WHITE PAPER

Andropause

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Abstract

Testosterone is associated with strength and virility, and its decline later in life may manifest as unpleasant symptoms including loss of libido, fatigability, and moodiness. Research reveals that a significant decline in testosterone may be due to factors beyond aging, including obesity and increased aromatization of testosterone to estrogen. Fully defined as a clinical syndrome, andropause or "late onset hypogonadism" can be evaluated and addressed fairly easily.

The syndrome is characterized by a consistently low total and free testosterone, elevated sex hormone binding globulin and luteinizing hormone, and persistent sexually-associated symptoms. Structured questionnaires and biochemical evaluation, combined with lifestyle changes and targeted support, can help resolve this existential midlife crisis.

Introduction

Andropause is a term used to describe decreased testicular production of testosterone (T) with subsequent decreases in serum levels. Technically, true andropause is caused by loss of testicular function due to disease, accidents, or therapeutic castration.[1] However, currently the term may be used to reference symptomatic decreases in T that occur later in life.

Andropause may also be referred to as[2] [3] [4]

- Adult male hypogonadism
- Aging male syndrome (AMS)
- Androgen decline in aging male (ADAM)
- Low T syndrome
- Late-onset hypogonadism (LOH)
- Male climacteric
- Male senescence
- Partial androgen deficiency in the aging male (PADAM)
- Symptomatic late-onset hypogonadism (SLOH)
- T deficiency syndrome
- Testosterone deficit syndrome
- Viropause

At present, the term low T syndrome is commonly used in online communications and commercial settings. In the published literature, the term late onset hypogonadism/LOH is often used and refers *to an age-related decline in testosterone accompanied by symptoms including a reduction in a general sense of well-being, declining libido, and erectile dysfunction.*[5]

Other concurrent symptoms that may affect quality of life include changes in skin quality, hair loss, mood changes, depression, low energy, memory issues, and loss of physical strength and agility.[6]

For diagnostic purposes, researchers suggest using a minimum of three symptoms in conjunction with consistently low serum T. The European Male Ageing Study (EMAS) specifies diagnostic criteria for LOH as: [7]

- ✓ At least 3 sexually-associated symptoms
  - Erectile dysfunction, decreased morning erections, and decreased libido or sexual thoughts

- ✓ Reproducibly low serum levels:
  - Total T below 320 ng/dL (11 nmol/L)
  - Free T below 64 pg/mL (220 pmol/L)
- ✓ If total T drops below 231 ng/dL (8 nmol/L), LOH is considered "severe."[8]

The main causes of low testosterone in LOH:[9]

- ✓ Primary testicular failure
  - Low T, high luteinizing hormone (LH is a pituitary hormone that stimulates testosterone production)
- ✓ Secondary to hypothalamic-pituitary failure
  - Low T, low or normal LH
  - More common
  - Associated with obesity or chronic disease (metabolic syndrome, diabetes, cardiovascular disease, COPD, frailty)

Testosterone

Testosterone is a steroid androgen hormone synthesized from cholesterol.[10] Circulating testosterone is found in three different forms, mainly:[11]

~60-70%	Bound tightly to sex hormone binding globulin (SHBG)
~30-40%	Bound loosely to albumin
~2-3%	Free, unbound, active form

However, research notes that some circulating T is also bound to cortisol-binding globulin (CBG) and orosomucoid, binding proteins that help regulate transport, delivery, and availability of testosterone.[12]

In LOH, both total and free T levels can decline by ~1% per year, a rate affected by disease state, emotional stress, medication, obesity, and especially expanded waist circumference (abdominal obesity). Free T may have a more pronounced decline due to alterations in SHBG.[13]

A 1-2% decline in total serum T translates into an annual decline of ~3.2–3.5 ng/dL (0.110–0.121 nmol/L) after age 30.[14]

Prevalence

While the exact prevalence is unknown, some clinical studies suggest hypogonadism may affect ~39% of men 45 years or older, using total testosterone (TT) cutoff of less than 300 ng/dL (10.4 nmol/L), a level associated with reduced bone mineral density.[15]

However, using strict diagnostic criteria, data from the EMAS suggests an overall LOH prevalence of 2.1%, with increased prevalence as BMI and comorbidities increase. Prevalence is expected to change with advancing age:[16]

0.1% 40-49 years old

0.6% 50-59 years old

3.2% 60- 69 years old

5.1% 70-79 years old

Additional observations suggest further variations in the prevalence of LOH, especially when diagnostic criteria vary:[17]

- Massachusetts Male Aging Study (MMAS)
  - 5.6% overall prevalence, 18.4% in those over 70 years
- Boston Area Community Health Survey
  - 5.6% prevalence ages 30-79 years, increased prevalence over age 70
- Baltimore Longitudinal Study of Aging (BLSA)
  - 12% for men in their 50s
  - 20% for men in their 60s
  - 30% for men in their 70s
  - 50% for men in their 80s
- Testosterone trials with cutoff of less than 275 ng/dL (9.5 nmol/L)
  - 3.8% for men over 65

Odds ratios of having LOH increased significantly in the presence of[18]

Prostate disease	1.29
Asthma or COPD	1.4
Hyperlipidemia	1.47
Hypertension	1.84
Diabetes	2.09
Obesity	2.38

Biology and Physiology of Andropause

Serum T levels are at their maximum between age 25 and 30.[19] An observed decline after age 40 had traditionally been attributed to "normal aging." However, more contemporary research suggests that annual age-related decline is no more than 0.5% or less in healthy men, so LOH is not simply a phenomenon of aging.[20]

Physiologically, LOH and related declines in serum T may be associated with a decrease in hypothalamic gonadotropin releasing hormone, disruptions in androgenic negative feedback systems, or possibly a decrease in sensitivity and responsiveness of testicular tissue.[21]

Researchers hypothesize that reduced sensitivity of testosterone receptors may account for some of the symptoms of LOH. Decreased receptor sensitivity in the central nervous system could help explain the decline in sexual desire seen in LOH as well as the need for higher doses of T to achieve symptom relief in some individuals. Reduced sensitivity could also help explain why some individuals have LOH symptoms despite "normal" T levels.[22]

A decrease in serum albumin and an increase in SHBG will also decrease the amount of biologically active T available. Since SHBG levels tend to increase ~2.7% per year with age, a decrease in active T is anticipated.[23]

Increased conversion of testosterone to estradiol via increased aromatase activity is also observed with advancing age and may contribute to low T.[24]

Chronic metabolic disorders, including chronic inflammation, diabetes, cardiovascular disease, and obesity may reduce serum T by a factor of 1.5-3.6.[25]

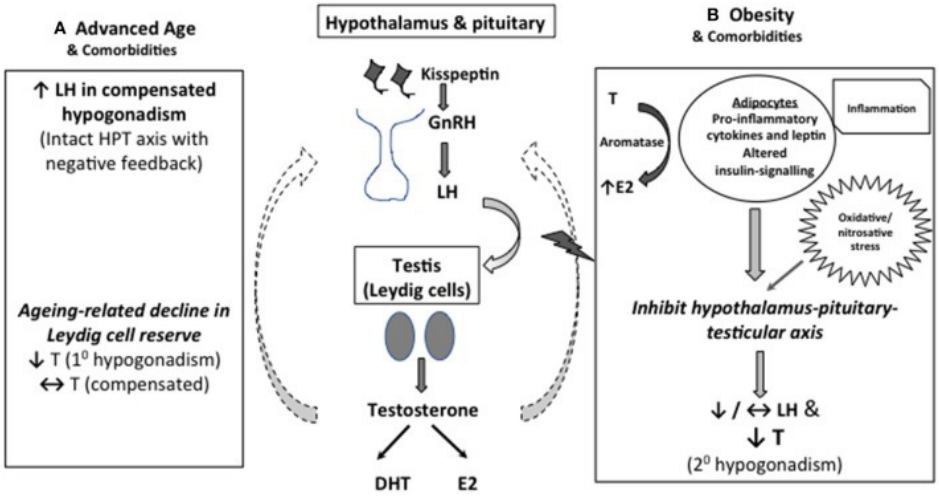
Diabetes appears to be a particularly significant factor in LOH and may accelerate its development.[26]

However, a vicious cycle may underlie the association as declining T levels lead to reduced insulin sensitivity and increased risk of glucose dysregulation and diabetes. The metabolic effects of testosterone include maintaining muscle mass and reducing visceral fat. Therefore, its decline can contribute to the development of metabolic syndrome.[27]

Acute conditions can reduce testosterone temporarily, these include stroke, myocardial infarction, gallbladder surgery, head trauma, severe burns, and even acute colitis.[28] It is important to repeat T testing to ensure that levels are chronically low before diagnosing LOH. Ideally two additional measurements should be taken at least 2-4 weeks after initial low T reading.[29]

Risk Factors for Low T and LOH:[30] [31] [32] [33] [34] [35] [36] [37] [38]

- ✓ Acute illness
- ✓ Asthma
- ✓ Diabetes mellitus
- ✓ Emotional stress
- ✓ Hemochromatosis
- ✓ HIV
- ✓ Hodgkin disease
- ✓ Hyperlipidemia
- ✓ Hypopituitarism
- ✓ Inflammatory arthritis
- ✓ Kidney disease, especially end-state on hemodialysis
- ✓ Lifestyle habits e.g., sedentary lifestyle, smoking, excess alcohol
- ✓ Liver disease, especially cirrhosis, fatty liver, NAFLD
- ✓ Medications may inhibit HPT axis (e.g., anti-depressants, glucocorticoids, opioids)
- ✓ Medications may inhibit T production (e.g., chemotherapy, GnRH analogs, mitotane, ketoconazole)
- ✓ Metabolic syndrome
- ✓ Nutritional deficiencies
- ✓ Obesity
- ✓ Obstructive sleep apnea
- ✓ Noise pollution (animal studies)
- ✓ Pesticide exposure
- ✓ Radiation exposure (ionizing and non-ionizing), testicular irradiation
- ✓ Rheumatoid arthritis
- ✓ Toxin exposure (e.g., chlorine, disinfectant by-products (DBPs)
- ✓ Variations in tissue sensitivity to testosterone



Mechanistic explanation for low serum T in middle-aged and older men.

(A) As Leydig cell reserve decline with aging, compensatory rise in luteinising hormone (LH) occurs to maintain circulating testosterone (T) concentrations (compensated hypogonadism). In more advanced state, elevated LH can no longer overcome the diminished testicular function, leading to overtly low T levels (primary hypogonadism). **(B)** Obesity is the predominant cause of functional suppression of hypothalamic-pituitary-testicular (HPT) axis in middle-aged and older men, manifesting as failure of LH response to low T (secondary hypogonadism). Multimorbidity is also associated with both primary and secondary hypogonadism, albeit to a lesser degree. Excess adiposity has been linked to altered insulin signaling, oxidative stress and increased pro-inflammatory cytokines and leptin levels, which act in concert to suppress the central HPT axis. Adipose tissues also express aromatase which convert testosterone to estradiol, especially in the inflammed state, exerting inhibitory effects on the HPT axis.

Source: Swee, Du Soon, and Earn H Gan. "Late-Onset Hypogonadism as Primary Testicular Failure." Frontiers in endocrinology vol. 10 372. 12 Jun. 2019, doi:10.3389/fendo.2019.00372 [R]

Overview of LOH

- ✓ In some men, testosterone production and availability decrease with advancing age.
- ✓ When the decline is associated with sexual symptoms, the phenomenon is described as late onset hypogonadism (LOH)
- ✓ Secondary LOH is more likely in those with obesity or chronic metabolic disorders such as diabetes and cardiovascular disease.
- ✓ Diagnosis is dependent on repeatedly low serum testosterone coupled with sexual symptoms.
- ✓ Prevalence increases with advancing age.
- ✓ EMAS criteria for diagnosis of LOH:
  - At least 3 sexually-associated symptoms
    Erectile dysfunction, decreased morning erections, and decreased libido or sexual thoughts
- ✓ Reproducibly low serum levels:
- ✓ Total T below 320 ng/dL (11 nmol/L)
- ✓ Free T below 64 pg/mL (220 pmol/L)

Manifestations of LOH can be categorized as:[39]	Fundamental causes of LOH include:[40]	Lifestyle and metabolic causes of LOH include:
✓ Cardiometabolic (metabolic syndrome, changes in body composition) ✓ Physical (gynecomastia, loss of hair, loss of height) ✓ Psychological (mood changes, altered sense of well-being) ✓ Sexual (erectile dysfunction)	✓ Aging affects gonad function ✓ Luteinizing hormone increases to compensate for reduced testosterone levels ✓ SHBG increases with age ✓ Obesity ✓ Aromatization of T to estrogen occurs in visceral adipose tissue ✓ Testosterone receptor sensitivity decreases	✓ Aromatization of testosterone into estrogen ✓ Obesity ✓ Poor nutrition ✓ Sedentary lifestyle ✓ Smoking, excess alcohol ✓ Stress overload

Identification of LOH

Prior to diagnosing andropause/LOH, certain conditions that may cause symptoms should be ruled out including:[41] [42] [43]

- ✓ Acute illness that temporarily reduces testosterone levels
- ✓ Adjustment disorder
- ✓ Adrenal insufficiency
- ✓ Alcoholism, excess alcohol intake
- ✓ Anxiety, depression
- ✓ Bipolar disorder
- ✓ Hyperprolactinemia
- ✓ Hypothyroidism
- ✓ Fatigue, various causes
- ✓ Growth hormone deficiency
- ✓ Lack of exercise or sleep
- ✓ Low self-esteem
- ✓ Medication use (e.g., antidepressants, antifungals, cimetidine, corticosteroids, digoxin, opioids, spironolactone)
- ✓ Midlife crisis
- ✓ Poor diet
- ✓ Smoking
- ✓ Stress
- ✓ Vitamin D deficiency

The presence of three or more symptoms related to sexual health (reduced libido/sexual thoughts, decreased morning erections, erectile dysfunction), should prompt further investigation into the possibility of late-onset hypogonadism. Repeated laboratory confirmation of low T in conjunction with symptoms is essential to diagnosis.[44]

It is important to investigate both symptoms and repeatedly low serum levels of testosterone as the occurrence of one without the other is unlikely to be genuine LOH.

Many symptoms reported in those with LOH may be due to other metabolic dysfunctions which should be investigated. For example, symptoms of fatigue, muscle weakness, and depression may be associated with hypothyroidism, warranting further evaluation of TSH and free T4 (free T3 may be recommended as well).[45]

Symptoms of low T reflect a wide-range of metabolic effects including[46] [47] [48] [49] [50] [51] [52] [53] [54]

- ✓ Anemia (normochromic, normocytic)
- ✓ Bone loss
- ✓ Cantankerous mood
- ✓ Cognitive decline
- ✓ Decreased body hair
- ✓ Decreased endurance
- ✓ Decreased vitality, energy
- ✓ Depression, depressed mood
- ✓ Declining libido
- ✓ Dyspnea on exertion
- ✓ Erectile dysfunction
- ✓ Fatigue
- ✓ Frailty
- ✓ Gynecomastia, breast discomfort
- ✓ Hot flushes, sweating
- ✓ Increased body fat
- ✓ Increased sweating
- ✓ Infertility
- ✓ Irritability
- ✓ Joint pain
- ✓ Loss of height
- ✓ Lack of motivation
- ✓ Loss of body hair
- ✓ Loss of muscle strength and physical agility
- ✓ Memory issues
- ✓ Metabolic dysfunction
- ✓ Muscle weakness
- ✓ Nervousness
- ✓ Osteopenia, osteoporosis, low bone mineral density
- ✓ Hypogonadal men are twice as likely to have osteoporosis than eugonadal men[55]
- ✓ Poor concentration and memory
- ✓ Reduced physical performance
- ✓ Reduced sense of well-being, self confidence
- ✓ Sarcopenia, muscle loss
- ✓ Skin changes
- ✓ Sleep disturbances, insomnia
- ✓ Sleepiness after meals
- ✓ Slowed beard growth
- ✓ Trouble at work
- ✓ Weight gain

Screening questions from the Androgen Deficiency in Aging Males (ADAM) questionnaire include [56] [57]

- ✓ Do you have a decrease in libido/sex drive?
- ✓ Do you have a lack of energy?
- ✓ Do you have a decrease in strength and/or endurance?
- ✓ Have you had a loss of height?
- ✓ Have you noticed decreased enjoyment of life?
- ✓ Do you feel sad and/or grumpy?
- ✓ Are your erections less strong?
- ✓ Have you noticed a recent deterioration in your ability to play sports?
- ✓ Do you fall asleep after dinner?
- ✓ Has there been a recent deterioration in work performance?

Because erectile dysfunction may be an early warning sign of cardiovascular disease, it should be followed up with a more in depth evaluation of cardiovascular risk.[58] Researchers note an association of erectile dysfunction with endothelial dysfunction and other factors related to blood vessel damage such as type 2 diabetes, hypertension, and cigarette smoking.[59]

Serial reductions in serum testosterone correlated significantly with specific disease states in a cross-sectional study of 1222 men over 40 years of age. Laboratory evidence of LOH was present in only 4.7% of symptomatic individuals without comorbidities but was found in 79% of symptomatic individuals with comorbidities.

Specific dysfunctions are associated with specific declines in T levels. In one cross-sectional study of 1222 men with LOH, significant decreases in serum TT and FT were observed with adiposity, arterial hypertension, COPD, and dyslipidemia compared to those men with LOH but none of the studied comorbidities.[60]

Characteristics of primary and secondary hypogonadism with organic versus functional causes.[61]

Hypogonadism	Primary	Secondary	Combined primary & secondary
Organic "Classical hypogonadism" Permanent testicular, pituitary, or hypothalamic dysfunction	Advanced age Cryptorchidism, myotonic dystrophy, anorchia, orchidectomy, orchitis Chemotherapy, radiation Klinefelter syndrome Testicular trauma or torsion	Idiopathic hypogonadotropic hypogonadism Iron overload syndromes Tumor or destructive disease of the hypothalamus or pituitary	
Functional Potentially reversible suppression of gonadotropin and testosterone levels	Medications (e.g., inhibitors of androgen synthesis) End-stage renal disease	Diabetes Excessive exercise Hyperprolactinemia Medications (e.g., opioids, anabolic steroids, glucocorticoids) Nutritional deficiencies Obesity, severe Sleep disorders (e.g., obstructive sleep apnea)	Aging comorbidities Alcohol abuse Organ failure (e.g., heart, liver, lung) Marijuana abuse Systemic illness

Overview: Identification of Andropause/LOH

- ✓ Other conditions should be ruled out before diagnosing LOH including alcoholism, mood disorders, hypothyroidism, medication use, midlife crisis, etc.
- ✓ Erectile dysfunction may be an early sign of cardiovascular disease and should be fully investigated.
- ✓ Non-sexual symptoms associated with LOH overlap with other conditions and can include decreased vitality, fatigue, irritability, lack of motivation, memory issues, muscle weakness, etc.
- ✓ Screening questionnaires help define and diagnose LOH
- ✓ The combination of symptoms and repeatedly low T is needed for diagnosis of LOH.
- ✓ Testosterone bioavailability decreases as binding globulins increase and tissue sensitivity decreases
- ✓ Primary and secondary functional hypogonadism is potentially reversible once the root causes are addressed. These include obesity, nutritional deficiencies, substance abuse, and medication use.

Laboratory Assessment and Biomarker Guideposts for LOH

Identifying and treating LOH is imperative due to its close association with morbidity and mortality.

Prospective data analysis of 2599 subjects in the EMAS revealed[62]

- 5-fold increased risk of all-cause mortality in those with severe LOH
- 2-fold increased risk of mortality in those with TT below 231 ng/dL (8 nmol/L) regardless of symptoms
- 3-fold increased risk of mortality and CVD mortality in those with 3 sexually-associated symptoms regardless of testosterone levels

Measurement of Total, Free, and Bioavailable Testosterone

It is important to measure T in the morning as levels peak at that time. Measurement between 7 and 11 am is customary.[63] Consistently testing levels at 8 am is prudent with repeat levels taken ~30 days apart.

It is also important to obtain a fasting level as food intake and glucose suppress T levels.[64] Even in individuals with normal glucose tolerance, a glucose load can reduce TT by 15-30%.[65] Serum T levels can also fluctuate seasonally.[66]

If serum levels are near low normal, or if SHBG levels are altered, assessment of free testosterone via equilibrium dialysis or calculation (using TT, SHBG, and albumin) is warranted. Direct analog-based free testosterone immunoassays may be inaccurate.[67]

Harmonized ranges for total T for healthy non-obese men 19-39 years old according to the CDC and adopted by the Endocrine Society:[68] [69]

264-916 ng/dL	9.2-31.8 nmol/L using 2.5th and 97.5 percentile
303-852 ng/dL	10.5-29.5 nmol/L using 5th and 95th percentile

Mean normal testosterone in young adults is ~627 ng/dL (21.8 nmol/L). Researchers suggest that a T level 2.5 standard deviations below the mean should define hypogonadism, i.e., a level of 319 ng/dL (11 nmol/L). Researchers note that levels below 300 ng/dL (10.4 nmol/L) are associated with reduced bone mineral density.[70]

Testosterone levels below those of a healthy young male adult in a symptomatic individual should be evaluated. Values of TT below 400 ng/dL (13.9 nmol/L) warrant further evaluation especially when coupled with symptoms that interfere with wellbeing. Once levels drop below 250 ng/dL, all-cause mortality risk doubles.[71]

Although individual levels can vary, total serum T may slowly decline with age from a mean of 600 ng/dL (20.8 nmol/L) at age 40 to 400 ng/dL (13.9 nmol/L) at age 80. Since testosterone bound to SHBG is not considered bioavailable, total levels can remain within normal range but symptoms may persist if SHBG is elevated. Assessment of free and bioavailable T and correlation with symptoms can help determine LOH on an individual basis.[72]

Free and Bioavailable Testosterone

As the fraction of testosterone tightly bound to SHBG increases, its availability to cells and tissues decreases.

Bioavailable testosterone (BAT) is considered that fraction not bound to SHBG. Technically, it includes free T and that bound to but easily dissociated from albumin, as well as that bound to CBG and orosomucoid. However, assessment methods define bioavailable T as free T plus albumin-bound T.[73] Free T can be difficult to measure accurately and is most often estimated through calculation using TT, SHBG, and albumin levels.[74]

Assessment of BAT is especially useful in subjects who are obese and/or 70 years or older. Researchers note a 35% reduction in TT is observed in men from age 25 to 75, and a 50-60% reduction in BAT is observed from 25 to 75.[75]

Methods of Testosterone Measurement Include: [76] [77] [78] [79]

Total T

- ✓ Immunoassay (correlated well with gold standard in EMAS cohort)
- ✓ Liquid chromatography-tandem mass spectrometry (LC-MS/MS) (gold standard)
- ✓ Mass spectrometry (MS)

Free T

- ✓ Calculation using TT, SHBG, albumin
- ✓ Direct immunoassays of FT are not accurate, not recommended
- ✓ Equilibrium dialysis (gold standard)
- ✓ Estimate using allosteric model, correlates with equilibrium dialysis method
- ✓ Free androgen index (FAI) is not recommended due to variations in SHBG
- ✓ Ultrafiltration method

Bioavailable T

- ✓ Ammonium sulfate precipitation
- ✓ Calculation using TT, SHBG, albumin
- ✓ Concanavalin A method

Calculators

- ✓ The International Society for the Study of the Aging Male free and bioavailable T calculator uses the Vermeulen formula.[80] http://www.issam.ch/freetesto.htm

Reference ranges for serum total and free T can vary due to lack of standardized assays, calibration variations, and differences in reference population. As always, it is important to utilize the same laboratory when repeating blood work.

If available, equilibrium dialysis is considered the gold standard for measuring free T, while precipitating out SHBG-testosterone using ammonium sulfate is considered the gold standard for measuring BAT.

Clinical Determination of LOH

LOH is likely if these minimum criteria are met, corroborated by EMAS: [81] [82] [83] [84]

- Three primary sexual symptoms (e.g., erectile dysfunction, morning erection, decreased libido)
- Total testosterone below 320 ng/dL (11 nmol/L)
- Free testosterone below 64 pg/mL (220 pmol/L)

A prospective observational study of 51 men 55-70 years old found that TT measurement and calculated free T (using TT, albumin, and SHBG) correlated best with gonadal function and clinical symptoms of androgen deficiency. Researchers discouraged the use of direct measurement of free T and/or calculation of free androgen index/FAI for diagnosing androgen deficiency in this age group, as neither measurement was a reliable reflection of free T.[85]

A cross-sectional observational study of 608 males over age 45 found that severity of symptoms correlated with low calculated free and bioavailable T but not with total T. Men with hypertension were noted to have free and bioavailable T levels that were significantly lower than men without hypertension. Researchers observed mean free T levels associated with LOH at levels higher than defined by EMAS which has a cutoff of 64 pg/mL (220 pmol/L):[86]

- ✓ 77.2 pg/mL (268 pmol/L) when AMS questionnaire scores were mild
- ✓ 69.8 pg/mL (242 pmol/L) when AMS scores were moderate to severe

However, some research suggests that certain thresholds of serum T may be associated with a specific set of symptoms. Results of a cross-sectional cohort study of 434 males aged 50-86 years old identified associations between symptoms and total serum T levels. Results were similar when calculated free T was applied:[87] [88]

Total testosterone		**Symptoms**
Below 432 ng/dL	15 nmol/L	Loss of libido or vigor (in 41% of subjects)
Below 346 ng/dL	12 nmol/L	Obesity, BMI greater than 30
Below 288 ng/dL	10 nmol/L	Depression, disturbed sleep, difficulty concentrating, type 2 diabetes
Below 230 ng/dL	8 nmol/L	Erectile dysfunction, hot flushes
Below 225 ng/dL	7.8 nmol/L	Loss of libido in 90% of subjects
Below 170 ng/dL	5.9 nmol/L	Loss of libido in 96% of subjects

Total testosterone levels of 175 ng/dL (6 nmol/L) or less should be further evaluated using MRI and advanced pituitary hormone assessments to rule out the possibility of organic versus functional hypogonadism.[89]

Although symptomatology can be significant, the European Male Ageing Study reserves the diagnosis of LOH for sexually-associated symptoms (i.e., decreased libido, poor morning erection, and erectile dysfunction) associated with a TT below 320 ng/dL (11 nmol/L) and a free T below 64 pg/mL (220 pmol/L).

Research suggests that sexual and physical symptoms may be present when TT is within normal range, but free T was low. Conversely, when free T was normal and TT was low (presuming low SHBG), sexual and physical symptoms were not present. Researchers suggest measuring free testosterone in men with conditions associated with altered SHBG and/or TT in the lower 200-400 ng/dL (7-13.9 nmol/L) range:[90]

According to the International Society for Sexual Medicine (ISSM) [91]

- ✓ SHBG should be evaluated following an initial low serum T in men who are older or obese.
- ✓ Altered SHBG can be anticipated in obesity, diabetes, chronic illness, elderly, especially when TT is in the low to normal range.
- ✓ Further evaluation is warranted if SHBG is elevated or if TT is between 230-345 ng/dL (8-12 nmol/L) in symptomatic individuals.
- ✓ Assessment of free or bioavailable T will provide valuable information about sufficiency of biologically active T.

In general, free or bioavailable testosterone should be measured when:[92]

- ✓ TT is 250-350 ng/dL (8.7-12.2 nmol/L)
- ✓ SHBG is decreased.
- ✓ SHBG is increased. Increased SHBG decreases tissue availability of testosterone.

Decreased SHBG associated with: [93] [94] [95]	**Increased SHBG associated with:**
Acromegaly	Aging
Androgen excess	Borderline total T 200-400 ng/dL (6.9-13.9 nmol/L)
Diabetes mellitus	Cirrhosis, hepatitis
Growth hormone excess	Estrogen use, elevated estrogen
Hypothyroidism	HIV disease
Insulin resistance	Hyperthyroidism
Liver disease	SHBG gene polymorphisms
Nephrotic syndrome	Use of some anticonvulsants
Obesity	
SHBG gene polymorphisms	
Use of glucocorticoids, some progestins, and androgenic steroids	

An epidemiological study of 2,588 men 40-80 years found an association between symptomatic LOH and levels of BAT and SHBG.[96]

Mean Values	**TT nmol/L**	**LH IU/L**	**FT nmol/L**	**SHBG nmol/L**	**BAT**
Case	13.99	8.28	0.45	52.01	4.85
Control	14.29	5.8	0.61	37.67	7.53

- ✓ Men with LOH and erectile dysfunction had an AMS score of 27 or greater, the level considered positive for LOH.
- ✓ Results demonstrated significant correlation between symptoms and serum levels of SHBG and BAT, but not between symptoms and TT or LH.
- ✓ There was an observed decrease in total and free T and an increase in SHBG as age increased.
- ✓ Researchers concluded that the strongest predictors of LOH symptoms and erectile dysfunction in this group was BAT and SHBG.

A population-based cross-sectional study of 965 men 40-80 years of age with AMS scores of 27 or greater found those with symptomatic LOH had lower levels of calculated free T, BAT, total cholesterol, and triglycerides, Levels of SHBG were significantly higher with a suggested 4.99 ug/mL (44.4 nmol/L) cutoff for diagnosing LOH in symptomatic individuals:[97]

The Hypogonadism in Males (HIM) study found that 38.7% of men 45 years or older had a TT of less than 300 mg/dL. Results indicated significant differences in SHGB, total, free, and bioavailable T in those with TT less than 300 ng/dL (hypogonadal) and those with TT of 300 ng/dL (10.4 nmol/L) or greater. Risk of hypogonadism increased 17% for every 10 year increase in age:[98]

Mean	Total T	Free T	Bioavailable T BAT	SHBG
Hypogonadal	245.6 ng/dL 8.52 nmol/L	47.9 pg/mL 166 pmol/L	86.1 ng/dL 3 nmol/L	4.9 ug/mL 43.7 nmol/L
Eugonadal	439.9 ng/dL 15.3 nmol/L	63.9 pg/mL 222 pmol/L	108.8 ng/dL 3.8 nmol/L	7.7 ug/mL 68.3 nmol/L

Different societies have proposed various cutoffs for the diagnosis of LOH[99]

Total T	Free T	Source
Men over 70 190 ng/dL 6.6 nmol/L Younger men 216 ng/dL 7.4 nmol/L	-	European Society of Australia 2016
264 ng/dL 9.2 nmol/L	-	Endocrine Society 2018
300 ng/dL 10.4 nmol/L	-	American Urological Association 2018
346 ng/dL 12 nmol/L	65 pg/mL 225 pmol/L	British Society for Sexual Medicine 2017
350 ng/dL 12.2 nmol/L	-	European Academy of Andrology 2020
350 ng/dL 12.2 nmol/L	65 pg/mL 225 nmol/L	European Association of Urology 2020
350 ng/dL 12.2 nmol/L	65-100 pg/mL 225-347 pmol/L	International Consultation for Sexual Medicine 2019
350 ng/dL 12.2 nmol/L	65-70 pg/mL 225-243 pmol/L	International Society of the Study of Aging Male 2015

Lab reference ranges

Quest male[100]

Total T	Adult	250-827 ng/dL	8.7-29 nmol/L
Free T			
	○ 18-69 yrs	46-224 pg/mL	160-777 pmol/L
	○ Over 69	6-73	21-253
Bioavailable T			
	○ 18-69	110-575 ng/dL	3.8-20 nmol/L
	○ Over 60	15-150 ng/dL	0.52-5 nmol/L
SHBG			
	○ 18-55	1.1-5.6 ug/mL	10-50 nmol/L
	○ Over 55	2.5-8.7 ug/mL	22-77 nmol/L

Labcorp male[101]

Total T	Adult	264-916 ng/dL	9-32 nmol/L
Free T, *calculated (best)*			
	○ 18-30 years	47.7-173.9 pg/mL	166-603 pmol/L
	○ 31-40	42.3-190	146-659
	○ 41-50	30.3-183.2	105-636
	○ 51-60	35.8-168.2	124-584
	○ 61-70	34.7-150.3	120-522
	○ 71-80	31.7-120.8	110-383
	○ 81-100	20.7-97.4	72-250
Free T, **direct**			
	○ 20-29 years	9.3-26.5 pg/mL	32-84 pmol/L
	○ 30-39	8.7-25.1	30-87
	○ 40-49	6.8-21.5	24-75
	○ 50-59	7.2-24	25-83
	○ Over 59	6.6-18.1	23-63
Bioavailable T		40-250 ng/dL	1.4-9 nmol/L
SHBG			
	○ 20-49	1.85-5.3 ug/mL	16.5-55.9 nmol/L
	○ Over 49	2.17-8.59 ug/mL	19.3-76.4 nmol/L
Free Androgen Index (Testosterone/SHBG Ratio)			
	○ 20-29 years	30-128	
	○ 30-39	24-122	
	○ 40-49	14-126	
	○ Over 49	18-82	

OptimalDX Male

Total T	700-1100 ng/dL	24-38.1 nmol/L
Free T	150-224 pg/mL	521-777 pmol/L
Bioavailable T	375-575 ng/dL	13-20 nmol/L
SHBG	3.37-4.5 ug/mL	30-40 nmol/L

Additional testing[102]

- Elevated LH and FSH are likely associated with primary hypogonadism.
- Low to low normal LH and FSH are likely associated with secondary hypogonadism.
- Age-related changes may be seen in other biomarkers though their significance to LOH has not been fully determined (e.g., estradiol, growth hormone, insulin-like growth factor-1, DHEA/S, thyroid hormone, melatonin).
- Assess FT or BAT if TT is in the low normal range or if alterations in SHBG are suspected:
    - Decreased SHBG in chronic illness, moderate obesity, diabetes, hypothyroidism, glucocorticoid use
    - Increased SHBG suspected in advanced age, cirrhosis, hepatitis, HIV, hyperthyroidism, estrogen use
- If TT is below 150 ng/dL (5.2 nmol/L), assessment of prolactin levels is recommended as well, in the event a prolactinoma is present.[103]

The European Male Ageing Study (EMAS) utilizes luteinizing hormone (LH) levels to categorize low serum testosterone and confirm that most have secondary hypogonadism with low to normal levels of LH. This category is primarily associated with comorbidities including visceral adiposity and general obesity.[104]

Primary hypogonadism/ testicular insufficiency	LH elevated, Testosterone below 303 ng/dL (10.5 nmol/L) LH greater than 9.4 u/L TT less than 303 ng/dL	Low annual incidence of ~0.2%, found in 2% of study cohort. Associated with poor baseline function, erectile dysfunction, decreased hemoglobin, comorbidities, and advanced age over 70. Persistently elevated LH indicates persistent Leydig cell failure
Secondary hypogonadism	LH normal/low, Testosterone below 303 ng/dL (10.5 nmol/L) LH 9.4 u/L or less TT less than 303 ng/dL	Annual incidence of ~1.6%, affects majority of cases ~85.5% Obesity is most significant risk factor, suppresses hypothalamus-pituitary-testicular (HPT) axis
Compensated primary hypogonadism	LH elevated, Testosterone above 303 ng/dL (10.5 nmol/L) LH greater than 9.4 u/L TT 303 ng/dL or greater	Present in 10% of study cohort. Some clinical features of hypogonadism despite maintaining normal testosterone levels.

Estradiol

Though considered primarily a female hormone, estradiol (E2) has important functions in men including prevention of body fat accumulation, limiting of vasomotor symptoms, and maintenance of bone mineral density and sexual function (in conjunction with testosterone).[105]

Though conversion of testosterone to estradiol tends to increase with age, levels of both hormones can decrease with age. Standard estradiol level in adult men is 39 pg/mL (143 pmol/L) or less.[106] However, levels of bioavailable estradiol below 11 pg/mL (40 pmol/L) may be associated with accelerated loss of bone density.[107] [108]

Obesity is associated with an increase in estrogen production in adipose tissue which in turn can inhibit pituitary luteinizing hormone release and testicular T release. However, low serum estradiol, along with low serum T and elevated SHBG, increases risk of non-vertebral fracture.[109] This balancing act exemplifies the importance of hormonal harmony in both men and women.

Investigation into the ratio of total testosterone to estradiol in 611 post-endarterectomy patients revealed that those with the lowest TT/E2 ratio had significantly higher[110]

- ✓ C-reactive protein: 2.81 v 1.22 ug/mL (27 vs. 11.6 nmol/L)
- ✓ White blood cell count: 8.98 vs. 7.75 10^9/L (especially higher neutrophils and monocytes)
- ✓ Atherosclerotic plaque neutrophils, IL-6, IL-6 receptors, plaque calcification
- ✓ BMI
- ✓ Risk of major cardiovascular events/MACE (MI, stroke, CVD death)
- ✓ Negative effects were worse in men with an elevated BMI (aromatase activity is high in white adipose tissue)

Laboratory evaluation

Measurement

- ✓ Testosterone should be measured in the fasting state in the morning between 7 and 11 am.
- ✓ Repeat levels should be taken 30 days apart
- ✓ Symptoms of LOH may persist with a “normal” TT level if SHBG is elevated
- ✓ Free testosterone should be measured using equilibrium dialysis or calculation using TT, SHBG, and albumin (most common), not direct analog-based immunoassays.
- ✓ Bioavailable T should be measured using ammonium sulfate or calculated using TT, SHBG, and albumin

Clinical Determination of LOH

LOH/Andropause is likely when[111] [112] [113] [114]

- ✓ Three primary sexual symptoms (e.g., erectile dysfunction, morning erection, decreased libido) are present along with laboratory confirmation
- ✓ Total testosterone below 320 ng/dL (11 nmol/L) (repeated 30 days apart)
- ✓ Free testosterone below 64 pg/mL (220 pmol/L)

Further evaluation

- ✓ Total T below 400 ng/dL (13.9 nmol/L) warrants further evaluation

- ✓ Free T should be evaluated when TT is 250-350 ng/dL (8.7-12.2 nmol/L) or in conditions of altered SHBG.[115]
- ✓ SHBG should be evaluated in obesity, diabetes, chronic illness, and the elderly, especially when TT is in the low to normal range.[116]
- ✓ Researchers suggest a cutoff for SHBG of 4.99 ug/mL (44.4 nmol/L) when diagnosing LOH.[117]
- ✓ Symptoms may coincide with specific serum levels of testosterone
- ✓

Additional testing

- ✓ Elevated LH and FSH are likely associated with primary hypogonadism
- ✓ Decreased or low normal LH and FSH are associated with secondary hypogonadism
- ✓ Estradiol has important functions in men though levels that are too high can feedback to decrease T release. Levels that are too low are associated with reduced bone mineral density.
- ✓ A low estradiol to testosterone ratio was associated with significantly higher CRP, WBC, and inflammatory atherosclerotic plaque.[118]

How do we treat and counteract andropause/LOH?

Once LOH and its causes have been identified, approaches to treatment include testosterone replacement therapy, non-hormonal natural medicine approaches, and lifestyle changes for those with obesity-related LOH.

Testosterone and hormonal therapy in andropause

Fortunately, testicular transplants became a thing of the past once testosterone was identified and made available in oral, transdermal, and intramuscular forms.[119]

Testosterone replacement tends to be the go-to treatment for symptomatic LOH and persistently low T once a full clinical workup is completed. Indiscriminate use of testosterone therapy is discouraged. Provision of exogenous T reduces pituitary release of FSH and LH leading to inhibition of testicular production of testosterone. This may have an effect on spermatogenesis and fertility.[120]

Endocrine Society guidelines for testosterone therapy emphasize reserving the diagnosis of hypogonadism for symptomatic men with consistently low fasting morning serum T levels.[121] It is important to rule out other causes of symptoms and assess for acute conditions that may reduce T levels temporarily.

As with any pharmaceutical or hormone treatment, Initiation of testosterone therapy should be a joint decision between patient and physician. The determination to go ahead should be fully informed, including a review of potential risks and benefits. The goal of testosterone therapy should be to maintain serum T within an optimal range. Restoring testosterone to levels found in “young men” reportedly induces a sense of well-being, enhances physical performance, and restores sex drive in some men.[122] [123]

Research confirms that increases in serum testosterone associated with T therapy positively correlate with improvements in quality of life, strength, physical function, body composition, mood, vitality, and overall well-being.[124]

Though the CDC ranges for T are broad at 303-852 ng/dL (10.5-29.5 nmol/L),[125] maintenance at the mid to upper range may be prudent and can be adjusted according to symptomology.

Testosterone replacement is available in several forms:[126]

- ✓ Tablets
- ✓ Patches
- ✓ Gels
- ✓ Implants
- ✓ Injections

In a randomized controlled trial of 39 men 50-70 years of age, testosterone gel therapy was found to improve body composition by significantly increasing lean body mass and significantly decreasing body fat mass in men with type 2 diabetes and bioavailable T levels of less than 210 ng/dL (7.3 nmol/L). Total, bioavailable, and free T increased, and SHBG decreased during the 24 week study period.[127]

Proceeding with Caution

Androgens stimulate prostate tissue, warranting the recommendation for periodic assessment of prostate specific antigen (PSA) and benign prostatic hyperplasia/BPH (digital rectal exam).[128] Serum testosterone and hematocrit levels, symptoms, adverse effects, and prostate cancer risk evaluation should be conducted during the first year of therapy.[129]

Subsequent monitoring is indicated to ensure efficacy and rule out adverse effects:[130]

- Assess PSA prior to therapy, 3-6 months following initiation, and assess regularly according to guidelines for prostate cancer screening.
  - If PSA increases above 1.4 ng/mL within the first year of testosterone therapy, obtain a urology consult.
- Maintain testosterone ~mid-normal range, assess 3-6 months after initiation
- Assess hematocrit 3-6 months after initiation and then annually.
  - Hold testosterone if hematocrit rises above 54% and re-evaluate before restarting therapy.
- Evaluate bone mineral density 1-2 years after testosterone initiation
- Benefits may include
  - Decreased fat mass, increased muscle mass and strength
  - Reduced risk of metabolic and cardiovascular dysfunction
  - Improved insulin sensitivity
  - Increased erythropoiesis, hemoglobin, and reticulocyte count
  - Possible improvement in bone mineral density of the lumbar spine
  - Possible improvements in cognitive function and mood
  - Improvements in libido and sexual satisfaction
  - No conclusive evidence that testosterone therapy increases risk of benign prostatic hypertrophy or prostate cancer, though these should be ruled out prior to initiation

Testosterone therapy is contraindicated in those with[131] [132] [133] [134] [135]

- ✓ Benign prostatic hyperplasia, severe or symptomatic
- ✓ Breast cancer
- ✓ Cardiac disease
- ✓ Congestive heart failure (uncontrolled)
- ✓ Elevated hematocrit
  - Greater than 48% at baseline
  - Greater than 50% if living at high altitude
  - 54% or greater during T therapy

- ✓ Hypertension, severe, uncontrolled
- ✓ International Prostate Symptom Score (IPSS) greater than 19
- ✓ Myocardial infarction or stroke (within past six months)
- ✓ Polycythemia
- ✓ Prostate cancer
- ✓ Prostate nodule or induration
- ✓ PSA level greater than 4 ng/mL or greater than 3 ng/mL in those at increased risk for prostate cancer without further workup
- ✓ Prostate symptomatology
- ✓ Sleep apnea, untreated
- ✓ Thrombophilia
- ✓ Urinary tract symptoms (severe)

Testosterone therapy [136] [137] [138] [139] [140] [141]	**Benefits**	**Risks, side effects**
	Improvements in: ✓ Anemia ✓ Body composition (decreased fat mass, increased lean body mass) ✓ Bone mineral density and strength ✓ Cognition ✓ Erectile function ✓ Libido ✓ Mood, depression ✓ Sexual satisfaction	• Acne • Aggression or violence, unexplained • Cardiovascular risk (odds ratio of 1.54, especially with large doses) • Erythrocytosis with increased hematocrit over 54% • Gynecomastia • Increased prostate volume • Increased PSA levels • Infertility • Male pattern baldness, sudden or worsening • Polycythemia • Sexual hyperactivity • Skin darkening
	For some, there may be no significant improvement in energy level, weight, mood, cognitive, or physical function	

Targets for T therapy vary between professional groups[142]

Mid-normal range for healthy young men	264-916 ng/dL 9.2-31.8 nmol/L	Endocrine Society 2018
Mid-normal range for young men	280-873 ng/dL 9.6-30 nmol/L	European Academy of Andrology 2020
Average normal range for young men	280-873 ng/dL 9.6-30 nmol/L	European Association of Urology 2020
Mid-normal for healthy young men	404-505 ng/dL 14-17.5 nmol/L	Canadian Medical Association 2015
Mid to upper range of normal for health young men	433-865 ng/dL 15-30 nmol/L	British Society for Sexual Medicine 2017
Middle third of normal	450-600 ng/dL 15.6-20.8 nmol/L	American Urological Association 2018
In lower part of range for eugonadal men	Not reported	Endocrine Society of Australia 2016
Within normal range	Not reported	International Society for the Study of Aging Male 2016

Testosterone Therapy Summary [143] [144]

- Avoid T therapy if any contraindications are present
- Natural preparations should be used, avoiding synthetic androgens
- Initiate therapy with short-acting (transdermal, oral, buccal) versus long-acting (intramuscular, subdermal) preparations
- Monitor red blood cell parameters, PSA, and digital rectal examination at 3, 6, and 12 months and then annually
- Monitor for progress and for development of contraindications

Aromatase Inhibitors

The use of aromatase inhibitors (AIs) in the treatment of low testosterone has been studied as well. Aromatase inhibitors reduce conversion of testosterone to estradiol and may help preserve serum levels of testosterone. However, drawbacks related to bone density must be considered.

Randomized, double-blind, placebo-controlled trials indicate that both transdermal T and aromatase inhibitors can help restore serum TT from below 350 ng/dL (12.2 nmol/L) to a mean of 473 ng/dL (16.4 nmol/L) or above. However, research suggests that aromatase inhibitors may be associated with a decrease in lumbar bone mineral density, highlighting the importance of estradiol to bone health.[145]

A 12-month randomized double-blind placebo-controlled trial of men aged 65-82 years who had a TT below 350 ng/dL (12.2 nmol/L) demonstrated:[146]

- Both 5 grams of transdermal testosterone gel and 1 mg of anastrozole aromatase inhibitor increased serum testosterone to greater than 500 ng/dL (17 nmol/L).
- An increase in lean body mass was seen in both treatment groups but the increase was only significant in the AI group.
- Lumbar spine BMD increased in the testosterone and the placebo groups but did not increase in the AI group.
- Researchers assert that conversion of testosterone to estradiol is vital to skeletal health.
- Increased BMD in the placebo group was attributed to supplementation with calcium and vitamin D that all participants received.

HCG

Human chorionic gonadotropin (HCG) is being explored as a therapeutic option in LOH. HCG appears to support testicular function including fertility; production of testosterone and

insulin-like factor 3; and hydroxylation of vitamin D. A 6-month trial of HCG versus T therapy in LOH revealed positive effects of HCG on 25(OH)D, estradiol, prostate volume, and hematocrit. Larger clinical trials are recommended.[147]

Addressing and Counteracting Andropause/LOH

Testosterone therapy should be based on clinically confirmed LOH and monitored closely for adverse reactions or contraindications.

- ✓ Exogenous testosterone may inhibit testicular production of T and affect spermatogenesis and fertility.
- ✓ Risks and side effects of T therapy must be reviewed with clients.
- ✓ Restoration of T to levels found in young men may promote significant improvements in physical function, body composition, and quality of life.
- ✓ A trial of T therapy is indicated if[148]
    - Total T is 230-345 ng/dL (8-12 nmol/L)
    - Free T is less than 65 pg/mL (225 pmol/L)
- ✓ Testosterone therapy is likely indicated if
    - Total T is 231 ng/dL (8 nmol/L) or less
    - Free T is 52 pg/mL (180 pmol/L) or less
- ✓ Use of aromatase inhibitors may help preserve serum T but reduce bone mineral density due to decreases in estradiol.

Lifestyle Approaches

Lifestyle factors play a role in the etiology and resolution of LOH, just as they play a role in some of the metabolic disorders that contribute to LOH, including type 2 diabetes and obesity.[149] Ideally, lifestyle improvements and weight loss when needed should precede testosterone therapy which then can be initiated in those with persistently low T.[150]

Lifestyle modifications are recommended for LOH individuals with obesity, metabolic syndrome, and type 2 diabetes.[151] Primary modifications include increased physical activity and maintaining a healthy diet and a healthy weight. In obese men, metabolic syndrome may be considered

a risk factor for low T. However, in non-obese middle-aged men with a BMI of less than 25, low testosterone itself may in turn be a risk factor for metabolic syndrome and therefore cardiovascular disease.[152]

Chronic lifestyle-related diseases, including cardiovascular disease, T2DM, and excess inflammation, increase risk of LOH by a factor of 1.5-3.6. A BMI of 30 or greater increases risk of LOH by a factor of 13, likely due to increased pro-inflammatory cytokines, leptin, increased oxidative/nitrosative stress, and disruptions in insulin signaling.[153].[154] Implementing lifestyle changes to address each of these related comorbidities would be most prudent. [155]

The Diabetes Prevention Program revealed that intensive lifestyle changes were effective in promoting weight loss and in increasing TT levels when compared to placebo or metformin intervention in men with a mean BMI of 32. Weight loss after 12 months in the lifestyle group was 17.3 pounds (7.87 kg) and TT levels increased by 33 ng/dL (1.15 nmol/L) with no changes in T in the placebo or metformin groups.[156]

It is possible to increase endogenous production of testosterone with healthy lifestyle choices, treatment of sleep apnea, discontinuation of interfering medications (e.g., opioids, carbamazepine), and weight loss. Although the International Society for Sexual Medicine (ISSM) does recommend non-pharmacological intervention for LOH, they also recognize that individual compliance can be low and T therapy may eventually be indicated.[157]

Diet and Nutrition

A healthy foundation replete in unprocessed foods, fruits, vegetables, legumes, whole grains, nuts, seeds, herbs, spices, and high-quality fats and protein can help maintain a healthy weight and reduce the risk of metabolic disorders that contribute to LOH.

An unhealthy diet, such as a Western-style diet high in processed foods and low in fruits, vegetables, whole grains, and fish, can have negative effects on men's sexual health and possibly fertility.[158]

In one pilot study of male obese secondary hypogonadism (MOSH) individuals with TT below 349 ng/dL (12.1 nmol/L), a balanced Mediterranean-style diet significantly increased TT within 2-4 months. Characteristics of the approach included:[159] [160]

- ✓ An abundance of fresh vegetables, fruit, extra virgin olive oil, protein, fish, legumes, grains
- ✓ A 170-250 kcal/d reduction from basal metabolic needs
- ✓ Protein 1.5 grams/kg ideal body weight
- ✓ 45-50% carbohydrate
- ✓ 30% fat
- ✓ 25-30 grams of fiber/day
- ✓ Less than 5 grams of sodium/day
- ✓ No alcohol
- ✓ Physical activity 150 minutes/week of mild intensity aerobic activity and/or 90 minutes high intensity activity at least 3 days per week.
- ✓ Goal was 10% reduction in weight from baseline

Micronutrient status is important to hormonal balance as well. Micronutrients being studied for their roles in testosterone metabolism include zinc, magnesium, boron, vitamin C, vitamin D, D-aspartic acid, and conjugated linoleic acid.[161] It remains practical to ensure optimal micronutrient status in those with LOH and its comorbidities, especially when micronutrient insufficiency is present.

A small study indicated that consumption of an organic diet was significantly associated with improvements in Sexual Health Inventory for Men (SHIM) scores before adjusting for age and BMI.

In those following an organic diet, hypogonadism was diagnosed in 3.3% versus 15.7% in those who did not. Intermittent fasting was also found to be beneficial, with hypogonadism being diagnosed in only 6.5% of those practicing intermittent fasting versus 15.5% in those who did not fast.[162]

Environmental toxins such as pesticides, phthalates, chlorinated pollutants, and other xenobiotics can act as endocrine disruptors, reduce testosterone, and contribute to hypogonadism and infertility.[163] [164] Exposure to them in the diet and the environment can have detrimental effects on health and hormone balance.

Weight Loss

It is generally accepted that most secondary hypogonadism caused by obesity can be reversed with weight loss. Indeed, weight loss in this population is considered first line therapy as the combination of low T and abdominal obesity may predict increased mortality risk.[165]

An interesting phenomenon occurs in obese hypogonadal men with insulin resistance. Elevated insulin inhibits SHBG secretion from the liver leading to a temporary increase in free T which can then be aromatized to estradiol in adipose tissue. This can create a negative feedback for the hypothalamic-pituitary-testicular axis. The inflammatory nature of obesity can also affect testosterone metabolism and contribute to hypogonadism. Research suggests that a weight loss of at least 10% be achieved in order to significantly increase circulating T and improve symptoms.[166]

The EMAS study established that weight gain and increased waist circumference can lead to a decrease in total and free T. Fortunately it also indicated that weight loss can increase both measurements, making weight and obesity a modifiable risk factor in LOH.[167]

A prospective follow up study of EMAS participants revealed that weight loss of 5% or more in obese men with LOH was found to improve serum T levels from 265 ng/dL (9.2 nmol/L) to 383 ng/dl (13.3 nmol/L). However, symptoms were not significantly improved in these individuals. Researchers note that these biochemical improvements were not as dramatic as with T therapy which can yield a 2-fold increase in serum T into the mid-normal physiological range in a 24-week period. Randomized controlled research also demonstrates improvements in physical strength, sexual function, and symptoms of depression with T therapy.[168]

Exercise

Exercise can improve T levels.[169]

- ✓ Acute exercise in conditioned individuals can induce significant increases in serum testosterone from pre- to post-exercise period.
- ✓ Moderate intensity resistance exercise induced an increase in young and middle-aged men.
- ✓ Exercise can increase growth hormone

A 12-week lifestyle modification program for overweight and obese men was associated with significantly increased T, with a subsequent significant decrease in central blood pressure. Intervention and results included:[170]

- ✓ Calorie restricted diet ~1680 Kcals/day with balanced macronutrients (50% carbs, 25% protein, 25% fat) and nutrition education regarding a healthy diet, vitamins, and minerals.
- ✓ Aerobic exercise incorporating walking or jogging 40-60 minutes three times per week
- ✓ Total and LDL cholesterol, triglycerides, and insulin decreased significantly.
- ✓ Serum TT increased from a mean of 355 to 380 ng/dL (12.3 to 13.2 nmol/L) respectively.

Plant-based Compounds

Plants are complex chemical factories, and many phytochemicals exert effects on testosterone levels via a variety of mechanisms, including modulation of gene expression.

Phytochemicals that appear to support testosterone metabolism include flavonoids apigenin, chrysin, luteolin, and quercetin. At the cellular level, these phytochemicals appear to promote entry of cholesterol into the mitochondria of testicular Leydig cells where increased testosterone production can take place. Some phytochemicals, including chrysin and apigenin, inhibit aromatase and conversion of testosterone to estradiol.

Food sources include: [171]

- ✓ Anthocyanidins found in berries, currants, grapes, tea, tropical fruits, and wine
- ✓ Apigenin and luteolin flavones found in celery, parsley, and thyme
- ✓ Catechin flavonoids found in apples, red wine, and tea
- ✓ Chrysin flavonoids found in chamomile, fruit bark, honey, mushrooms, propolis, and other plant extracts
- ✓ Naringenin and hesperidin flavanones found in citrus and plums
- ✓ Quercetin, myricetin, and kaempferol flavonols found in apples, berries, broccoli, cherries, onions, and tea

Adequate endogenous levels of relevant phytochemicals can be achieved with a robust intake of fresh fruits and vegetables. Also note that many phytochemicals and antioxidants increase in produce as it ripens, so crops should be harvested accordingly.[172] [173]

Medicinal Plants

Many plant-based herbal compounds have been studied for their effects on testosterone and symptoms of LOH. Although many have been used in traditional medicine throughout time, existing research may be limited or primarily conducted on animals. Researchers recommend more in depth high-quality studies before drawing conclusions in a 2014 review:[174]

- ✓ Astragalus root (Astragalus membranaceus) (limited research)
- ✓ Barrenwort (herba epimedium) (warrants further research)
- ✓ Chinese yam (limited research)
- ✓ Fenugreek (Trigonella foenum-graecum) (ongoing research)
- ✓ Ginkgo biloba (warrants further research)
- ✓ Ginseng
- ✓ Longjack root (eurycoma longifolia) (ongoing research)
    - o One month supplementation with 200 mg standardized extract highly significantly increased serum T in LOH subjects from a mean of 163 to 240 to ng/dL (5.66 to 8.31 nmol/L) and highly significantly improved symptoms.[175]
- ✓ Passionflower (Passiflora incarnate) (ongoing research)
- ✓ Tribulus terrestris (ongoing research)
- ✓ Velvet bean extract (mucuna pruriens) (warrants further research)

In China, Malaysia, and Indonesia, several plant-based compounds have been used traditionally to improve testosterone metabolism by facilitating its release from binding globulins or enhancing receptor engagement. Though researchers encourage more stringent evaluation via controlled

studies, the following compounds have been used traditionally with positive results:[176]

- ✓ Ashwaganda
- ✓ Epimedium Extract (Horny Goat Weed)
- ✓ Ginseng (Panax Ginseng)
- ✓ Lunasia amara Blanco (Sanrego)
- ✓ Muira Puama
- ✓ (Ptychopetalum olacoides)
- ✓ Nettle leaf
- ✓ Pimpinella alpina (Purwoceng)
- ✓ Pumpkin seed
- ✓ Pygeium
- ✓ Rye grass
- ✓ Saw palmetto
- ✓ Tongkat Ali (Eurycoma longifolia)
- ✓ Tribulus terrestris
- ✓ Wild oats, Avena sativa

The plant-based compound Trigonella foenum-graecum seed extract (fenugreek) was tested via a double-blind placebo-controlled study of 120 males with symptoms of androgen deficiency aged 43-75. Results demonstrated a significant decrease in symptoms determined by the Aging Male Symptoms Questionnaire. Sexual health and serum testosterone also increased after the 12-week treatment period. In this study:[177]

- ✓ Serum testosterone in the treatment group increased significantly from a mean of 355 ng/dL to 398 ng/dL, 12.3 to 13.8 nmol/L respectively.
- ✓ Free testosterone increased from a mean of 69.4 pg/mL (241 pmol/L) to 76 pg/mL (264 pmol/L).
- ✓ Treatment was well tolerated.
- ✓ Total sexual function score increased in the active group from 66.2 at baseline to 76.3 at week 12; the score in the placebo group went from a baseline of 57.8 to 57 at week 12.

Animal studies reveal a number of food components and supplements that positively impact T levels and may have applications in humans pending further research. The main mechanisms observed were:[178]

- ✓ Promotion of T-production, including regulation of LH (which stimulates T production) and testosterone synthase (which synthesizes T)
- ✓ Inhibiting enzymes that degrade T
- ✓ Alleviating testicular toxicity and T suppression, especially via antioxidant activity

Actions of food components on T metabolism (- = no data)

Promoting T-production / Inhibiting T-degradation / Alleviating testicular toxicity

Garlic + - +

Ginger + - -

Lactic acid bacteria + - +

Soybeans + - +

Amino acid + - +

L-arginine + - +

L-carnitine + - +

Linoleic Acid + - -

Selenium + - +

Vitamin (C/E) + - +

Zinc + - +

Beta-caryophyllene - + -

Chrysin - + -

Coenzyme Q10 + - +

Cordyceps Militaris + - -

Curcumin - - +

Cuscuta chinensis - - +

Emu oil - - +

Fish oil + - -

Fucoxanthin + - -

Geranylgeraniol + - -

Guarana + - +

Hazelnut + (Aged only) - -

Lutein - - +

Maca + - +

Melatonin + - +

Milk thistle seed and rosemary leaf + - -

Moringa + - +

N-acetyl-cysteine - - +

Oleuropein + - -

Piperine + - -

Propolis and Royal Jelly + - +

Resveratrol + - +

Rooibos + - -

Saccharomyces cerevisiae + - -

Taxifolin - - +

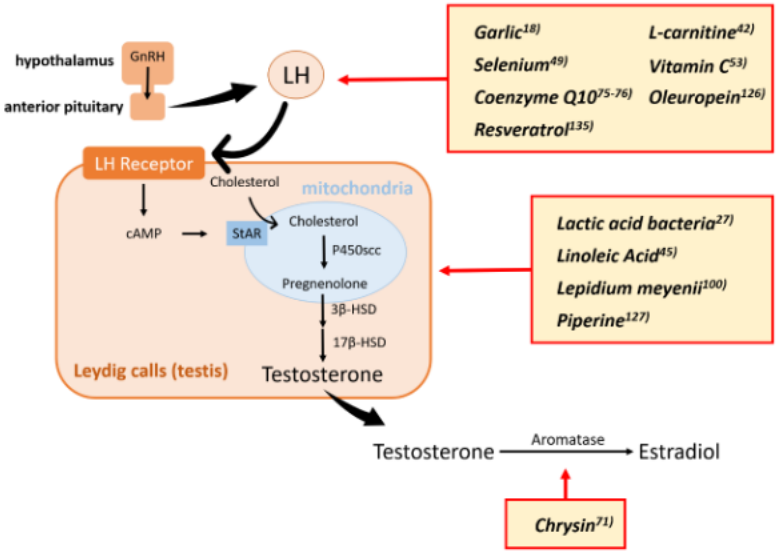


FIG. 1. Targets of testosterone production effected by food or supplements. GnRH: Gonadotropin-releasing hormone, LH: Luteinizing hormone, cAMP: Cyclic adenosine monophosphate, StAR: steroidogenic acute regulatory protein, 3β-HSD: 3β-hydroxysteroid dehydrogenase, 17β-HSD: 17β-hydroxysteroid dehydrogenase.

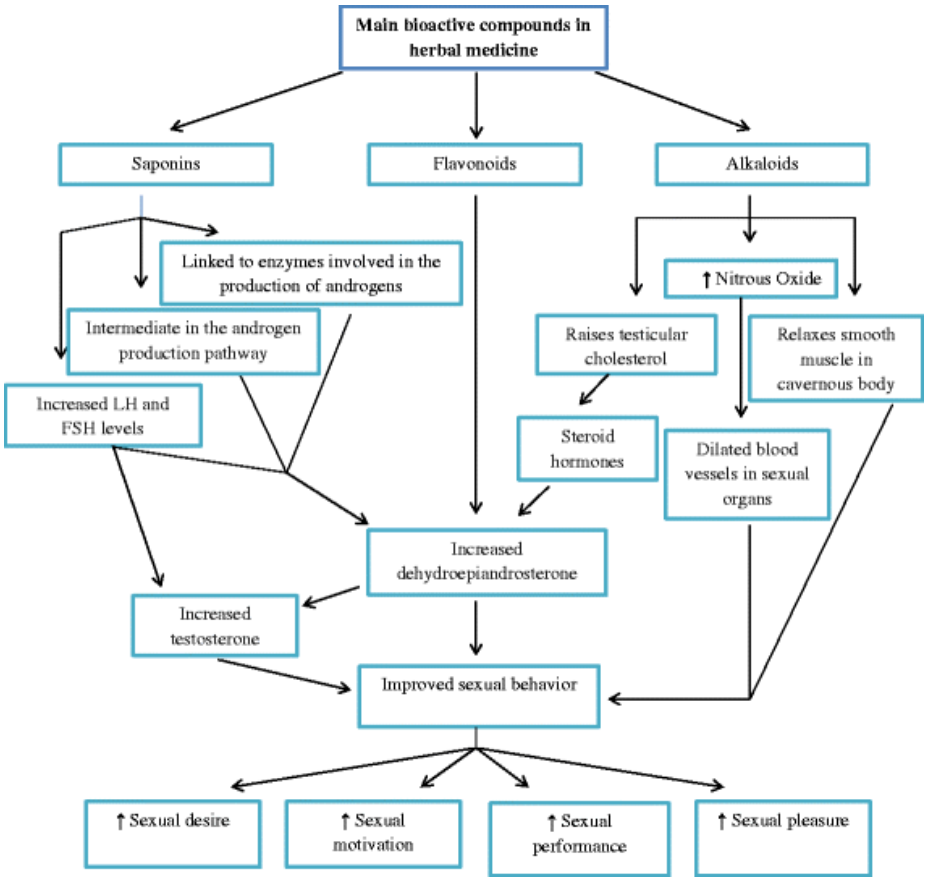
Source: Kataoka, Tomoya, Yuji Hotta, and Kazunori Kimura. "A Review of foods and food supplements increasing testosterone levels." (2021). [R] This is an open access article under the CC BY 4.0 license ([R])

Herbal Medicine Mechanisms of Action[179]

Intervention	Gender (n)	Action mechanism	Reference
T. terrestris	M (30)	A saponin that acts in the erectile function, when converted into Dehydroepiandrosterone (DHEA), which acts on ↑ intracavernous pressure.	[[R]]
E. longifolia	M (109)	↑ Testosterone → range of bioactive phenolic compounds: polypeptides, diterpenoids, alkaloids, quassinoids, and others.	[[R]]
Low-energy diet and low-fat, high-protein diet	M (31)	Diet ↑ testosterone and improves sexual function.	[[R]]
Maca root	F (17) M (3)	Effect on serum levels of gonadal hormone, LH, FSH, PRL, 17-alpha hydroxyprogesterone, TST, and 17-beta-estradiol.	[[R]]
Vigodana supplement consisting of *Rhodiola rosea* combined with vitamins and minerals	F (83) M (37)	Influences the metabolism of neurotransmitters, such as serotonin, dopamine, noradrenalin, acetylcholine; ↑ permeability of the hematoencephalic barrier.	[[R]]
Essential phospholipids	M (23)	↓ Number of patients with erectile dysfunction and loss of libido. ↑ Number and motility of spermatozoids and ↑ activity of enzymes involved in lipidic metabolism.	[[R]]
Alcohol	F/M (17000)	↑ Sexual excitement; ↓ sexual function, reproduction, performance, ejaculatory capacity, insemination, masculine hormones, and spermatogenesis. May also cause infertility.	[[R]]
Zinc sulfate	M (8)	Important in biosynthesis of RNA and DNA. Improves testicular function ↑ plasmatic testosterone, and ↑ FSH.	[[R]]

F female, *M* male

Adapted from da Cruz, Amanda Cássia, et al. "The action of herbal medicine on the libido: aspects of nutritional intervention in increasing sexual desire." Nutrire 42.1 (2017): 1-8. [R] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License ([R]), Does not include exclusively female research.



Source: da Cruz, Amanda Cássia, et al. "The action of herbal medicine on the libido: aspects of nutritional intervention in increasing sexual desire." Nutrire 42.1 (2017): 1-8. [R] This article is distributed under the terms of the Creative Commons Attribution 4.0 International License ([R]).

Overview: Lifestyle, Nutrition, and Naturopathic Approaches

Remember the LEMON mnemonic when evaluating dysfunction:

- ✓ **L** Lifestyle
- ✓ **E** Endocrine
- ✓ **M** Medical/metabolic
- ✓ **O** Observer-induced/iatrogenic
- ✓ **N** Nutritional

Important lifestyle modifications that support healthy testosterone metabolism include

- ✓ A healthy balanced Mediterranean-style diet that includes an abundance of vegetables, fruits, whole grains, legumes, nuts, seeds, herbs, spices, and fish, organic as available.
- ✓ Regular activity including 90-150 minutes of mild to moderate intensity exercise at least 3 days per week.
- ✓ Weight loss of at least 10% in obese men with LOH
- ✓ Micronutrient sufficiency, supplementation as needed
- ✓ Some plant-based compounds and herbs may have beneficial effects on T levels though additional research is indicated. The most promising compounds include
  - Longjack root (eurycoma longifolia)
  - Fenugreek seed extract (trigonella foenum-graecum)
  - Tribulus terrestris

Optimal Takeaways

Assessment and treatment of late onset hypogonadism should be a priority for men's health because of its close association with morbidity and mortality. It can interfere with function and quality of life and should be addressed as early as possible. LOH is most often associated with older age, obesity, co-morbidities, and general poor health.

Diagnosis depends on:

- ✓ Ruling out conditions with overlapping non-sexual symptoms
- ✓ Addressing acute and chronic conditions that can reduce testosterone levels
- ✓ Measurement of T in the fasting state between 7 and 11 am.
  - TT below 400 ng/dL (13.9 nmol/L) warrants further evaluation especially when coupled with symptoms that interfere with wellbeing.
  - Once levels drop below 250 ng/dL, all-cause mortality risk doubles.[180]
- ✓ Repeating measurements to confirm LOH and association with symptoms
- ✓ Official diagnosis of LOH includes:
  - At least 3 sexually-associated symptoms
    - Erectile dysfunction, decreased morning erections, decreased libido or sexual thoughts
  - Reproducibly low serum levels:
    - Total T below 320 ng/dL (11 nmol/L)
    - Free T below 64 pg/mL (220 pmol/L)
- ✓ Measure free or bioavailable testosterone when[181]
  - TT is 250-350 ng/dL (8.7-12.2 nmol/L)
  - SHBG is *decreased*, e.g., hypothyroidism, insulin resistance, diabetes, obesity, excess growth hormone, exogen androgens, liver disease, nephrotic syndrome
  - SHBG is *increased*, e.g., aging, liver disease, hyperthyroidism, elevated estrogen, anti-seizure medication

Testosterone Replacement Therapy

- ✓ Decisions should be made jointly between patient and practitioner, and contraindications must be considered.
- ✓ A trial of testosterone therapy is indicated if:[182]
  - Total T is 230-345 ng/dL (8-12 nmol/L)
  - Free T is less than 65 pg/mL (225 pmol/L)
- ✓ The goal of testosterone therapy is to restore or improve anabolic, psychological, and sexual symptoms.[183]
  - Testosterone therapy is likely indicated if
    - Total T is 231 ng/dL (8 nmol/L) or less
    - Free T is 52 pg/mL (180 pmol/L) or less

Lifestyle Modification

- ✓ A healthy whole-foods Mediterranean-style diet.
- ✓ Micronutrient sufficiency, supplementation as needed.
- ✓ Consider plant-based compounds that support testosterone metabolism.
- ✓ Healthy weight loss of at least 10% if needed.
- ✓ Regular activity including 90-150 minutes of mild to moderate intensity exercise at least 3 days per week.
- ✓ Minimize exposure to environmental hazards such as pesticides, phthalates, and other xenobiotics.
- ✓ Minimize stress exposure and maximize stress management

Additional references[184]

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