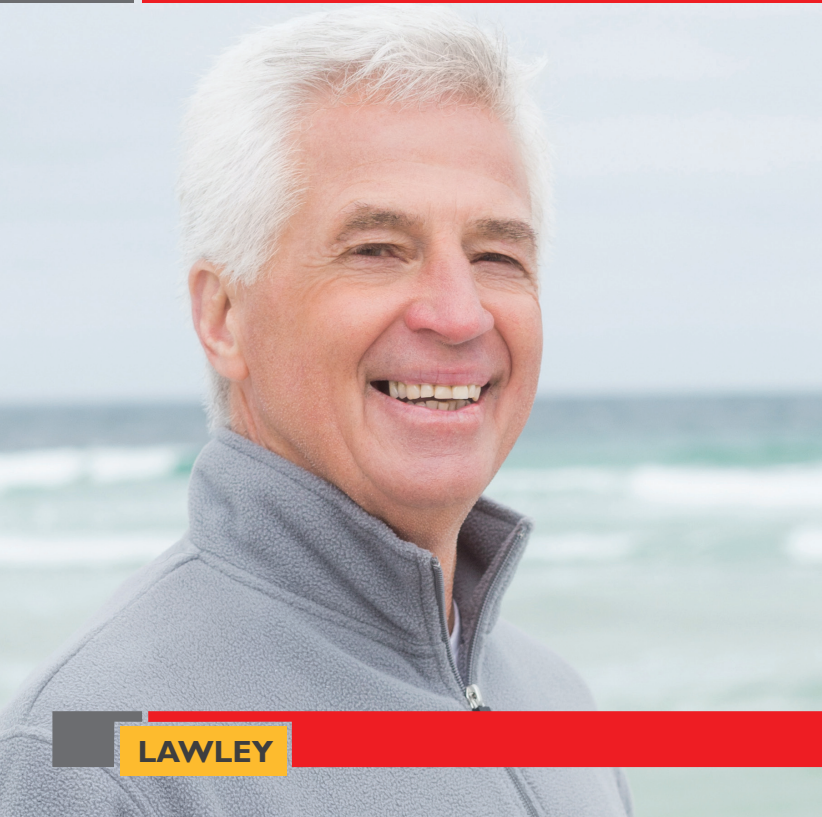


# Testosterone for Men

Information on the use of testosterone in males



**LAWLEY**

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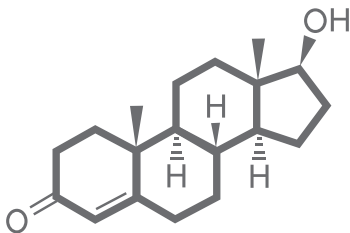
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## Testosterone Introduction

Testosterone is an essential hormone produced by both men and women. It plays a crucial role in the health and well being of our bodies.

Many myths and misunderstandings exist as to the activity and effects that hormones, including testosterone, exert on humans.

Testosterone supplementation for many years was considered a taboo area of medicine, due primarily to side effects following abuse by athletes and bodybuilders using super potent anabolic steroids. However, focus has shifted in recent years and the benefits of pure testosterone (not synthetic anabolics) for patients has become apparent with research.



Today, the variety of treatment options is greater, how testosterone works is extremely well understood and the newer testosterone treatments are more refined and tailored to meet individual requirements.

Not all aspects of testosterone are covered within this booklet. Further advice and information should be sought from your medical practitioner if areas of clarification are required. For health professionals and users requiring more technical information on testosterone use in men, please visit [www.lawleypharm.com.au](http://www.lawleypharm.com.au).

If you feel you have some of the symptoms mentioned in this booklet, please visit your doctor so he or she can investigate the cause and outline an appropriate course of treatment.

## What is Testosterone?

Natural testosterone is a term used to describe the hormone testosterone that is naturally produced by the testes in men.

Testosterone has long been recognised as exerting a significant effect on the human body.

For centuries, the testes have been identified as the primary source of sexual potency and virility in men. In the early 1900s the hormone testosterone was identified. With the advent of pharmaceutical chemistry, pure testosterone was first manufactured synthetically in the late 1930s.

Today, natural testosterone and synthetic analogues with testosterone-like actions are manufactured for pharmaceutical purposes from soya substrates in laboratories. Pure testosterone is not found in plants.

Testosterone is classified as an androgen. Androgens are a group of hormones that control masculine sex characteristics. They play a role in maintenance of systemic anabolic effects, particularly metabolism of salts, fluid balance and bone growth.

In men, testosterone exerts a positive effect on libido, sexual function, body shape and muscle mass, mood and energy levels.

Testosterone is crucial for the development and maintenance of the male sex organs and secondary sex characteristics. These include muscle bulk, facial and axillary hair, changes in fat distribution and deepening of the voice.

It also produces systemic anabolic effects which include retention of nitrogen, calcium, sodium, potassium, chloride and phosphate. This leads to an increase in water retention and bone growth.

Testosterone makes the skin more vascular (better blood flow) and less fatty.

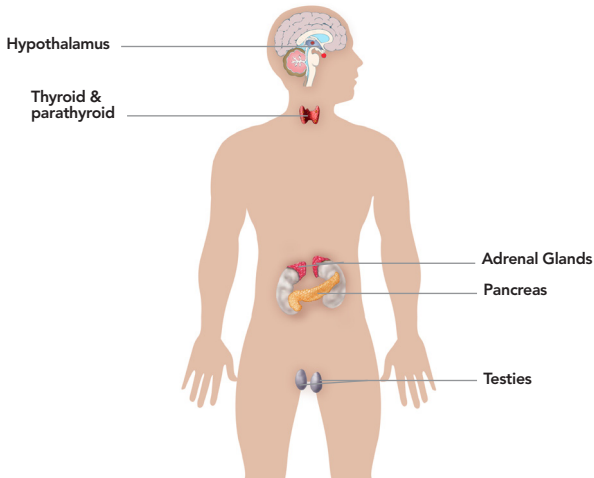
## Causes of Testosterone Deficiency

Male hypogonadism is the medical phrase used to describe men with a testosterone deficiency. The severity of the condition can vary from individual to individual.

Male hypogonadism is most frequently due to testicular damage, disease or genetic disorder (primary hypogonadism) e.g. Klinefelter's syndrome. It may also result from malfunctioning of the pituitary gland or hypothalamus in the brain (secondary hypogonadism).

Primary and secondary hypogonadism has a prevalence of 5 cases per 1000 men. This makes it one of the most common forms of hormonal deficiencies in men, yet only one in five men are diagnosed early in life.

Testosterone replacement therapy (TRT) effectively restores blood testosterone concentrations in men with hypogonadism to the normal levels of healthy young males.



Common causes for reduced testosterone production resulting in a deficiency state include:

### **Testicular Disorders (Primary Hypogonadism)**

- Klinefelter's syndrome (a genetic disorder)
- Cryptorchidism and defects of testis development (twisted or strangulated testes)
- Orchitis (Inflammation of the testes resulting in permanent damage)
- Orchiectomy (surgical removal of the testes)
- Toxin exposure (radiation, chemotherapy or radiotherapy, domestic, industrial or environmental poisons)
- Haemochromatosis (too much iron in the blood may cause testicular failure)

### **Brain Disorders - Hypothalamic-Pituitary Dysregulation (Secondary Hypogonadism)**

- Kallmann syndrome (a genetic disorder)
- Other genetic causes
- Pituitary gland tumour and treatment (surgery and/or irradiation)
- Haemochromatosis (too much iron in the blood can also affect the pituitary gland)
- Craniopharyngioma (benign tumour of the brain)

### **External Factors**

- Acute critical illness, burns, major trauma or surgery
- Drug use (e.g., opiates, glucocorticoids, anabolic steroids)
- Chronic disease and its treatment
- Alcohol abuse
- Smoking
- Ageing

Regardless of the underlying cause of the testosterone deficiency, the treatment is universally testosterone supplementation. Testosterone replacement therapy (TRT) aims to restore circulating testosterone concentration to within the normal healthy male range with the absence of symptoms. TRT safely and effectively resolves most, if not all, symptoms associated with testosterone deficiency.

## How is Testosterone Deficiency in Men Diagnosed?

There are two key parameters which determine if a man requires testosterone replacement – his testosterone blood level and the range and severity of his symptoms.

### Symptoms

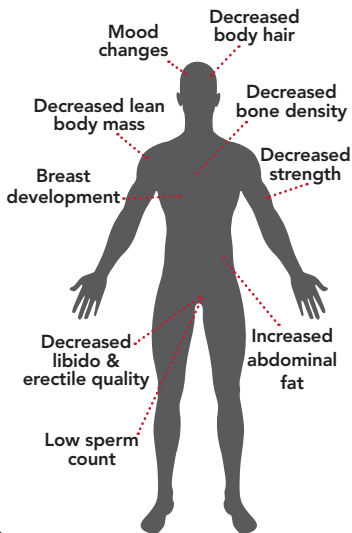
Doctors experienced in treating androgen deficiency will often use a questionnaire to assist in assessing the symptoms experienced by a patient.

Whether due to testicular failure, brain disorder or ageing, the signs and symptoms as a result of testosterone deficiency are consistent.

Testosterone deficient men may exhibit some or all of the following:

- Changes in mood (fatigue, depression, anger, lack of motivation, ill temper, poor memory, depressive feelings, and lethargy)
- Decreased body hair (feminisation)
- Decreased bone mineral density and possible resulting osteoporosis
- Decreased lean body mass and muscle strength
- Decreased libido and erectile quality
- Increased abdominal fat
- Rudimentary breast development (man boobs)
- Low or zero sperm in the semen

Gauging the severity of symptoms provides a yardstick for both patients and doctors to measure the success of testosterone treatment if initiated.



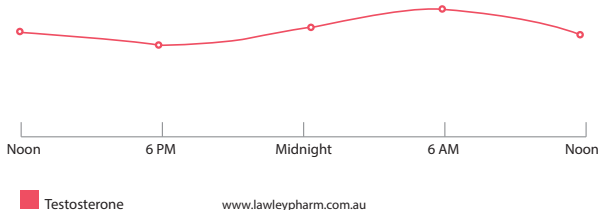
## Blood Testing

The measurement of testosterone levels in the blood provides a snapshot of what the testosterone status of the person is at the time of taking blood.

Testosterone secretion follows a diurnal rhythm in men. That is, it rises and falls over a 24 hour period. Testosterone production occurs during the night and early morning with levels highest on waking. This higher level of testosterone in the morning explains why healthy men generally experience an early morning erection. Serum testosterone levels slowly decrease during the day and are lowest in the late afternoon and early evening.



### Testosterone Circadian Rhythm in Men



Therefore, blood samples should preferably be taken in the morning when testosterone levels are at their highest. Individual variations in serum testosterone levels can occur due to time of day, medication usage, stress, illness or recent surgery.

The testes do not store testosterone. Once produced, testosterone is secreted into the blood stream where it is rapidly adhered to by the protein sex hormone-binding globulin (SHBG). SHBG is a transporter protein found in the blood. It acts as a carrier to move hormones around the body. Up to 99% of testosterone produced is bound to SHBG and inactive. Testosterone to which SHBG does not attach is the biologically available testosterone and is free to act on and enter into cells throughout the body. This “free testosterone” is very important in determining how testosterone has an impact upon the cells and tissue of the body.

Some doctors will measure only total testosterone levels (i.e. both free and SHBG bound testosterone). Measuring total testosterone does not take into account the SHBG levels. While not technically wrong, total testosterone measurement alone is not the most accurate representation of how much testosterone is free to act in the body. As a consequence, the total testosterone reference ranges commonly adopted by pathology laboratories for determination of “normal” and “low” testosterone are potentially misleading. This is because the

results do not take into account the effects of SHBG. SHBG is elevated with age, smoking, high alcohol intake, insulin and some medications.

It is always best to measure both the “total” and the “free” or “calculated free” testosterone in the blood if the lab has the technical capacity to do so. An alternative option which takes into account SHBG levels is the “free androgen index” or FAI. This is calculated by the total testosterone level in the blood divided by the SHBG level multiplied by 100. Pathology labs will automatically do this calculation and the result will be the FAI reading. Generally, in men the FAI is over 75.

The table on the following page provides a guide to the “normal” ranges in men for the most common components measured in blood.

These are guidelines only. Your laboratory adjusts its normal values for the local population it serves. It may use different units of measure.



		UNIT OF MEASURE	NORMAL ADULT MALE
Complete Blood Count (CBC)	Red Cells	million/mm <sup>3</sup>	4.7 to 6.1
	White Cells	million/mm <sup>3</sup>	5,000 to 10,000
	Haemoglobin	g/dl	14 to 18
	Haematocrit	%	42 to 52
	Platelets	mm <sup>3</sup>	150,000 to 400,000
	MCV	µm <sup>3</sup>	80 to 95
	MCH	pg	27 to 31
	MCHC	%	32 to 36
	Retics	% of total RBC	0.5 to 2
	Iron Studies	Serum Iron	µg/dl
Ferritin		ng/mL	123
TIBC		µg/dl	250 to 420
Thyroid Profile	T3	ng/dL	110 to 230
	T4	µg/dL	5 to 10
	TSH	µU/mL	1 to 4
Liver Profile	AST	IU/L	5 to 40
	ALT	IU/L	5 to 35
	ALP	ImU/mL	30 to 85
	Bilirubin	mg/dL	0.1 to 10
	Cholesterol	mg/dL	150 to 250
Kidney Profile	Creatinine	mg/dL	0.57 to 1.00
	BUN	mg/dL	7 to 20
Adrenal Profile	Cortisol	µg/dL	4.3 to 22.4
	ACTH	pg/mL	6 to 48

		UNIT OF MEASURE	NORMAL ADULT MALE
Sex Hormones	GH	ng/mL	0 to 8
	FSH	mIU/mL	1.4 to 18.1
	LH	mIU/mL	1.5 to 9.3
	HCG	mIU/mL	0
	Progesterone	ng/mL	<1
	Oestradiol	pg/mL	<54
	Prolactin	ng/mL	< 20
	Testosterone	ng/dL	375 to 1,200 USA
		nmol/L	10 to 35 AUS
	Free testosterone	pg/mL	50-175 USA
		pmol/L	175-600 AUS
	nmol/L	6 to 50	
	Free Androgen Index (FAI)		> 75

## Testosterone Replacement Therapy (TRT)

Testosterone replacement therapy is initiated by a medical practitioner when clinical complaints are accompanied by decreased testosterone levels and confounding factors have been excluded. The aim of therapy is to re-establish normal sexual functioning, general mental health (e.g., mood, mental acuity, clear thinking) and physical status (e.g., muscle mass, muscle strength, virilisation) appropriate to age by the most physiological and risk-free means available.

Testosterone replacement restores serum testosterone to physiological circulating concentrations in men with hypogonadism and reverses the symptoms of androgen deficiency. Thus, it is able to produce an improvement in libido, an increase in bone mineral density and an increase in muscle mass. Testosterone produces favourable changes

in body composition, with a reduction in fat mass and an increase in lean body mass; improvement in mood; correction of anaemia; and improvement in memory performance and cognitive status.

## Testosterone Treatment Options

Testosterone has been used for many decades for the treatment of testosterone deficiency in males.

Today, options for the treatment of testosterone deficiency include topical creams, gels and solutions, injections, transdermal skin patches and oral capsules. The testosterone creams, gels and solutions have largely replaced other forms due to the patient-friendly mode of application and flexibility with regards to dose.

### Topical Treatments

Testosterone creams, gels, solutions and patches required daily application and provide physiological replacement that mimic natural production with good results. Testosterone for men creams are available in 2% and 5% strengths. A 1% testosterone gel and a 2% testosterone solution is also available.

**Creams:** A 5% testosterone cream is available which is applied to the torso. Patients need to wear covered clothing on the site of application when in contact with partners or children to avoid passive transfer of residual testosterone from the skin.

A 2% testosterone cream is available which is applied scrotally.

Scrotal skin compared to the upper body is five times more receptive to testosterone because scrotal skin is



thinner, has a higher blood flow and low fat content. Additionally the risk of passive transfer to partners and children is significantly reduced.

**Gels and Solutions:** These products are applied to the upper body, chest, shoulders, torso and upper arms/armpit. Patients need to wear covered clothing on the site of application to prevent passive transfer of residual testosterone to others. Alcohol based gels and solutions cannot be applied scrotally.

**Patches:** Testosterone skin patches are applied at night time and generally produce a pattern of circulating testosterone blood levels similar to what is seen in healthy males. Patches must be applied daily and there is a relatively high incidence of adverse skin reactions sufficiently severe enough to lead to discontinuation of use.

## Injections

Testosterone injections are oil based and are given by deep intramuscular injection that may be painful. They come in two forms, short and long acting injections. Short acting injections result in high circulating concentrations of testosterone for several days after administration with a progressive fall to normal or subnormal levels over two to three weeks. The longer acting injections last up to three months. The rise and fall in testosterone blood levels with injections may be accompanied by fluctuations in symptoms – commonly known as the peak and trough effect.

## Oral Testosterone

Oral testosterone capsules are a less favoured replacement option. They can have wide fluctuations in circulation concentrations due to erratic absorption and sometimes gastrointestinal intolerance. The use of oral testosterone is generally confined to patients who are intolerant of other preparations.

## Potential Risks of Testosterone Treatment (Short and Long Term)

Testosterone should not be used in men with breast cancer or known or suspected prostate cancer.

Patients with severe unstable heart disease, severe liver disease or severe kidney disease are not recommended to use testosterone supplements unless under close medical supervision.

Before initiating TRT, your doctor should check for prostate abnormalities by means of a digital rectal examination and a blood test for Prostate Specific Antigen (PSA).

These tests will ensure complications of the prostate should not arise from testosterone usage.

Side effects can occur if testosterone is used in excessive quantities. These may include;

- Too frequent or persistent erections of the penis (priapism)
- Nausea and vomiting
- Swelling of the ankles
- Acne
- Headache
- Gynaecomastia (breast development)
- Increased appetite

### Prostate Disease

**A.** Benign prostatic hyperplasia (enlarged prostate): The use of testosterone will increase the size of the prostate, mainly during the first six months of treatment. Men with testosterone deficiency often have reduced prostate size and most increases

in prostate size result in a return to “normal” prostate volume. Deterioration of obstructive symptoms due to benign prostatic hyperplasia and urinary retention has not been reported at rates any higher than control subjects.

- B. Prostate cancer:** Published review articles have stated that on the balance of evidence there is no conclusive relationship between testosterone replacement therapy and prostate cancer incidence and progression. Prior to initiation all patients must undergo an examination to rule out pre-existing prostate cancer (digital rectal examination and estimation of serum PSA (Prostate Specific Antigen). Yearly follow up and twice yearly follow up for elderly and at risk patients (those with clinical or familial risk-factors) is essential. Regular monitoring of men on testosterone replacement therapy for early prostate cancer detection is beneficial compared to men not monitored at all.

Men with low testosterone levels may be at more risk of developing prostate cancer, for these men testosterone may have a protective effect on the prostate.

## Adverse Changes in Serum Lipids

Synthetic testosterone derivatives are associated with adverse changes in serum lipids. The use of pure testosterone is not associated with any changes to total cholesterol concentration, however there may be a reduction in HDL levels. Monitoring of blood lipids is recommended during treatment. There is no known interaction between testosterone and lipid lowering medications.

## Coronary Heart Disease

In 2013 there was a concern that testosterone administration increased the risk of cardiovascular disease.



In October 2014 a European Medicines Agency investigation on testosterone safety in men, particularly in relation to the heart, found there was not consistent evidence that the use of testosterone created an increased risk of heart problems in men with hypogonadism. The American Association of Clinical Endocrinologists (AACE) released a statement in 2015 announcing there is no compelling evidence that testosterone either increases or decreases cardiovascular risk. The AACE also recommends that men with low testosterone levels should have underlying cardiovascular risk factors addressed prior to therapy.



## Polycythaemia

A well know side effect of chronic testosterone administration is the occurrence of polycythaemia, with a rise in haematocrit (the percentage of whole blood composed of red blood cells). This is particularly common when the intra-muscular route (injections) is used and high serum testosterone levels are present for some weeks following each injection. Interestingly, men with hypogonadism tend to have anaemia and reduced hematocrit concentrations. In these men, testosterone replacement may lead to normalisation.

There is a direct relationship between testosterone dose and the incidence of polycythaemia. This effect, while not life threatening or severe, requires the need for regular monitoring (yearly) by a medical professional. If polycythaemia occurs, a reduction of the dose of testosterone is required and/or phlebotomy (drawing of blood) to reduce the red blood cell count and resolve the situation.

Please refer to the full Product Information and Consumer Medicine Information leaflet for further information.

## **Testosterone Check List**

- Identify symptoms and possible causes of low testosterone
- Consult your local medical professional
- Exclude other factors that may cause symptoms
- Have free and total testosterone levels checked to confirm testosterone deficiency
- Have prostate gland checked (PSA and physical exam)
- If it is determined by your doctor that you require treatment then generally a three month trial of testosterone is initiated and then reviewed.

Having regular monitoring of on-going treatment by your doctor is essential.

## About Lawley Pharmaceuticals

Lawley Pharmaceuticals is a privately owned pharmaceutical company which focuses on the transdermal administration of the naturally occurring hormones testosterone and progesterone. Founded in 1995 by pharmacist Michael Buckley, Lawley has grown to become a world leader in research and development of transdermal hormone preparations.

## Our Mission Statement

Lawley Pharmaceuticals provides the optimal delivery systems for the administration of the naturally occurring human hormones (testosterone, progesterone, oestradiol and oestriol) to counter endocrine deficiency states. Our philosophy is to use a natural hormone in preference to a synthetic hormone, when it is a viable clinical option. Our goal is to establish through evidence-based medical research, naturally occurring hormones as cornerstone treatments for diseases such as breast cancer, infertility, first-term miscarriage, male hypogonadism, post-partum depression and endometriosis. We have established strong links with centres of research excellence around the world and continue to push the boundaries of medical research.

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