FOUNDATION LABORATORY

Corporate Office • 1716 West Holt Ave. • Pomona, CA 91768 • (909) 623-9301 • FAX (909) 623-9306

TOTAL, FREE, AND BIOAVAILABLE TESTOSTERONE

Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior.

In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In menopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone productions significantly diminished. Testosterone production in testes and ovaries is regulated vi pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins.

Most circulating testosterone is bound to sex hormone binding globulin (SHBG), which in men is also called testosterone binding globulin. A lesser fraction is albumin bound and a small portion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable.

During childhood, excess production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild to moderate testosterone elevation is usually asymptomatic in males, but can cause distressing symptoms in females. The exact cause of mild to moderate elevations in testosterone often remain obscure. Common causes of pronounces elevations of testosterone include genetic conditions (e.g., congenital adrenal hyperplasia); adrenal testicular, and ovarian tumors and abuse of testosterone or gonadotropins by athletes.

Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by male secondary sexual characteristics and reproductive function. The cause of primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there is also a gradual modest, but progressive decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing non-specific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging is rare.

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Measurement of total testosterone is often sufficient for diagnosis particularly if it is combined with serum LH and serum FSH. However, these test may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG function or levels are present. Additional measurement of free testosterone and bioavailable testosterone are recommended in this situation, bioavailable testosterone is the preferred assay.

INTERPRETATION

Total testosterone and general interpretation of testosterone abnormalities:

Males:

Decreased testosterone levels:

Indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure.

Primary testicular failure is associated with increased LH and FSH levels and decreased total, bioavailable testosterone levels. Causes include:

1. Genetic cause (Klinefellter syndrome, XX males).
2. Developmental causes (testicular maldescent).
3. Testicular trauma or ischemia (testicular torsion, surgical mishap including hernia operations).
4. Infections (mumps).
5. Autoimmune disease (autoimmune polyglandular endocrine endocrine failure).
6. Metabolic disorders (hemochromatosis, liver failure).
7. Orchiectomy.

Secondary/tertiary hypogonadism, also known as hypogonadotropic hypogonadism, shows low testosterone and low or inappropriately "normal" LH/FSH levels; causes include:

1. Inherited or developmental disorders of hypothalamus and pituitary (Kallamann syndrome, congenital hypopituitarism).
2. Pituitary or hypothalamic tumors.
3. Hyperprolactinemia of any cause.
4. Malnutrition of excessive exercise.
5. Cranial irradiation.
6. Head trauma.
7. Medical or recreational drugs (estrogens, GNRH analogs, cannabis).

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Increased testosterone levels:

In pre-pubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause(s) of precocious puberty.

In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by 50%.

Monitoring testosterone replacement therapy:

Aim of treatment is normalization of serum testosterone and LH. During the treatment with testosterone preparations, trough levels of serum testosterone should still be within normal range, while peak levels should not be significantly above the normal young adult range.

Monitoring of anti-androgen therapy:

Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range).

Females:

Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have significant decrease in testosterone levels.

Increased testosterone levels:

1. Congenital adrenal hyperplasia: non-classical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17OH-progesterone, often to a greater degree than testosterone.
2. Pre-pubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty.
3. Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal". Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values >200 ng/dL.
4. Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form a part of this syndrome. Total testosterone levels may be normal or mildly elevated and, uncommonly, >200 ng/dL.

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Monitoring testosterone replacement therapy:

The efficacy of testosterone replacement in females is under study, if it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid overtreatment.

Monitoring of anti-androgen therapy:

Androgen therapy is most commonly employed in measurement of mild to moderate "idiopathic" female hyper-androgenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical endpoints and the primary treatment endpoint is the clinical response.

Bioavailable and free testosterone:

Usually bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the serum SHBG concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentrations, or vice versa.

Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex hormone binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult.

1. Inherited abnormalities in SHBG binding.
2. Liver disease and severe systemic illness.
3. In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total.
4. In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated.
5. Either bioavailable or free testosterone should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels but albumin levels also may vary due to coexisting illness.

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Cautions:

1. Early morning testosterone levels in young male individuals are, on average, 50% higher than p.m.
2. Testosterone levels can fluctuate substantially between different days, and sometimes even more rapidly. Assessment of androgen status should be based on more than a single measurement.
3. The low end of the normal reference range for total testosterone in pre-pubertal subjects is not yet very clear.
4. While free testosterone can be used for the same indications as bioavailable testosterone, determination of bioavailable testosterone levels may be superior to free testosterone measurement in most situations.

Clinical Reference:

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