MONASH University

PUBLIC HEALTH AND PREVENTIVE MEDICINE

Therapeutic use of testosterone for women

Testosterone patient information sheet (https://www.monash.edu/__data/assets/pdf_file/0005/1003397/testosterone-patient-information-sheet.pdf) (PDF, 145kB)

The available clinical evidence supports efficacy of testosterone therapy for the treatment of postmenopausal women with sexual desire/arousal disorder who have undergone a comprehensive clinical evaluation. Although, few preparations designed to deliver an appropriate dose of testosterone for women are available, use of testosterone by women for the management of low libido is widespread. Issues that continue to simulate debate regarding the use of testosterone therapy for women include whether HSDD is a condition that merits pharmacotherapy, how effective is such treatment and whether testosterone therapy is safe.

Testosterone physiology

Circulating levels of testosterone and the major adrenal pre-androgens, dehydroepiandrosterone (DHEA), DHEA sulphate (DHEAS) and androstenedione decline with age in women, with the maximal rate of decline occurring in the premenopausal years[1]. However, there is no diagnostic lower limit for any of these circulating steroids which can be used to classify a woman as androgen deficient[2]. Thus the use of testosterone therapy for women is not based on an established link between symptoms and biochemistry, but rather clinical evidence that testosterone therapy improves specific parameters of sexual function in women.

The most commonly reported sexual problems in women relate to sexual desire and interest, pleasure and global satisfaction[3-5]. Hypoactive sexual desire disorder (HSDD) is diagnosed when a woman presents with loss of sexual desire in association with personal distress [6]. The prevalence of HSDD amongst postmenopausal women is in the order of 9 to 14%, with no differences between natural in surgically menopausal women[7, 8]. Most studies evaluating the efficacy of testosterone for the treatment of female sexual dysfunction have required women to fulfill the diagnostic criteria of HSDD. They have also mostly been conducted in postmenopausal women in monogamous relationships for at least 12 months. Two studies of the use of testosterone in premenopausal women have been published and each of these have shown efficacy similar to that seen in postmenopausal women[9, 10].

The importance of satisfactory sexual well-being for women should not be underestimated. Sexual satisfaction is associated with better general health[11]. More than 80% of women over the age of 30 years believe that an active sex life is important for one's sense of wellbeing, with higher levels of physical pleasure in sex were significantly associated with higher levels of emotional satisfaction[12]. At the other end of the spectrum, low sexual wellbeing is associated with significant decreases in health-related quality of life in both naturally and surgically menopausal women[13, 14]. The largest significant,

negative effects are seen in the mental health, vitality, social function, and bodily pain subscales. Affected women were more likely to be depressed, be dissatisfied with their home life and with the emotional and physical relationships with their sexual partner. The overall effect of HSDD on quality of life in women with HSDD is similar to in magnitude to that seen in adults with other common chronic conditions such as diabetes and back pain[13].

Both men and women reporting a discrepancy between their own and their partner's sexual desire have lower relationship satisfaction[15] and individuals in sexually inactive marriages report less marital happiness[16]. Sensitive to the importance of sexual intimacy in the relationship, women commonly continue to engage in sexual activity despite experiencing dyspareunia and /or little sexual desire or pleasure[17-19].

In summary, loss of sexual desire for many women is a significant cause of loss of personal wellbeing, personal distress and relationship disharmony, often with an unavoidable negative ripple effect from the impact of relationship dynamics, impacting other household members. Just as individuals seek treatment for other factors that impact negatively on their quality of life such as depression, many women experiencing HSDD also seek and merit treatment.

Does testosterone therapy help women who experience loss of sexual desire?
No single therapy will be effective in all women experiencing low sexual function. Sexual function is complex and impacted upon by a number of factors. That any single intervention might therefore improve sexual function in itself is somewhat remarkable. Large studies consistently show that the administration of testosterone to naturally or surgically postmenopausal women improves sexual desire, arousal, orgasm frequency, pleasure and sexual satisfaction, reduces personal distress associated with HSDD and increases the number of occasions on which a woman experiences as satisfactory sexual event[20].

There has been a consistency across published studies of the testosterone patch that at baseline on average women enrolled in the various studies have reported 50% of sexual events were not satisfying events[21-24]. With testosterone treatment women report on average 80% of sexual events to be satisfactory, which translates into 1-2 extra satisfactory sexual events per month above that seen with placebo, and for women treated with testosterone without concurrent oestrogen, more than a 115% increase in reported orgasms compared to placebo (38% increase)[21]. In these studies not all women responded to treatment, with about 50 to 60% of women being actual responders. However the efficacy of therapy in women who self identify as responders is quite substantial, with some studies showing responders reporting on average 4 extra satisfactory sexual events per month.

Assessing candidates for testosterone therapy

Evaluation of loss of libido requires a multi-system approach such that both physical and psychosocial factors must be evaluated for all patients.

History and examination
In defining the problem it is important to determine whether the problem of low libido is causing the women personal distress. The duration of decreased libido and when the women last felt she had normal libido should be established. Assessment should be non judgmental as what is normal for one woman may not be acceptable to another. Evaluation of psychosocial factors as discussed elsewhere

is vital, however the presence of psychosocial components do not exclude a contributing organic component and should not exclude a woman from full biological assessment. All women should be carefully screened for depression as a cause of their sexual difficulties. Similarly the presence of chronic illness does not exclude a hormonal cause. Indeed a hormonal cause may be more likely in women with illness or therapy that causes adrenal suppression.

A complete gynecological history should be taken. History should also identify possible iron deficiency, thyroid disease and galactorrhoea.

In premenopausal women adequacy of oestrogenisation should be evaluated by taking a menstrual history. In the presence of regular cycles (periods every 21 to 35 days) dysfunction of the hypothalamic-pituitary-ovarian axis is extremely unlikely, such that estrogen is usually adequate and prolactin is normal. Amenorrhea prior to the age of 40 years requires full assessment.

A general physical examination should include assessment of thyroid status, presence of anaemia or galactorrhoea. Gynaecological examination should include a pelvic examination with attention to signs of vaginal atrophy, size of introitus, presence of discharge or evidence of infection, vulvodynia and deep tenderness. Evaluation of the vulvar and vaginal tissues on exam relates more closely to sexual function than oestradiol levels.

Laboratory assessment

Women presenting with low libido and fatigue should have routinely measured:

- iron stores (which might be low despite normal hemoglobin);
- thyroid stimulating hormone (TSH) to exclude subclinical thyroid disease, and on clinical suspicion a screen for autoimmune disease causing chronic fatigue. The incidence of undiagnosed subclinical hypothyroidism is high – about 10% of women over 40. The relation of mild hypothyroidism to symptoms of fatigue and sexual complaints is unclear. Women treated with thyroxine who are started on oral (but not parenteral) oestrogen therapy need to have their TSH measured 6 weeks after commencement as oestrogen, as oral oestrogens may increase the thyroxine requirement by increasing thyroid binding globulin.

Measurement of oestradiol and FSH is indicated to diagnose premature ovarian failure in amenorrhoeic young women or to evaluate menopausal status in hysterectomised women. However in the latter a full symptom history is often more useful. Amenorrhoea with low FSH and low oestradiol is suggestive of hypothalamic amenorrhoea, hyperprolactinaemia or other rare pituitary disease. Not all immunoassays reliably distinguish normal oestradiol from low levels.

Prolactin should be measured in premenopausal women with oligomenorrhoea, amenorrhoea and/or galactorrhoea.

Testosterone
Free or bioavailable (non-SHBG-bound) testosterone measures are the most reliable indicators of tissue testosterone exposure. High levels do not predict higher libido, however, a level above average probably rules out androgen insufficiency.

Timing of measurement to prevent misdiagnosis of low testosterone: Ideally blood should be drawn between 8:00 and 10:00 am due to the diurnal variation of testosterone, resulting in higher levels at this time. In premenopausal women, testosterone is at its nadir during the early follicular phase, with small but less significant variation across the rest of the cycle. Thus, blood should be drawn after day 8 of the cycle, and preferably before day 20. A serum sample is preferred over plasma.

Free testosterone: The gold standard methodology for measurement of free testosterone is considered by many investigators to be equilibrium dialysis. However, this method is influenced by dilution of the analyte. Furthermore, it is labor intensive and expensive, and not feasible for clinical practice. Bioavailable testosterone, which correlates highly with free testosterone quantified by equilibrium dialysis, can be measured by the ammonium sulfate precipitation technique. However, frequently encountered sources of error in this assay include incomplete precipitation of globulins, use of impure tritiated testosterone, and insufficient counting time of the relatively small amount of radiolabeled bioavailable testosterone in the assay. The equilibrium dialysis and ammonium sulfate precipitation methods generate a percentage of free testosterone and bioavailable testosterone, respectively. This percentage is then multiplied by the concentration of total testosterone to determine the free and bioavailable testosterone concentrations. The Sodergard equation can be reliably used to calculate free testosterone if total testosterone, albumin and SHBG are known. This method requires a reliable determination of total testosterone and SHBG; albumin is quantified by routine methodology. Measurement of free testosterone by analogue assays are notoriously unreliable, particularly at the lower end of the normal female range and are not recommended for use.

Salivary testosterone has been used reliably in studies of women with hyperandrogenism, but has never gained wide support because the normal range seems excessively large and also has questionable accuracy in the lower ranges. It is important to realize that salivary testosterone levels should not be equated to levels of free testosterone in serum. The free androgen index (FAI) [nmol/L total testosteronex100/nmol/L SHBG] has been used as a surrogate for free testosterone, but it is unreliable when SHBG levels are low.

Total testosterone: No rapid, simple assay of total testosterone has been shown to produce reliable results in women with low testosterone levels. Direct testosterone immunoassays are limited by “noise” from assay interference and by cross-reactivity with other steroids, which become worse at low testosterone concentrations. Furthermore, testosterone is sometimes not completely dissociated from SHBG in a direct assay. Inclusion of organic solvent extraction will increase specificity, and if combined with chromatographic separation of testosterone from interfering steroids, a reliable result can be obtained. However, this technique is frequently not available or cost-effective in clinical settings.

Gas chromatography combined with mass spectrometry (GC-MS) for total testosterone measurement requires multiple steps including liquid-liquid extraction, and may not be reliable when testosterone levels are very low. However, liquid chromatography (LC)-MS/MS appears to provide reliable measurement of low testosterone concentrations.

Regardless of which assay method for measuring an analyte is used, a thorough validation of each method is required. The validation should include assay sensitivity, precision, accuracy and specificity.

Importance of sex hormone binding globulin (SHBG)
SHBG is a pivotal determinant of the bioavailability of sex steroids and variations in the plasma levels of SHBG impact significantly on the amount of free, or bioavailable testosterone and other bound sex steroids. In normal reproductive aged women 82% of the binding sites of SHBG are unoccupied. The binding affinity for steroids bound by SHBG is DHT> testosterone > androstenediol > estradiol > estrone. SHBG also weakly binds DHEA, but not DHEA-S. Under normal physiological conditions in women only 1 to 2 % of total circulating testosterone is free or biologically available. The rest is bound by SHBG (66%) and albumin (30%).

- Elevations in oestradiol (as occurs during pregnancy), hyperthyroidism and liver disease cause a marked increase in SHBG levels.
- Hypothyroidism, obesity, and hyper-insulinemia are associated with decreased SHBG levels.

In addition oral administration of steroid hormones and their analogues can markedly alter SHBG levels whereas parenteral administration of these compounds typically has a much weaker influence. Standard dose of oral estrogen as used in hormone therapy (HT) will increase SHBG with little or no effect seen with standard oestradiol patch therapy. However when very high levels of oestradiol are achieved for several weeks to months with parenteral therapy (as seen with oestradiol implants) SHBG will increase.

When exogenous testosterone is administered the rise in concentration of total testosterone will greatly depend upon SHBG concentration. Thus women with high SHBG will have a marked increase in total testosterone whereas women with low SHBG will have little change in their total testosterone level with exogenous therapy. As total testosterone is a poor indicator of androgen exposure, following testosterone therapy, the concentration of free testosterone or non-SHBG-bound testosterone, so called bioavailable testosterone, should be measured.
As SHBG levels may fall somewhat with increased circulating testosterone, baseline SHBG may be a useful predictor of risk of excess androgenisation with testosterone treatment, and should be measured in all women prior to such therapy.

Summary of androgen measures

1. Total testosterone is notoriously difficult to measure at lower levels, as seen in women, with sensitivity and precision[25]. Total testosterone and SHBG should be measured and from these, free testosterone can be reliably estimated using the Sodergard equation[26]. The measurement of free testosterone in women by direct “kit” assays is generally completely unreliable[27].
2. SHBG provides additional information regarding overall androgen exposure, as it is sensitive to total body androgen status**. Low SHBG levels indicate a considerable increase in risk of androgen excess with testosterone therapy**, whereas high levels indicate a reduced clearance of testosterone.
3. In postmenopausal women transdermal testosterone is likely to be ineffective if the SHBG level is high (>160pmol/L)[22] or if used by women taking conjugated equine oestrogens[28].
4. **Serum for testosterone measurement should be drawn between 8:00 and 10:00, and not during the early follicular phase in premenopausal women for either research or diagnostic purposes.**
5. As there is no level of testosterone, total or free, below which a woman can be diagnosed as

being androgen deficient, the measurement of testosterone should not be used as an indicator as to which women merit treatment. However a testosterone level should be measured prior to therapy primarily to exclude women who may be at risk of side-effects if treated (see below).

Loss of sexual desire is not uncommon amongst women using the combined oral contraceptive pill (COCP), particularly those containing an anti-androgenic progestin. The COCP suppresses ovarian testosterone production and increases sex hormone binding globulin (SHBG) thus reducing free testosterone. Switching from a COCP to another form of contraception will often improve sexual well-being in younger women.

Antidepressant use (notably the SSRIs) may be associated with sexual dysfunctionreflecting either inadequate treatment of depression or a drug side-effect[29]. Women who present primarily with arousal disorder and inability to achieve orgasm, but no significant loss of libido, in association with antidepressant therapy may respond well to phosphodiesterase type 5 inhibitor therapy[30].

Contraindications to testosterone therapy

Women with a low SHBG level are likely to have a more rapid clearance of administered testosterone, and thus are much more likely to experience androgenic side-effects. Similarly women with a free testosterone level in the high normal or above normal range for healthy young premenopausal women[1] is more likely to achieve supraphysiological levels with treatment, and hence experience side-effects.

Testosterone should not be administered to women who:

- Are pregnant or lactating
- have troublesome acne or hirsutism
- have been treated with anti-androgens in the last five years for acne or hirsutism
- are experiencing scalp hair loss
- have a current or past sex steroid dependent malignancy
- have an SHBG level below the lower limit of normal
- have a free testosterone in the mid-range for healthy young women or above

Safety of exogenous testosterone

The links between postmenopausal oestrogen-progestin use and both breast cancer and cardiovascular disease have created a level of concern regarding any form of hormone use in postmenopausal women[31]. Testosterone has been widely used by women as an unapproved therapy for decades. Excessive therapy will clearly result in undesirable androgenic effects such as hirsutism and acne, although this is not common when treatment is aimed at achieving testosterone levels in the female range[22-24]. About 20% of women report increased hair growth, as opposed to hirsutism, and this rarely results in the decision to discontinue therapy[10, 21]. There is no evidence from studies of premenopausal women and postmenopausal women that systemic transdermal testosterone is associated with a change in the risk of invasive breast cancer[32-34] or increased cardiovascular morbidity or mortality[21, 35]. Oral methyltestosterone is associated with a reduction in HDL-cholesterol, an effect not seen with transdermal therapy[20]. However, long term safety data for the use of

testosterone in women are limited[33, 34]. Only two small studies have provided safety data for premenopausal women[9, 10]. There is uncertainty as to the consequences of restoring testosterone levels to those of premenopausal women in women who are many years past menopause.

Treatment options

Presently there is a lack of approved preparations of testosterone specifically suitable for use in women. Use of preparations designed to deliver a dose of testosterone to men cannot be condoned. In several countries testosterone therapy is commonly initiated with testosterone pellets implanted under local anaesthetic subcutaneously. Most commonly a dose of 50mg is used[36]. These implants remain effective for periods of 4 to 6 months. Repeat implantation should not be undertaken without confirmation that total testosterone corrected for SHBG, or free testosterone has fallen back into the lower quartile of the normal female range. Testosterone transdermal patches have been shown to be effective and have a good short term safety profile when used by naturally or surgically postmenopausal women with and without concurrent oestrogen therapy[21, 35]. The Intrinsa® patch which delivers 300 μg of testosterone daily has been approved for use by surgically menopausal women using concurrent systemic oestrogen therapy in European Union countries. A transdermal testosterone cream for women, marketed as Androfeme1%®, is available in Australia[9] and testosterone gels for women and a transdermal spray are in development.

Various pharmacists prepare testosterone for buccal administration in the form of troches, or as creams, but there are no published pharmacokinetic or safety data or efficacy studies to validate this method of administration.

Some clinicians undertake a clinical trial of an intramuscular injections of testosterone esters 50 to 100mg. This may or may not result in a clinical response over 1-2 weeks or more. A positive response supports the initiation of longer term therapy. However, as peak levels are supraphysiological, testosterone esters should not be considered a long-term treatment option.

Another agent which can be conceived as having androgenic effects (in addition to having properties as an estrogen and a progestin) is tibolone. In a dose of 2.5mg daily, it improves sexual function in postmenopausal women[37]. DHEA therapy has not been covered in this paper. There is little data to support the use of DHEA for the treatment of sexual dysfunction and safety data is limited[38-40].

Evaluating efficacy

The time between commencement of therapy and improvement in symptoms varies according to the mode of administration of testosterone which most probably reflects the serum levels achieved with different delivery modes.

Testosterone implants provide an initial supraphysiological rise in serum testosterone which lasts a few days after which levels fall to the upper level of the normal female range with a 50mg testosterone implant. Women consistently report experiencing an effect about 2 weeks after insertion of the implant. Subsequent implants should not be inserted without first checking the serum testosterone level to ensure that it has fallen to the low normal young female range of below. Otherwise insertion of an implant prematurely may well result in supraphysiological levels and androgen side effects.

When testosterone is administered transdermally as a cream, patch or skin spray at a dose that brings free testosterone into the range of that of young women, an effect is consistently experienced after 6 to 8 weeks[9, 10, 21, 22]. It is critical women are made aware of this when such therapies are prescribed. Improvement is unlikely to occur beyond 16 weeks of therapy and if by 26 weeks no improvement has been experienced then the woman should be considered a non responder.

In general therefore it is recommended that if a woman is commenced on transdermal testosterone cream (such as Androfeme 1%®), a serum testosterone blood level should be checked after the woman has been using it for three or four weeks, primarily to ensure that she is not self administering an excessive dose. The woman should be review to evaluate efficacy at about 12 weeks. An earlier review is not necessary as efficacy may well not have been experienced. If no efficacy is experienced by the woman after six months of treatment, treatment should be discontinued.

In general about 60% of women treated with active therapy in clinical trials are responders to testosterone in the setting of strict participant inclusion criteria [10].

Summary

Taken together, the available clinical evidence supports the efficacy of testosterone therapy for the treatment of some but not all postmenopausal women experiencing losses sexual desire and/or diminished arousal, who have undergone a comprehensive clinical evaluation. Evidence to support the use in women in their late reproductive years remains limited.

Evidence from randomised controlled trials to date do not indicate any serious safety concerns, however further studies are required to determine the long term safety of testosterone in women.

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