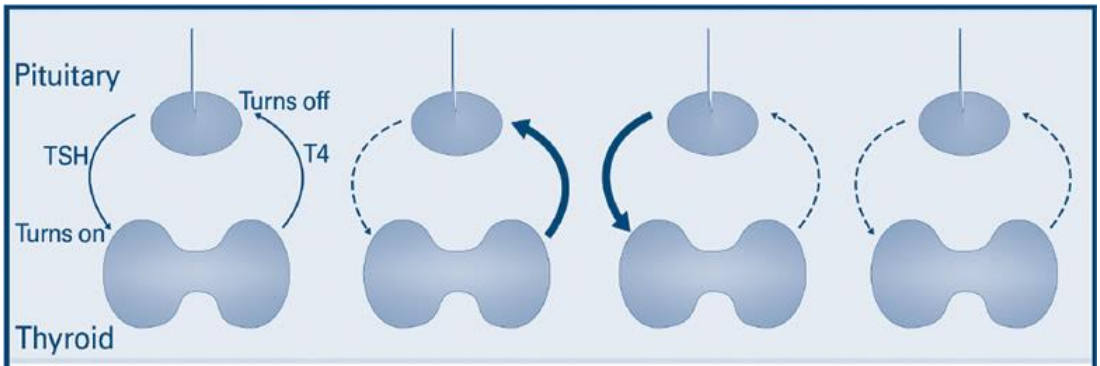
The thyroid secretes about 80 µg of T4, but only 5 µg of T3 per day. However, T3 has a much greater biological activity (about 10 X) than T4. An additional 25 microg/day of T3 is produced by peripheral monode-iodination of T4.

Role of iodine:

- Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys.
- Iodide taken up by the thyroid gland is oxidized by peroxidase (Iodide into zero charged Iodine
- Oxidized iodine can then be used in production of thyroid hormones.

➢ HOW DOES THE THYROID GLAND FUNCTION?

The major thyroid hormone secreted by the thyroid gland is thyroxine, also called T4 because it contains four iodine atoms. To exert its effects, T4 is converted to triiodothyronine (T3) by the removal of an iodine atom. This occurs mainly in the liver and in certain tissues where T3 acts, such as in the brain. The amount of T4 produced by the thyroid gland is controlled by another hormone, which is made in the pituitary gland located at the base of the brain, called thyroid stimulating hormone (abbreviated TSH). The amount of TSH that the pituitary sends into the bloodstream depends on the amount of T4 that the pituitary sees. If the pituitary sees very little T4, then it produces more TSH to tell the thyroid gland to produce more T4. Once the T4 in the bloodstream goes above a certain level, the pituitary's production of TSH is shut off. In fact, the thyroid and pituitary act in many ways like a heater and a thermostat. When the heater is off and it becomes cold, the thermostat reads the temperature and turns on the heater. When the heat rises to an appropriate level, the thermostat senses this and turns off the heater. Thus, the thyroid and the pituitary, like a heater and thermostat, turn on and off. This is illustrated in the figure below.



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low

- T4 and T3 circulate almost entirely bound to specific transport proteins. If the levels of these transport proteins changes, there can be changes in how much bound T4 and T3 is measured. This frequently happens during pregnancy and with the use of birth control pills. The "free" T4 or T3 is the hormone that is unbound and able to enter and affect the body tissues.

- **Transport of Thyroid Hormones:**

Thyroid hormones are lipid-soluble. Thus, they are need binding proteins; namely, thyroid Hormone-Binding Globulin (~70% of hormone, pre-albumin (~15%) and albumin (~15%).On the other hand, less than 1% of thyroid hormone is found free in the circulation. **Only free and albumin-bound thyroid hormone is biologically available to tissues via cAMP production and hormone-receptor complex.**

T3 has much greater biological activity than T4. A large amount of T4 (25%) is converted to T3 in peripheral tissues mainly in the liver and kidneys.

- **Regulation of Thyroid Hormone Levels:**

Thyroid hormone synthesis and secretion is regulated by an auto-regulation mechanism (via the available iodine levels) and regulation by the hypothalamus (Thyrotropin-releasing or inhibiting hormone (TRH) which control the anterior pituitary (TSH) function.

- **Diet**: a high carbohydrate diet increases T3 levels, resulting in increased metabolic rate (diet-induced thermogenesis).
- **Low carbohydrate diets:**decrease T3 levels, resulting in decreased metabolic rate.
- **Cold Stress:** increases T3 levels in other animals, but not in humans.
- **Other stresses**: increased or decreased?

- **Any condition** that increases body energy requirements (e.g., pregnancy, prolonged cold).
- **All of these stimulate hypothalamus → TRH → TSH (Pituitary) → (Thyroid).**

➢ **<u>Actions of Thyroid Hormones</u>**:

- Thyroid hormones are essential for normal growth of tissues, including the nervous system.
- Lack of thyroid hormone during development results in short stature and mental defects or what is called **cretinism.**
- Thyroid hormone stimulates basal metabolic rate (keep the metabolic status at the lowest rate).
- Required for GH action and for prolactin production and secretion
- Increases intestinal glucose reabsorption via what is called glucose transporter.
- Increases mitochondrial oxidative phosphorylation (ATP production)
- Increases activity of adrenal modularly hormones (sympathetic nerves ; glucose production)
- Induces enzyme synthesis

The result is: stimulation of growth of tissues, increased metabolic rate and increased heat production (calorigenic effect).

➢ **<u>Effects of Thyroid Hormone on Nutrient Sources:</u>**

❖ **Effects on protein synthesis and degradation:**

i- Increased protein synthesis at low thyroid hormone levels (low metabolic rate; growth).

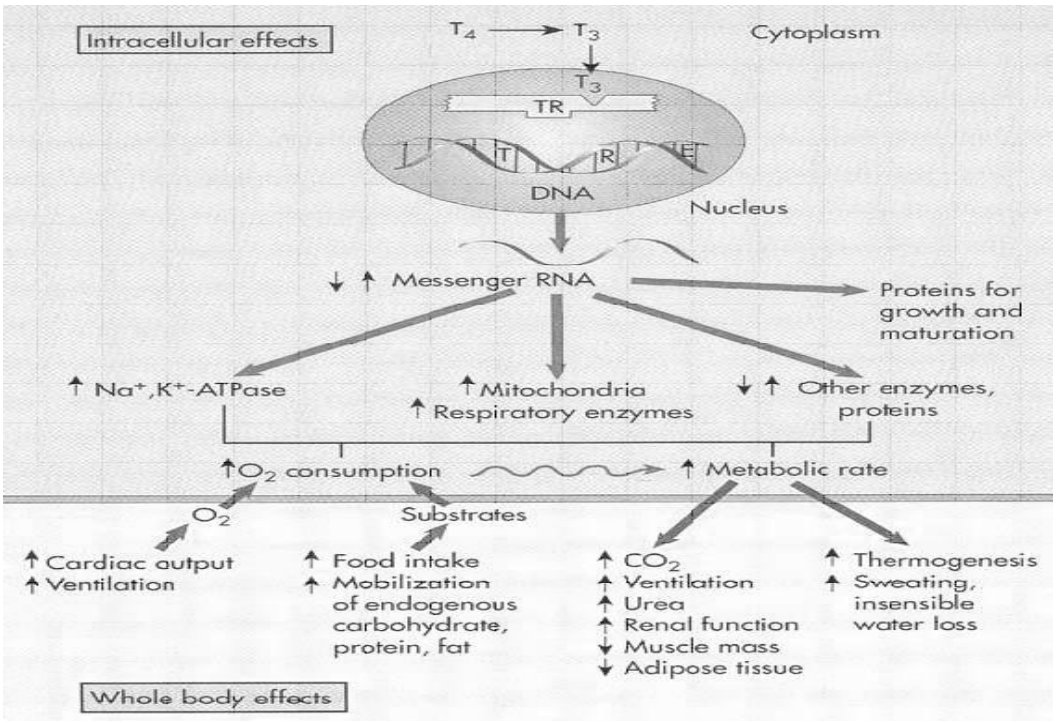
ii- Increased protein degradation at high thyroid hormone levels (high metabolic rate; energy production)

❖ **Effects on carbohydrates:**

i- Low doses of thyroid hormone increase glycogen synthesis (low metabolic rate; storage of energy).

ii- High doses increase glycogen breakdown (high metabolic rate; ; glucose production).

- **Thyroid Hormone Act to Increase Oxygen Consumption:**
  - **i-** Increase mitochondrial size, number and key enzymes.
  - **ii-** Decrease superoxide dismutase activity.
  - **iii-** Increase thermogenic energy cycles.
  - **iv-** They increase plasma membrane Na-K ATPase activity.
- **<u>Effects of Thyroid Hormones on the Cardiovascular System:</u>**
  - **i-** Increase heart rate.
  - **ii-** Increase force of cardiac contractions.
  - **iii-** Increase stroke volume.
  - **iv-** Increase Cardiac output.
  - **v-** Up-regulate catecholamine receptors.
- **Effects of Thyroid Hormones on the Respiratory System** :
  - **i-** They increase resting respiratory rate.
  - **ii-** They increase minute ventilation.
  - **iii-** They increase ventilatory response to hypercapnia and hypoxia.
- **Effects of Thyroid Hormones on the Renal System:**
  - **i-** They increase blood flow.
  - **ii-** They increase glomerular filtration rate (**please see figure below).**



TESTS

Blood tests to measure these hormones are readily available and widely used, but not all are useful in all situations. Tests to evaluate thyroid function include the following:

TSH TESTS:

The best way to initially test thyroid function is to measure the TSH level in a blood sample. Changes in TSH can serve as an "early warning system" – often occurring before the actual level of thyroid hormones in the body becomes too high or too low. A high TSH level indicates that the thyroid gland is not making enough thyroid hormone (primary hypothyroidism). The opposite situation, in which the TSH level is low, usually indicates that the thyroid is producing too much thyroid hormone (hyperthyroidism). Occasionally, a low TSH may result from an abnormality in the pituitary gland, which prevents it from making enough TSH to

stimulate the thyroid (secondary hypothyroidism). In most healthy individuals, a normal TSH value means that the thyroid is functioning properly.

T4 TESTS

T4 is the main form of thyroid hormone circulating in the blood. A **Total T4** measures the bound and free hormone and can change when binding proteins differ (see above). A **Free T4** measures what is not bound and able to enter and affect the body tissues. Tests measuring free T4 – either a free T4 (FT4) or free T4 index (FTI) – more accurately reflect how the thyroid gland is functioning when checked with a TSH.

The finding of an elevated TSH and low FT4 or FTI indicates primary hypothyroidism due to disease in the thyroid gland. A low TSH and low FT4 or FTI indicates hypothyroidism due to a problem involving the pituitary gland. A low TSH with an elevated FT4 or FTI is found in individuals who have ***hyperthyroidism***.

T3 TESTS

T3 tests are often useful to diagnosis hyperthyroidism or to determine the severity of the hyperthyroidism. Patients who are hyperthyroid will have an elevated T3 level. In some individuals with a low TSH, only the T3 is elevated and the FT4 or FTI is normal. T3 testing rarely is helpful in the hypothyroid patient, since it is the last test to become abnormal. Patients can be severely hypothyroid with a high TSH and low FT4 or FTI, but have a normal T3.

FREE T3

Measurement of free T3 is possible, but is often not reliable and therefore not typically helpful.

REVERSE T3

Reverse T3 is a biologically inactive protein that is structurally very similar to T3, but the iodine atoms are placed in different locations, which makes it

inactive. Some reverse T3 is produced normally in the body, but is then rapidly degraded. In healthy, non-hospitalized people, measurement of reverse T3 does not help determine whether hypothyroidism exists or not, and is not clinically useful.

THYROID ANTIBODY TESTS

The immune system of the body normally protects us from foreign invaders such as bacteria and viruses by destroying these invaders with substances called antibodies produced by blood cells known as lymphocytes. In many patients with hypothyroidism or hyperthyroidism, lymphocytes react against the thyroid (thyroid autoimmunity) and make antibodies against thyroid cell proteins. Two common antibodies are thyroid peroxidase antibody and thyroglobulin antibody. Measuring levels of thyroid antibodies may help diagnose the cause of the thyroid problem. For example, positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies in a patient with hypothyroidism result in a diagnosis of Hashimoto's thyroiditis. While detecting antibodies is helpful in the initial diagnosis of hypothyroidism due to autoimmune thyroiditis, following their levels over time is not helpful in detecting the development of hypothyroidism or response to therapy. TSH and FT4 are what tell us about the actual thyroid function or levels.

A different antibody that may be positive in a patient with hyperthyroidism is the stimulatory TSH receptor antibody (TSI). This antibody causes the thyroid to be overactive in ***Graves' Disease***. If you have Graves' disease, your doctor might also order a thyrotropin receptor antibody test (TSHR or TRAb), which detects both stimulating and blocking antibodies. Following antibody levels in Graves' patients may help to assess response to treatment of hyperthyroidism, to determine when it is appropriate to discontinue antithyroid medication, and to assess the risk of passing antibodies to the fetus during pregnancy.

THYROGLOBULIN

Thyroglobulin (Tg) is a protein produced by normal thyroid cells and thyroid cancer cells. It is not a measure of thyroid function and it does not diagnose thyroid cancer when the thyroid gland is still present. It is used most often in patients who have had surgery for thyroid cancer in order to monitor them after treatment. Tg is included in this brochure of thyroid function tests to communicate that, although measured frequently in certain scenarios and individuals, Tg is not a primary measure of thyroid hormone function.

NON-BLOOD TESTS

RADIOACTIVE IODINE UPTAKE

Because T4 contains iodine, the thyroid gland must pull a large amount of iodine from the bloodstream in order to make an appropriate amount of T4. The thyroid has developed a very active mechanism for doing this. Therefore, this activity can be measured by having an individual swallow a small amount of iodine, which is radioactive. The radioactivity allows the doctor to track where the iodine goes. By measuring the amount of radioactivity that is taken up by the thyroid gland (radioactive iodine uptake, RAIU), doctors may determine whether the gland is functioning normally. A very high RAIU is seen in individuals whose thyroid gland is overactive (***hyperthyroidism***), while a low RAIU is seen when the thyroid gland is underactive (***hypothyroidism***). In addition to the radioactive iodine uptake, a thyroid scan may be obtained, which shows a picture of the thyroid gland and reveals what parts of the thyroid have taken up the iodine (see ***Thyroid Nodules brochure***).

MEDICATIONS THAT INTERFERE WITH THYROID FUNCTION TESTING

There are many medications that can affect thyroid function testing. Some common examples include:

- **Estrogens**, such as in birth control pills, or in pregnancy, cause high levels of total T4 and T3. This is because estrogens increase the level of the binding proteins. In these situations, it is better to ask both for TSH and free T4 for thyroid evaluation, which will typically be in the normal range.
- **Biotin**, a commonly taken over-the-counter supplement, can cause the measurement of several thyroid function tests to appear abnormal, when they are in fact normal in the blood. Biotin should not be taken for 2 days before blood is drawn for thyroid function testing to avoid this effect.

➢ Thyroid Hormone Deficiency (Hypothyroidism):

- **Early ages** : Delaying in physical and mental development
- **Later onset (youth)** : Impaired physical growth
- **Adult onset (myxedema)**: **Gradual changes in the followings occur:** Tiredness, decreased metabolic rate, slowing of mental function and motor activity, cold intolerance, weight gain, goiter, hair loss, dry skin.) which eventually may result in coma.

❖ Causes of hypothyroidism

Insufficient iodine, Lack of thyroid gland, lack of hormone receptors, lack of TH binding globulin….)

How is Hypothyroidism Related to Goiter?

- During iodine deficiency, thyroid hormone production decreases.
- This results in increased TSH release (less negative feedback).

- TSH acts on thyroid, increasing blood flow, and stimulating follicular cells with a resultant increasing in colloid production, thus causing **Goiter**.
- If goiter is due to decrease in iodine level, then thyroid gland enlarges (called endemic or colloidal goiter).
- Therefore, pituitary gland release → TSH **to stim thyroid gland to produce** its thyroid hormones, **but the only result is that the follicles accumulate more and more unusable colloid**.
- Cells eventually die from over-activity and the gland atrophies.

❖ **Hyperthyroidism**

- Emotional symptoms (which include nervousness and irritability), fatigue, heat intolerance, elevated metabolic rate, weight loss, tachycardia, goiter, muscle wasting, apparent bulging of eyes and may develop congestive heart failure **(WHY?).**
- Also, due to many causes (excessive TSH release, **autoimmune disorders** or **thyroiditis**,……)

➢ Parathyroid Hormone (PTH): (lecture 8)

Test Overview:

PTH test in the blood to diagnose hyperparathyroidism or to determine the cause of abnormal calcium levels in the blood. PTH is produced by the parathyroid glands (are embedded in the thyroid gland). PTH regulates calcium and phosphorus levels in the blood.

If the blood calcium level is too low, the parathyroid glands release more PTH. This causes the bones to release more calcium into the blood and reduces the amount of calcium released by the kidneys into the urine. In addition, vitamin D is converted to a more active form, causing the intestines to absorb more calcium and phosphorus. If the calcium level is too high, the parathyroid glands release less PTH and the whole process is reversed.

Abnormally high or low levels of PTH can affect kidney function, bone integrity, and calcium and vitamin D levels.

Note: Tests for calcium and phosphorus levels in the blood may be done at the same time.

It is done to:

1. Help diagnose hyperparathyroidism.
2. Evaluate the cause of an abnormal blood calcium level.
3. Determine whether a problem with the parathyroid glands is causing the abnormal calcium level.
4. Monitor people with chronic kidney disease.

➢ **Recommendation for accurate test results:**

1- You must not eat or drink anything for 10 to 12 hours before the test.

2- It is preferred that your blood tesi9t be done before 10 a.m., because PTH levels change between sleep and wakefulness.

- **Results:** A parathyroid hormone (PTH) blood test measures the level of parathyroid hormone to help diagnose hyperparathyroidism or to determine the cause of abnormal calcium levels in the blood.
- **High values:**
  a- A high parathyroid hormone (PTH) level along with a high blood calcium level may indicate excessive parathyroid gland growth (hyperplasia) or a parathyroid tumor.
  b- A high PTH value is the body's normal response to a low level of calcium in the blood. A low blood calcium level can be caused by conditions such as kidney disease, kidney failure, severe vitamin D deficiency, or an inability of the intestines to absorb calcium from food.
  c- In rare instances, some types of cancer (such as of the lung, kidney, pancreas, or ovaries) can cause an increase in the blood level of PTH and calcium.
- **Low values:**
  a- A low level of parathyroid hormone (PTH) along with a low calcium level may indicate parathyroid gland damage, which may occur from neck surgery. In rare cases, a low PTH level along with a low calcium level may result from an autoimmune disease or an infiltrative disease e.g. histiocytosis X).
  b- A low level of PTH along with a high level of calcium can indicate sarcoidosis or an overdose vitamin D or calcium.
  c- A protein called PTH-related protein, or PTH-RP, causes an increase in blood calcium levels and a decrease in PTH levels. A high level of calcium along with a low level of PTH can indicate certain types of cancer that produce PTH-RP, including lymphoma and multiple myeloma.
  d- A low magnesium level may cause a low parathyroid level.

- **Factors that can interfere with your test and the accuracy of the results include:**
  - **a- Medications that can increase parathyroid hormone (PTH) levels** (lithium, anticonvulsants, diuretics and those contain phosphate.
  - **b- Medications that can slightly decrease** PTH levels (Tagamet and propranolol).
  - **c-** Pregnancy or breast-feeding.
  - **d-** Increased lipids levels.
  - **e-** Radioactive tracer scan within 1 week of PTH test.
  - **f-** Milk or milk products taken right before the test.

Notes:

a- Because parathyroid hormone (PTH) can raise calcium levels and lower phosphorus levels, blood tests for calcium and phosphorus are often done along with a test for PTH .

b- Since, about half of all calcium in the blood is bound to albumin, the changes in albumin level can affect the level of calcium in the blood. For this reason, most doctors check blood albumin levels when testing calcium levels.

c- Kidney function can affect the amount of PTH in the blood. For this reason, tests to measure the amount of creatinine in the blood may be done along with a PTH test (creatinine and creatinine clearance tests).

d- An elevated PTH level along with an elevated calcium level can cause problems such as osteoporosis, kidney stones, hypertension, kidney failure, peptic ulcer disease, cognitive changes, and problems with the balance of water in the body. About half of all people diagnosed with elevated PTH and calcium in the blood need treatment to correct the abnormal levels. Further

testing (such as bone mineral density testing or 24-hour urine calcium testing) may be needed to guide treatment.

e- Overactive parathyroid glands are often the result of noncancerous (benign) tumors of the parathyroid glands. Parathyroid tumors tend to grow slowly and may not cause any symptoms for many years. Parathyroid tumors are more common after age 50 and are often discovered with routine blood tests that are done for other reasons.

➢ Calcium (Ca^{2+}) in Blood:

Calcium is the most important mineral in the body. The body needs it to build and repair bones and teeth, help nerves function, make muscles contract, clot blood, and allow proper function of the heart. Almost all of the calcium in the body is stored in bone. The rest is found in the blood. A test for calcium in the blood measures the calcium level in the body that is not stored in the bones.

Under normal conditions, the level of calcium in the blood is carefully controlled. When blood calcium levels fall (hypocalcemia), calcium is released from bones to restore proper blood levels. When blood calcium levels rise (hypercalcemia), the excess calcium may be stored in bone or passed out from the body into urine and stool.

This control depends upon the:

- ❖ Amount of calcium in the diet.
- ❖ Amount of calcium and vitamin D absorbed by the intestines.
- ❖ Amount of phosphate in the body.
- ❖ Production of certain hormones, including parathyroid hormone, calcitonin, and estrogen.

Vitamin D and certain hormones (such as parathyroid hormone and calcitonin) help control the total amount of calcium in the body. They also regulate the amount of calcium absorbed from food and the amount removed from the body by the kidneys. The blood levels of phosphate are closely linked to calcium levels. They usually work in opposite directions: As blood calcium levels rise, phosphate levels fall.

Getting enough calcium [at least 1000 mg(1 g) a day] in the diet is important, since the body loses calcium every day. The main sources of calcium are dairy products (milk, cheese), eggs, fish, green vegetables, and fruit. Most people who have abnormal blood calcium levels do not have any symptoms. Usually, calcium levels need to be extremely high or low to cause symptoms.

❖ **A blood calcium test may be done to:**

- Evaluate suspected problems with the parathyroid glands or kidneys, certain types of cancers and bone diseases, inflammation of the pancreas (pancreatitis), kidney stones, and some abnormal results noted on an electrocardiogram (EKG) test.
- To investigate symptoms that **may be caused by a very low calcium level in the blood** which may include muscle cramping and twitching, tingling in the fingers and around the mouth, spasms, confusion, or depression.
- To investigate symptoms **that may be caused by a very high calcium level in the blood**. which may include weakness, lack of energy, poor appetite, nausea and vomiting, constipation, frequent urination, or abdominal or bone pain.

Blood calcium levels are usually kept within normal limits even when a person's diet does not contain enough calcium. Calcium is removed from the bones to keep blood levels normal. This is because calcium is important to brain, muscle, heart, and nerve function. Other tests, such as bone densitometry, measure the amount of calcium in the bones.

Note: Patient does not take calcium supplements for 8 to 12 hours before having a blood calcium test.

❖ **Results**

A test for calcium in the blood measures the calcium level in the body that is not stored in the bones.

❖ **Normal values:**

Normal values may vary from lab to lab. (Adults: 9.0–10.5 mg/dL). Normal blood calcium values are higher in children because of their rapid growth and active bone formation. Calcium levels in children can rise to 12 mg/dL during periods of rapid bone growth.

An ionized calcium test measures the amount of calcium that is not bound to protein in the blood. The level of ionized calcium in the blood is not affected by the amount of protein in the blood.

➢ **Ionized calcium:**

❖ **High values:**

- High levels of calcium in the blood may be caused by prolonged immobilization (such as bed rest), hyperparathyroidism, kidney disease, tuberculosis, or cancer that has spread to the bones. Certain cancers may produce a substance that raises blood calcium levels.
- High levels of calcium in the blood can be caused by eating a diet with excessive amounts of vitamin D, vitamin A, or calcium. Eating large

amounts of milk products or taking too many calcium-containing medications (such as antacids or vitamin supplements) can cause high blood calcium levels.

- High levels of calcium in the blood can be caused by dehydration, sarcoidosis, chronic liver or kidney problems, Paget's disease, and Addison's.
- In rare cases, hyperthyroidism may increase blood calcium levels.

❖ **Low values:**

- Low levels of calcium in the blood can be caused by **(hypo-parathyroidism),**
- Malabsorption, bone problems, kidney disease, acute pancreatitis, or decreased amounts of the protein albumin in the blood (hypo-albuminemia).
- Decreased ionized calcium levels may be caused by decreased magnesium levels.
- Pregnant women and older men may also have low calcium levels.

Factors that can interfere with your test and the accuracy of the results include:

- Drinking excessive amounts of milk, antacids, calcium salts, and calcium supplements.
- Diuretics, estrogen, birth control pills, corticosteroids.
- Long-term or excessive use of vitamin D.
- Having many blood transfusions in a short period of time.

➢ Phosphate in Blood:

The body needs phosphate to build and repair bones and teeth, help nerves function, and make muscles contract. Most of the body's phosphate (about 85%) is found in bones. The rest of it is stored in tissues throughout the body.

The kidneys can control phosphate level in the blood. **Extra-phosphate** is filtered by the kidneys and passes out of the body in the urine. Therefore, a high level of phosphate in the blood is usually caused by a kidney problem.

The levels of phosphate in the blood affect that of calcium in the blood. Usually, If the blood calcium levels rise, phosphate levels fall. For this reason, phosphate and calcium levels are usually measured at the same time.**It may be done to:**

- Check phosphate levels if you have kidney disease or bone disease.
- To find problems with the parathyroid glands.
- Check phosphate levels if you have diabetic ketoacidosis.

Normal values in blood vary from lab to lab.

Adults:	2.3–4.5 milligrams per deciliter (mg/dL)
Children:	4–6 mg/dL
Babies:	4.5–9 mg/dL
Premature babies:	5.4–10.9 mg/dL

High phosphate levels may be caused by:

1. Kidney disease, underactive parathyroid glands (hyperparathyroidism), acromegaly, healing fractures, untreated diabetic ketoacidosis, or certain bone diseases.
2. Too much vitamin D in the body.
3. Decreases in magnesium levels.
4. Pregnancy.

❖ **Low phosphate levels may be caused by:**

1- Hyperparathyroidism, certain bone diseases (such as osteomalacia), lack of vitamin D, severe burns, or some kidney or liver diseases.

2- Severe malnutrition or starvation.

3- High calcium levels 4-Malabsorption.