Testosterone for Women

Information for women on the safe and effective use of the hormone testosterone

LAWLEY

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Testosterone Introduction

Women provide a far more complex sex-hormone picture than men, with three hormones contributing to the overall makeup of their hormonal balance.

Women produce oestrogen, progesterone and testosterone. The ovaries produce the bulk of oestrogen during the years leading up to menopause and substantially less post menopause.

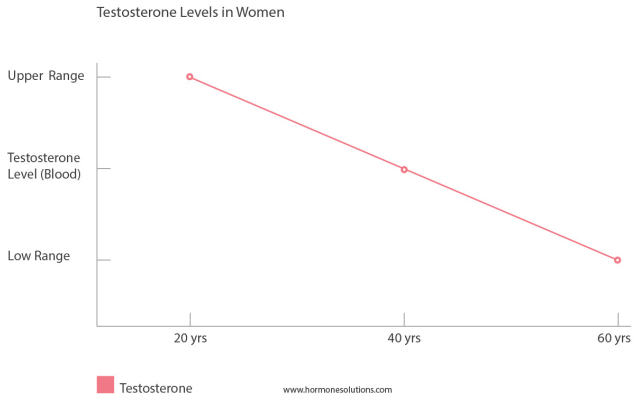
During the menstrual years, progesterone is produced once ovulation has taken place. Progesterone ceases to be produced when ovulation stops at or before the onset of menstruation ceasing and the menopause.

Testosterone in women is produced by the ovaries and adrenal glands on a continual basis. Testosterone blood levels are at their highest around age 20 and decline steadily with time. At the age of 40 a woman's serum testosterone levels are approximately half what they were at age 20. This level continues to fall with age.

Testosterone is vital in the preservation of bone, for its positive effect on libido and for maintenance of energy levels.

Supplementing small amounts of testosterone in women experiencing symptoms of testosterone insufficiency results in increased energy, improved libido and sexual response, and clarity of thought for many patients.

In the last decade there has been increased interest in administering low doses of testosterone to postmenopausal women, with reduced desire and sexual motivation, especially when this causes personal distress. The use of testosterone to manage low libido in women has been extensively reviewed in medical literature.



What is Testosterone?

Testosterone is a hormone naturally produced by the testes and adrenal glands in men and the ovaries and adrenal glands in women.

Testosterone is not produced anywhere in the plant kingdom. Testosterone has, for over 80 years, been recognised as exerting a significant effect on the human body.

With the advent of pharmaceutical chemistry, pure testosterone was first manufactured synthetically in the late 1930s. Today, testosterone and synthetic analogues with testosterone-like actions are manufactured for pharmaceutical purposes from soya or wild yam substrates.

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

Testosterone plays a significant role in sexual function (motivation, desire, thoughts, fantasy, arousal and orgasm), self-esteem, energy levels, metabolism, mood and emotions.

The amount of testosterone produced by women is 5-10% that of men and does not have a strong masculinising effect, yet it plays a pivotal role in sexuality and metabolic function.

History of Testosterone Use in Females

There is universal acceptance amongst reproductive endocrinologists, gynaecologists, sexual health physicians and those specialising in the area of women's health that female sexual dysfunction (FSD) affects a substantial proportion of women.

FSD has significant psychological ramifications and can adversely impact social and personal relationships. Various studies indicate between 30-43% of women aged between 18 to 59 years experience some degree of sexual dysfunction. Of these, 18-22% list low libido as their primary symptom.

Classifications and the defining of criteria for sexual dysfunction in women are well established. Validated assessment scales and questionnaires, such as the Female Sexual Function Index (FSFI), have been developed to assist with the diagnosis and monitoring of management regimes for sexual dysfunction.

Female sexual dysfunction is a multifactorial condition requiring careful evaluation. Treatment may involve several management strategies.

The hormonal profile of a patient is only one part of the assessment to determine the origins of sexual dysfunction.

Testosterone is a vital component of female sexuality, enhancing desire to initiate sexual activity and intensifying the response to sexual stimulation. It is associated with greater well-being and increased energy and vitality. Testosterone also plays a part in reducing anxiety and depressive feelings.

Surgically menopausal women (hysterectomised women with ovaries removed) and women with premature ovarian insufficiency (POI also called early menopause) are among populations most likely to experience low testosterone levels. This is characterised by blunted or diminished motivation, persistent fatigue and lethargy, decreased sense of personal well-being, low-circulating serum testosterone levels and low libido.

In contrast to oestrogen, serum testosterone levels do not fall precipitously at the time of menopause, but rather decline with age.

Early scientific evidence from the 1940's and 1950's showed testosterone was the libido-enhancing hormone in the human female.

In the mid-1970's, the vital role of the ovary in testosterone production was established. Subsequent research has recognised sexual function declines following oophorectomy (surgical removal of the ovaries). Additional research has found administration of testosterone reverses the decline in sexuality experienced after oophorectomy.

Prior to 2000, the majority of medical research conducted on testosterone use in women focused on testosterone implants and injections. While therapeutically effective these dose forms had significant shortcomings when used in women.

Because testosterone implants and injections are formulated for use in men they produce extremely high serum testosterone levels in women, even when administered at reduced doses. At high levels, testosterone has the potential to cause side effects including masculinisation, hirsutism (body hair growth), acne and voice changes.

Many women who suffer from loss of libido date their symptoms to removal of their ovaries (oophorectomy) and/or uterus (hysterectomy).

Removal of the ovaries in both pre and postmenopausal women results in an immediate 50% or more reduction in circulating serum testosterone levels.

Standard medical practice over the past 40 years has been to supplement women with oestrogen after removal of the ovaries, but ignore the hormones testosterone and progesterone.

Oestrogen therapy alone usually does not restore lost libido in oophorectomised women. Medical studies comparing oestrogen alone versus oestrogen plus testosterone have shown a significant improvement in energy and libido with the combined treatment.

Combination therapy did not show an increase in side effects. Additional medical trials have also shown testosterone has an additive effect on bone density when combined with oestrogen – a very important consideration for prevention of osteoporosis.

The problem of reduced libido and unexplained fatigue is not confined to women who have undergone surgical removal of the ovaries.

Pre and postmenopausal women with intact ovaries can also have low testosterone levels and experience the same symptoms of low sexual desire and lethargy as oophorectomised women. Small doses of testosterone can result in significant improvements in quality of life and sexual fulfilment for these women.

Currently there is no female-specific testosterone product for the management of any form of female sexual dysfunction anywhere in the world except Australia.

In many countries this has lead to male-approved testosterone products prescribed to women in reduced doses. This is common place by doctors around the world - a practice called "off-label" usage.

Causes of Testosterone Deficiency

- Disruption to Testosterone Production
- High Sex Hormone-Binding Globulin (SHBG) Levels
- Oestrogen Tablets and Oral Contraceptives
- Non-Hormonal Drug Therapies

Disruption to Testosterone Production

When areas in the body responsible for directly or indirectly producing testosterone (the ovaries, the brain and the adrenal glands) are diseased or compromised, the result is a significant reduction in overall testosterone levels.

If both ovaries are removed (bilateral oophorectomy) or the ovaries fail for whatever reason, there is an immediate 50% reduction in serum testosterone levels.

If the adrenal glands are removed (adrenalectomy) there is also a 50% reduction in testosterone levels.

If certain areas of the pituitary gland in the brain are affected by disease or damaged (hypopituitarism), the chemical messengers that stimulate the adrenals and ovaries to produce testosterone are affected. This can result in as much as a 100% reduction in testosterone production.

High Sex Hormone-Binding Globulin Levels

Sex hormone-binding globulin (SHGB) 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 by the body is bound to SHBG. Once testosterone is bound to SHBG it is inactive and unable to enter cells.

Testosterone to which SHBG does not attach is biologically available or 'free' testosterone and is free to act on cells throughout the body. At present, direct assay measurement of free T is highly unreliable for the female range.

The Free Androgen Index (FAI) is a mathematical calculation which determines the percentage of testosterone relative to level of SHBG and is a useful assessment tool for determining whether there is sufficient biologically available testosterone.

Because SHBG has such a significant effect on testosterone, it is essential SHBG levels be considered when evaluating testosterone blood tests. High SHBG will result in free testosterone being low, hence a potential underlying cause of lowered energy and libido. For more information on hormone blood testing, see pages 17-20.

Factors which increase SHBG and therefore lower FAI and free T.

- Oral oestrogen (including oral contraceptives, HRT tablets)
- Thyroxine tablets
- Increasing age
- Alcohol
- Smoking
- Some medications e.g. phenytoin, opiate pain killers.
- Pregnancy
- Reduced liver function

Oestrogen Tablets and Oral Contraceptives

There is a very close relationship between the hormones testosterone and oestrogen. The most common form of oestrogen supplementation used in hormone replacement therapy (HRT) and for oral contraception (the Pill) is the oestrogen tablet. Taking oral (by mouth) oestrogen increases the blood levels of sex hormone-binding globulin (SHBG) as it is metabolized by the liver. SHBG binds to testosterone circulating in the blood and reduces the 'free testosterone'. This reduction potentiates the chance for women to experience signs and symptoms of low testosterone.

There is no effect on SHBG levels with the use of an oestrogen patch or topical oestrogen gels, due to the different route of administration (via the skin) because this by-passes the liver.

If a woman is using oral hormone therapy or an oestrogen-based 'Pill' and experiencing low sexual desire or unexplained lethargy/fatigue, it is advisable to change to a non-oral dosage form of therapy. This will reduce SHBG levels in the blood, freeing up testosterone. This increase should result in an improvement of symptoms. If not, then testosterone therapy can be considered.

Non-Hormonal Drug Therapies

The use of certain medications is not directly linked to testosterone production, however, they are still an important consideration in determining causes of decreased sexual desire.

Medications which may interfere with sexual desire include:

MEDICATION	USE
SSRI's, tricyclics	Depression
Oral oestrogen	Oral contraceptive pill, HRT
Clonidine	Hot flushes
Medroxyprogesterone acetate (MPA)	Contraception, HRT
Spironolactone, cyproterone acetate	Hirsutism
Danazol	Endometriosis
Benzodiazepines	Anxiety, insomnia
Beta blockers	Hypertension
H2 antagonists	Oesophageal reflux
Ketoconazole	Vulvo-vaginal candidiasis
Gemfibrozol	Hyperlipidaemia

Under no circumstances should patients change or cease taking medications without the consent of their doctor. If a patient is taking one or more of these medications and experiencing a lowered sexual desire, he or she should consult their medical practitioner.

Signs and Symptoms of Low Testosterone

In 2002, many of the world's leading medical researchers and clinicians in the areas of endocrinology, gynaecology and sexual health met at Princeton University, in the USA. They produced a document entitled "The Princeton Consensus Statement". This document provided a definitive classification of female androgen insufficiency.

The androgen-insufficient female was defined as having:

- Diminished sense of well-being, dysphoric mood and/or blunted motivation
- Persistent, unexplained fatigue
- Sexual function changes including decreased libido, sexual receptivity and pleasure
- (Potential) bone loss, decreased muscle strength and/or changes in cognition/memory

The Princeton Statement set these symptoms against a background of women having adequate oestrogen levels, testosterone blood levels being in the lower range of normal healthy females and the ability to exclude other causes that could bring about their symptoms.

In October 2014 the Endocrine Society (USA) published guidelines for the use of androgens in women. This document provided clinicians with a clinical practice road map for the use of testosterone in women based upon the best available scientific evidence.

More recently (September 2019) the Global Consensus Position Statement on the Use of Testosterone Therapy for Women was published which provides the most comprehensive summary of the medical evidence for the use of testosterone in women. It provides guidance as to which women might benefit from testosterone therapy, identifies symptoms, signs and conditions for which evidence does **not** support the prescribing of testosterone, explores areas of uncertainty, and identifies any prescribing practices that have the potential to cause harm.

This comprehensive document has been endorsed by over 14 of the world's most prestigious and authoritative medical societies, associations and colleges.

The international panel that authored the Statement concluded the only evidence-based indication for testosterone therapy for women is for the treatment of hypoactive sexual desire dysfunction (HSDD).

The World Health Organisation International Classification of Disease (ICD-11) definition for HSDD (updated in 2018) states:

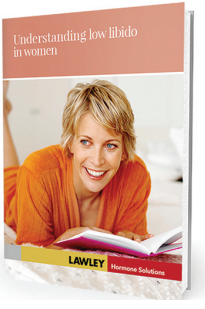
Hypoactive Sexual Desire Dysfunction is characterised by absence of marked reduction in desire of motivation to engage in sexual activity as manifested by any of the following:

1. *reduced or absent spontaneous desire (sexual thoughts or fantasies):*
2. *reduced or absent responsive desire to erotic cues and stimulations: or*
3. *inability to sustain desire or interest in sexual activity once initiated.*

The pattern of diminished or absent spontaneous or responsive desire or inability to sustain desire or interest in sexual activity has occurred episodically or persistently over a period of at least several months, and is associated with clinically signficant distress.

Other women, for various reasons, have lower than normal testosterone production even without removal of the ovaries. Their symptoms are no different to those listed above.

Theses issues are covered in greater detail in the booklet Understanding Low Libido in Women.



Testosterone for Women – Treatment

The majority of female patients with symptoms of low testosterone exhibit reduced sexual drive and/or unexplained lethargy and fatigue. They may also experience altered mood.

Management requires a multidisciplinary, integrated approach. This should be co-ordinated by a suitably trained medical practitioner.

- Specific medical conditions such as iron deficiency, abnormal bleeding, diabetes, depression and thyroid disease should be addressed before considering hormonal therapies.
- Lifestyle changes such as exercise, smoking, alcohol intake and weight loss need to be reviewed.
- Vaginal lubricants provide symptomatic relief for vaginal dryness and dyspareunia (difficult or painful sexual intercourse). Localised oestrogen pessaries, vaginal tablets, creams and gels can also be of great assistance.
- Pelvic floor physiotherapy will improve vaginal muscle tone, muscle associated with orgasm and in managing incontinence.
- Alteration of prescribed medications which may interfere with sexual function, if appropriate. Special attention should be paid to oral hormone replacement therapy (HRT), oral contraceptives and antidepressants. See the table under Non-Hormonal Therapies on page 12.

A medical practitioner's assessment of a patient must include:

Medical History Including Sexual History

It is very important for your doctor to be skilled in discussing, understanding and managing problems associated with sexual matters. In terms of obtaining your sexual history, it is vital your doctor knows his or her limits. If your doctor has little or no training in sexual counselling a referral to a trained sex counsellor is recommended.

A doctor should:

- Not be judgemental due to his or her own sexual prejudices or "hang-ups"
- Ensure the patient understands the principle of doctor-patient confidentiality
- Be sensitive and optimistic when dealing with relationship issues
- Encourage consultation with partner present
- Allow extended time for consultations
- Understand problems may not be revealed without specific enquiry
- Understand sensitive and embarrassing issues may not be readily volunteered

Examination

It is important a general "good female health" check be undertaken by your doctor.

Routine screening should include: a mammogram, a Pap smear, testing of cardiovascular parameters, a fasting blood glucose test, a serum thyroid stimulating hormone (TSH) level test, a full blood examination and iron studies.

Further investigations of specific medical disorders such as abnormal bleeding, breast lump(s), incontinence and osteoporosis are essential before any consideration of testosterone treatment.

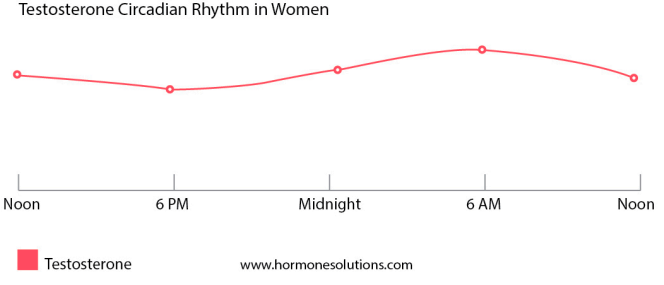
A psychological evaluation of mood, well-being and sexual function may need to be conducted.

Hormone Blood Testing

The testosterone blood test result is not the only factor for determining whether to treat a patient with testosterone - it is one small part of a multi factorial decision making process. It is an important part of on-going patient management to ensure levels are maintained within the approximate physiological concentration for premenopausal women, if testosterone therapy is initiated.

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

Testosterone secretion follows a diurnal rhythm in females. This means it rises and falls over a 24 hour period. Testosterone production occurs during the night and early morning with levels highest on waking. Serum testosterone levels slowly decrease during the day and are lowest in the late afternoon and early evening.



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

The ovaries and adrenal glands do not store testosterone. Once produced, testosterone is secreted into the blood where it is rapidly adhered to by the protein sex hormone-binding globulin (SHBG).

Up to 99% of testosterone produced in the body is bound to SHBG. Once testosterone is bound to SHBG (bound testosterone) it is inactive.

Testosterone to which SHBG does not attach is biologically available testosterone. This is free to act on cells throughout the body (free testosterone or free T).

Because SHBG has such a significant effect on testosterone, it is essential SHBG levels be considered when doing blood tests. High SHBG will result in free testosterone being lowered, hence a potential cause of symptoms.

Some doctors will measure only serum testosterone levels (called total testosterone) and 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, using only total testosterone reference ranges for determination of "normal" and "low" testosterone is potentially misleading. Two measures which take into account the effects of SHBG are 'free testosterone' (cFT) and the free androgen index (FAI).

In order to establish an accurate diagnosis for a patient, it is essential all factors that contribute to the decision making process of whether to treat with testosterone or not are considered. Direct assays for measuring free testosterone are unreliable and therefore not recommended for use. A more common and equally accurate method is cFT a mathematical calculation that takes into account total testosterone and SHBG levels.

The FAI uses less complex maths and is calculated by dividing the total serum testosterone level by the SHBG level, multiplied by 100. Pathology labs will automatically do this calculation and the result will be the FAI percentage. Generally a FAI of less than two indicates there is very little free testosterone and testosterone use may be an option.

The table on the page below provides a summary of hormone blood test values.

PROFILE	TEST	NORMAL ADULT NON-PREGNANT FEMALE VALUE
Hormones	GH	0 to 8 ng/mL
	FSH	3 to 20 mIU/mL
	LH	<7 mIU/mL
	HCG	Negative unless pregnant
	Progesterone	<2 ng/mL before ovulation >5 ng/mL after ovulation
	Oestradiol	Varies from 25 pg/mL (150 pmol/L) on Day 3 to 200 pg/mL (1200 pmol/L) around ovulation
	Prolactin	< 24 ng/mL
	Testosterone	28 to 80 ng/dL 1.0 – 2.8 nmol/L
	Free Testosterone	1.3 – 6.8 pg/mL 4.5 – 23.6 pmol/L
	Free Androgen Index (FAI)	2 – 6%
	SHBG	18 to 114 nmol/L

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

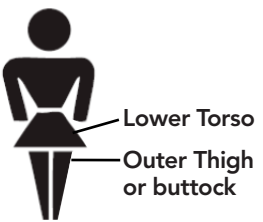
Total testosterone and calculated free testosterone, or total testosterone and FAI, is essential in the assessment of a patient's true testosterone profile. These measures are important regardless of menopausal status, age or ethnic background. Other factors such as pre-existing illnesses; physical, hormonal, psychological or relationship issues; and mental health must be taken into account before considering testosterone treatment.

Testosterone Therapy in Women

Testosterone therapy for women is most commonly prescribed to address low libido and/or fatigue and, usually after blood tests have identified that the patient's testosterone levels are lower than normal.

In Australia, the only commercially-available clinically trialled testosterone product for use in women is a 1% (10mg/mL) cream which is applied to the skin. It can only be dispensed from a pharmacy with a valid doctor's prescription. The recommended starting dose is 5mg (0.5mL) using a graduated syringe-style applicator.

The cream is applied daily to the lower torso, buttock or upper outer thigh. Once applied it should be massaged evenly until absorption is complete. This can take around 30 seconds.



It is **very important** that patients have a follow-up blood test to measure their testosterone levels **within three to six weeks** of starting therapy.

Dose may need to be adjusted based on the results.

Testosterone therapy can take **up to eight weeks** for the full clinical benefit to be felt.

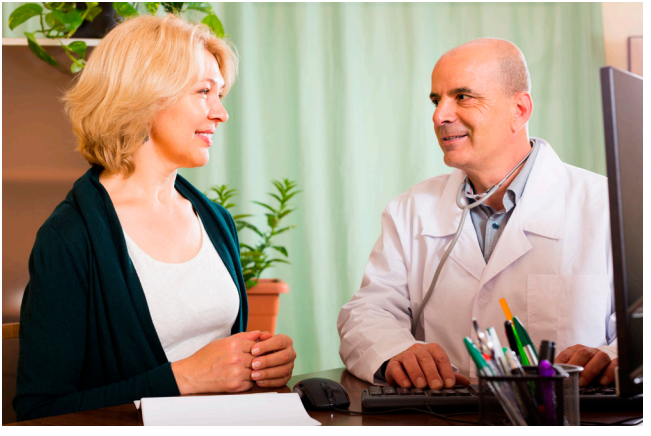
For women with low libido, testosterone therapy is beneficial in around 6 out of every 10 situations. If no benefit is gained after 6 months of use, testosterone therapy should be discontinued.

Quality and independent information on the use of testosterone in women and menopause can be found on the Australasian Menopause Society website at www.menopause.org.au. or the International Menopause Society website at www.imsociety.org.

Risks of Testosterone Treatment in Women

A full health check including testing blood testosterone levels should always be performed before using any testosterone replacement. It is essential a medical practitioner closely monitors testosterone therapy.

Provided blood testosterone levels are maintained within the normal range, side effects generally do not occur. Side effects may be induced when testosterone blood levels exceed the normal upper limits. This can happen with sustained high dose supplementation of testosterone.



Possible side effects of testosterone include the following:

- Nausea and vomiting
- Jaundice
- Joint swelling
- Increased body hair
- Deepening of the voice
- Increased acne
- Signs of virilisation
- Weight gain
- Persistent headaches

It is very important to understand these side effects are extremely unlikely when doses are monitored and blood levels are kept within the normal physiological concentrations for premenopausal women.

In general, testosterone supplementation should only be used when a woman's oestrogen levels are replete. Post menopausal women who are not taking an oestrogen supplement may still benefit from testosterone alone.

About Lawley Pharmaceuticals

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

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