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British Menopause Society Tools for Clinicians: Testosterone replacement in menopause.

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1) How much and where does it come from?

Testosterone is an important female hormone. Healthy young women produce approximately 100–400 mcg per day. This represents three to four times the amount of estrogen produced by the ovaries. Approximately half of endogenous testosterone and precursors are derived from the ovaries e.g. androstenedione and half from the adrenal glands e.g. dehydroepiandrosterone. Some of the effects are direct and some due to peripheral conversion to estrogen by aromatase. Testosterone levels naturally decline throughout a woman's lifespan. Loss of testosterone is particularly profound after iatrogenic i.e. surgical and medical menopause and premature ovarian insufficiency when testosterone production decreases by more than 50%.

2) What is its role in women?

Testosterone contributes to libido, sexual arousal and orgasm by increasing dopamine levels in the central nervous system. Testosterone also maintains normal metabolic function, muscle and bone strength, urogenital health, mood and cognitive function.

3) What is the impact of testosterone deficiency?

This can lead to a number of distressing sexual symptoms such as low sexual desire, arousal and orgasm. Other contributory factors which should be taken into account when assessing women with these symptoms include psychosexual, physical, iatrogenic and environmental. Testosterone deficiency can also contribute to a reduction in general quality of life, tiredness, depression, headaches, cognitive problems, osteoporosis and sarcopenia.

4) What other effects can testosterone have in the post-menopause?

After the menopause, estrogen levels fall to undetectable levels. Consequently, the small amount of remaining testosterone may predispose to androgenic symptoms, especially acne, increased facial hair growth and male pattern baldness. Personal genetics are key to the susceptibility to these problems.

5) Diagnosing Female Androgen Deficiency Syndrome (FADS) also referred to as Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest and Arousal Disorder (FSIAD)

Although for research purposes validated questionnaires are used, the diagnosis of FADS in the clinical setting should be a pragmatic one based primarily on symptoms. Testosterone levels may be supportive of the diagnosis but symptoms do not always correlate with low testosterone levels as brain intracrinology may be more important than peripheral levels.

6) Testosterone assays – measurement

The assessment and interpretation of testosterone levels is problematic, particularly as the majority of testosterone is protein bound. Free testosterone assays are the gold standard but are rarely available, particularly in the public sector. Total testosterone can be measured, but for greater accuracy sex hormone binding globulin (SHBG) levels should be taken into account using the following calculation to work out the Free Androgen Index = Total Testosterone × 100/SHBG.

7) Testosterone assays – interpretation of results

Although it is not mandatory to perform testosterone level estimation prior to or for monitoring treatment, it can be useful. A low FAI < 1.0% in women with symptoms of low sexual desire and arousal, supports the use of testosterone supplementation. Repeat estimation at the 2–3 month follow up visit can be performed to demonstrate if there has been an increase in levels, though clinical response is of paramount importance. It is also useful to demonstrate that values are being

maintained within the female physiological range, typically < 5%, thus making androgenic side effects less likely.

8) Female Testosterone Replacement - indications

There are no testosterone products for female use licensed in the UK. The previous license for female testosterone patches was for women with HSDD following surgical menopause on concomitant estrogen; similar efficacy and safety data also exist for natural menopause and for women not using concomitant HRT. The licenses for patches and implants were both withdrawn for commercial reasons;however, the safety and efficacy data for these products remain valid. By extrapolation of these data it is deemed acceptable for products licensed in men (mainly gels) to be prescribed off label in female doses. It is not uncommon in clinical practice to use medicines outwith their product licence as long as this meets the criteria proposed by the GMC and MHRA on prescribing an unlicensed medicine or using a medicine off-label (i.e. No suitably licensed products available/Be satisfied there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy/Make a clear record of reasons for prescribing an unlicensed medicine/Give patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment).

Note 1: This tool for clinicians refers to testosterone replacement in menopause, both natural and surgical. There are very few data for testosterone replacement in premenopausal women which remains a controversial area requiring more research.

9) What are the currently available options

The available products keep changing for commercial reasons – this section of the online tool for clinicians in particular will be updated regularly to maintain its relevance. An audit will be carried out to assess what preparations are available in different areas of the UK to make this guidance as realistic as possible.

Note 1: When treating low sexual desire/arousal it is also important that urogenital tissues are adequately estrogenised in women with vulvovaginal atrophy/genitourinary syndrome of the menopause e.g. through use of vaginal estrogen, to avoid dyspareunia.
Note 2: Although the NICE NG23 guideline recommends that systemic HRT should be prescribed before a trial of testosterone, there are trial data in women with HSDD which indicate that testosterone used without systemic estrogen, is equally effective and safe.
Note 3: Tibolone is weakly androgenic, progestogenic and estrogenic – although it is an option for women with low sexual desire it is not sufficiently androgenic nor estrogenic in many women. The progestogenic effect is not required in hysterectomised women and may cause unnecessary adverse effects.
Note 4: Compounded bioidentical testosterone preparations are not recommended by the regulatory authorities or the menopause societies.

- Testogel [Besins Healthcare UK] (1% testosterone gel in 5.0 g sachets containing 50 mg testosterone): Starting dose 1/10 of a sachet/day = 5 mg/day i.e. each sachet should last 10 days.
- Tostran [Kyowa Kirin Ltd] (2% testosterone gel in a canister containing 60 g) : Starting dose 1 metered pump of 0.5 g = 10 mg on alternate days – each canister should last 120 days.
- AndroFeme[1] [Lawley Pharma] (1% testosterone cream in 50 ml tubes with screw cap): Starting dose 0.5 ml/day = 5 mg/day i.e. each tube should last 100 days.
- Testosterone Implants[2] [Smartway Pharma] (100 mg implanted pellets) Unlicensed – imported from USA

1. *AndroFeme is not currently available in the NHS and is being imported from Western Australia by special license from the MHRA. Designed for female usage.*
2. *Testosterone implants are currently unlicensed in the UK and can only be used privately or through agreement of the local formulary committee with appropriate monitoring of hormone levels and adverse effects. Designed for female usage.*

10) How should testosterone gel/cream be used?

The testosterone gel/cream should be to applied to clean dry skin (lower abdomen/upper thighs) and allowed to dry before dressing. Skin contact with partners or children should be avoided until dry and hands should be washed immediately after application. The area of application should not be washed for 2–3 hours after application.

11) Response to testosterone therapy and duration of use

The loss of sexual desire is complex and may have hormonal, medical, psychosexual and psychosocial aetiologies. In clinical trials of women with HSDD, approximately 2/3 of women responded positively to testosterone therapy (compared to 1/3 using placebo). The trials demonstrated that response may not be immediate, taking 8-12 weeks in some instances for the effect to become clinically significant. It is therefore advised that treatment should trialled for a minimum of 3 months and maximally for 6 months before being

discontinued due to lack of efficacy. Duration of use should be individualised and evaluated at least on an annual basis, weighing up pros and cons according to benefits and risks, as per HRT advice from all menopause societies.

12) What are the possible adverse effects of testosterone therapy

Response to testosterone with regards to efficacy and adverse effects, is highly variable. This is most likely due to varying absorption, metabolism and sensitivity to testosterone. Not uncommonly, adverse effects occur because healthcare professionals and their patients are confused about the appropriate preparation and dose which should be used in women, due to the lack of specific female preparations and information sheets. Clinical trials have demonstrated that as long as appropriate female physiological doses are prescribed adverse androgenic effects are not problematic and virilising problems do not occur.

Reported adverse effects are shown below; if thought to be linked, the dosage should be reduced or treatment stopped.

- Increased body hair at site of application (occasional problem) – spread more thinly, vary site of application, reduce dosage.
- Generalised Hirsutism (uncommon)
- Alopecia, male pattern hair loss (uncommon)
- Acne and greasy skin (uncommon)
- Deepening of voice (rare)
- Enlarged clitoris (rare)

Randomised controlled trials and meta analyses have not shown an increased risk of cardiovascular disease or breast cancer although longer term trials would be desirable.

13) When should testosterone be avoided or used with caution?

- During pregnancy or breastfeeding
- Active liver disease
- History of hormone sensitive breast cancer – off label exceptions to this may be agreed in fully informed women with intractable symptoms not responding to alternatives
- Competitive athletes – care must be taken to maintain levels well within the female physiological range
- Women with upper normal or high baseline testosterone levels/FAI.

14) Further Reading

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