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Review

Androgens, health and sexuality in women and men

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ABSTRACT

The importance of good sexual function for individuals is well recognised. Testosterone is contributory to a healthy sex life for both women and men. The British Society for Sexual Medicine (BSSM) has initiated and led the development of these guidelines for the assessment of testosterone deficiency in both women and men, for use within the UK and beyond. Clinical awareness of the possibility of testosterone deficiency and the impact this may have on an individual's sexual and somatic function and the need to make sufficient enquiry about the sex life of patients attending a broad spectrum of clinical services is emphasised. The management of testosterone deficiency is outlined in detail for both women and men.

Contents

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1. Introduction

For several decades sex has been recognised as beneficial for health. There is, though, a lack of awareness of the importance of sex to patients on the part of many physicians in primary and secondary settings, including gynaecology, urology, psychiatry and endocrinology. Even when testosterone is considered to be relevant, there is often a reluctance to enquire about sexual symptoms, and this leads to incomplete assessment of the sex lives of patients of both sexes and a failure to legitimise the needs and requests of patients for healthy sex lives. For these reasons, the British Society for Sexual Medicine (BSSM) initiated and led the development of these guidelines for the management of testosterone deficiency in both women and men. We have involved a number of learned colleges and societies whose members may be expected to encounter these clinical scenarios, and have encouraged their professional contribution to and endorsement of the guidelines.

Androgens are chiefly used in the treatment of sexual disorders, in both men and women. Moreover, the somatic, psychological and sexual effects of reduced androgen levels may affect both general well-being and sexuality. Androgens also have a role in female and male fertility, and this is briefly considered in these guidelines.

2. Women

2.1. Androgens and female physiology

The role of androgens in maintaining well-being in women is not clearly understood [1,2]. Testosterone and precursor sex hormones are produced by both the ovaries and adrenals. Before the menopause, testosterone and its precursors dehydroepiandrosterone (DHEA) and androstenedione are produced by the ovaries and adrenals [3]. The adrenals also produce the precursors dehydroepiandrosterone sulfate (DHEAS), androstenediol. These precursor sex hormones can be converted to estrogen and/or testosterone in peripheral cells, including those of the brain, breast, bone and genitalia. Between a woman's mid-30s and early 60s, adrenal androgen production reduces by about two-thirds [4]. After a natural menopause, ovarian production continues, albeit to a variable degree. Precursor sex hormone production from the ovaries and adrenals continues but declines. After bilateral oophorectomy, ovarian production of androgens and precursor sex hormones is lost.

2.2. Laboratory measurements of androgens in women

Measurement of testosterone levels in plasma or serum as performed in most laboratories and the interpretation of the results suffer from a number of serious problems [5] (Box 1). Testosterone circulates bound to at least two plasma proteins, sex hormone binding globulin (SHBG) and albumin, leaving around 1–3% of the total in the free or unbound state. As SHBG levels can fluctuate, measurement of total testosterone (TT), which is the most common measure, does not give meaningful information about tissue androgen exposure. SHBG levels are reduced in obesity and hypothyroidism, and raised in women taking exogenous estrogens, those with hyperthyroidism and women of increasing age. That which is unbound (free testosterone, FT) is often considered the component that has access to the cell and results in androgenic effects. In addition, there exists the concept of bioavailable testos-

Box 1
Problems with testosterone assays (adapted from Rosner et al. [5])

- Total testosterone concentrations in plasma vary with disease and exogenous hormones.
- The concentration of total testosterone varies with the time of day.
- Other steroids of similar structure can interfere with the assay.
- It is not known whether total testosterone or free testosterone is the more clinically useful measure.
- Age- and gender-corrected normal ranges, using a standardised assay, are generally lacking.
- There is no universally recognised testosterone-calibrating standard.

Table 1
International classification of female sexual problems.

Classification	Definition
I Sexual desire disorders	
A. Hypoactive sexual desire disorder (HSDD)	The persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts and/or desire for or receptivity to sexual activity, which causes personal distress
B. Sexual aversion disorder (SAD)	The persistent or recurrent phobic aversion and avoidance of sexual contact with a sexual partner, which causes personal distress
II Sexual arousal disorders	The persistent or recurrent inability to attain or maintain sufficient sexual excitement, which causes personal distress, and which may be expressed as a lack of subjective excitement, or genital (lubrication/swelling) or other somatic responses
III Orgasmic disorder	The persistent or recurrent difficulty, delay in or absence of attaining orgasm after sufficient sexual stimulation and arousal, which causes personal distress
IV Sexual pain disorders	
A. Dyspareunia	Recurrent or persistent genital pain associated with sexual intercourse
B. Vaginismus	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina, which interferes with vaginal penetration and causes personal distress
C. Non-coital sexual pain disorders	Recurrent or persistent genital pain induced by non-coital sexual stimulation

terone (bio-T), defined as the concentration of testosterone that is free plus that which is weakly bound, for example to albumin.

The problems of sensitivity and specificity of total testosterone assays have been addressed by extraction and separation procedures before immunoassay assay but the cost and manpower needed mean that they are not routinely available. Free testosterone levels can be measured using equilibrium dialysis but again there are methodological issues. Bio-testosterone is the fraction thought to be available to tissues. It is measured after precipitation of SHBG with ammonium sulfate. Variations in precipitation and assay methodology make comparison of results between different studies difficult.

The current methodological limitations of testosterone measurements (Box 1) mean it is difficult to make correlations between levels and well-being in women.

2.3. Classification of sexual problems in women

An international classification of sexual problems was elaborated by the International Consensus Development Conference on Female Sexual Dysfunction [6] (Table 1). There are four main categories:

(a) sexual desire disorders—hypoactive sexual desire disorder (HSDD), sexual aversion disorder (SAD);
(b) sexual arousal disorders;
(c) orgasmic disorder;
(d) sexual pain disorders.

Each of the categories is subtyped on the basis of the medical history, physical examination and laboratory tests as:

(a) lifelong versus acquired;
(b) generalised versus situational;
(c) of organic, psychogenic, mixed or unknown aetiology.

The four main categories are not exclusive and can overlap, and one may cause another. For example, dyspareunia is likely to lead to avoidance of sexual activity, and anticipation of pain leads to lack of arousal, loss of orgasm and an increased chance of pain recurring. Nonetheless, the classification has made it easier to understand sexual well-being and dysfunction in women [7]. A number of models have been proposed to try to help physicians understand the female sexual response and earlier linear models have evolved to incorporate a more sophisticated understanding of the complexity of female sexuality and how this may influence the development of the various sexual dysfunctions [8].

2.4. Epidemiology of sexual problems in women

Sexual problems in women are common, with lack of desire being the most prevalent. Interest in sex declines in both sexes with increasing age, but this change is more pronounced in women. The US National Health and Social Life Survey, which was undertaken in people aged 18–59 years, reported that sexual dysfunction is more prevalent for women (43%) than men (31%) [9]. Another US study, of 1550 women and 1455 men aged 57–85 years, found that the prevalence of sexual activity declined with age (73% among respondents who were 57–64 years of age, 53% among respondents who were 65–74 years of age, and 26% among respondents who were 75–85 years of age); women were significantly less likely than men at all ages to report sexual activity [10]. The most prevalent sexual problems among women were low desire (43%), difficulty with vaginal lubrication (39%) and inability to climax (34%). A European study of 750 women aged 40–80 years similarly found that the most common problems were a lack of sexual interest (34%) and a lack of pleasure in sex (25%) [11].

The large US PRESIDE study, of 31,581 women with a mean age of 49 years (range 18–102), similarly found that the most common sexual problem was low desire (38.7%), followed by low arousal (26.1%) and orgasm difficulties (20.5%) [12]. The prevalence of any sexual problem was 44.2%. Age stratification revealed a sharp increase in the prevalence of all three of these sexual problems by age group: only 27.2% of women aged 18–44 years reported any of the three problems, compared with 44.6% of middle-aged women (45–64 years) and 80.1% of elderly women (>65 years). Low desire was the most common of the three among all age groups. Sexually related personal distress (determined by rating scale) was observed in 22.2% of respondents. This was lowest in elderly women (12.6%), and present in 25.5% and 24.4% of middle-aged and younger women, respectively. The age-stratified prevalence of any distressing sexual problem was highest in women aged 45–64 years (14.8%), lowest in women 65 years or older (8.9%), and intermediate in women aged 18–44 years (10.8%). A similar age pattern was seen for distressing low desire and low arousal, but not for orgasm problems, in which the prevalence was similar in middle-aged and in older women. In conclusion, although studies have reported a prevalence of low sexual desire of around 30% [13], the PRESIDE study [12] showed a prevalence of around 10% for true HSDD in women, with arousal and orgasmic disorders around 5% each.

Similar prevalence results were obtained for desire problems with associated distress in European women [14] and slightly higher figures were reported in the WISHeS study of US women [15]. The latter was restricted to women with a current sexual partner and the sample size was relatively small.

It should be noted that the different instruments currently used to assess female sexual disorder (see below) can produce substantially different prevalence estimates.

2.5. Risk factors for female sexual dysfunction

Risk factors for female sexual dysfunction can be divided into two categories: non-hormonal and hormonal. The latter involve estrogen and androgen deficiency.

2.5.1. Non-hormonal risk factors

Non-hormonal factors include conflict between partners, insomnia, inadequate stimulation, life stress and depression; these are important contributors to a woman's level of interest in sexual activity. In addition, sexual problems in the woman's partner – for example, loss of libido or erectile difficulties – should not be overlooked. Concomitant medical disease such as hypothyroidism or diabetes may also be involved [16,17].

2.5.2. Hormonal risk factors

2.5.2.1. Estrogens and female sexual dysfunction. Postmenopausal estrogen deficiency causes atrophic changes [18]. The vaginal mucosa becomes thinner, and the vulva and the vaginal walls also become pale and thin and lose their elasticity. Vaginal secretions also decrease, leading to reduced lubrication. Reduced levels of estrogen can also impair peripheral sensory perception, and women may experience discomfort from contact with the skin by clothes or their partner.

There has been debate in the literature on the effect of hysterectomy and oophorectomy on sexual function. The effect depends on several factors, such as age, preoperative mental health and preoperative sexual function, the indications for surgery, whether the woman chose to have an oophorectomy, the specific procedure performed and whether or not estrogen was used postoperatively. The majority of research on the effects of surgical menopause shows improved psychological well-being and sexual function after hysterectomy for benign disease [19–21]. However, women with depression or sexual problems preoperatively are at increased risk of experiencing a worsening of mood and libido postoperatively [22].

2.5.2.2. Androgens and female sexual dysfunction. Although surgical menopause represents an androgen-depleted state, the prevalence of subsequent sexual dysfunction is unknown. However, women choosing (as opposed to just consenting to) bilateral oophorectomy with a simple hysterectomy required for benign reasons do not develop sexual dysfunction over the next one to three years [19–21].

It has been suggested that low circulating levels of androgens are associated with low sexual desire and a diminished sense of well-being; however, the results of studies addressing this are contradictory and no level of a single androgen is predictive of low sexual function in women. Methodological issues with androgen measurements (see Box 1) are a significant contributory factor to this uncertainty.

Guay et al. [23] studied 32 healthy premenopausal women: 18 with one or more complaints of sexual dysfunction and 14 without. Assays of ovarian and adrenal androgens were done before and after stimulation with adrenocorticotrophic hormone (ACTH). The women with complaints of sexual dysfunction had significantly lower levels of adrenal androgen precursors and testosterone than the control women. There were no differences in the basal ovarian androgen levels or cortisol levels.

A community-based, cross-sectional study of 1021 Australian women aged 18–75 years found no clinically significant associations between having a low score on any domain on the Profile of Female Sexual Function rating scale and having a low serum total or free testosterone or androstenedione level [24]. For women aged 45 years or more, a low domain score for sexual responsiveness was associated with a serum DHEAS level below the 10th percentile for this age group. For women aged 18–44 years, low domain scores for sexual desire, sexual arousal and sexual responsiveness were associated with having a DHEAS level below the 10th percentile. However, no single androgen level was predictive of low female sexual function, and the majority of women with low DHEAS levels did not have low sexual function.

In a community-based baseline cohort of women aged 42–52 years from the US Study of Women's Health Across the Nation [25], circulating levels of SHBG and androgens were most strongly associated with body mass index, waist circumference and waist–hip ratio. SHBG was associated prominently inversely with the metabolic syndrome (obesity, hypertension, dyslipidaemia, impaired glucose regulation and insulin resistance). Androgen levels were related weakly to physical functioning and sexual desire, sexual arousal and well-being.

A study of 81 women with premature ovarian failure (POF) found that they were less satisfied with their sexual life than were the 68 controls [26]. They had fewer sexual fantasies and masturbated less frequently. Sexual contact was associated with less sexual arousal, reduced lubrication and increased genital pain. However, the frequency of desire to have sexual contact and the frequency of actual sexual contact with the partner did not differ between women with POF and control women. Women with POF had lower levels of estradiol, total testosterone and androstenedione. Multiple regression analysis revealed that androgen levels had only a weak influence on sexual functioning; higher total testosterone levels were associated with increased frequency of desire for sexual contact, and higher androstenedione levels were associated with more frequent sexual contact. Thus this study did not find an important independent role for androgens in various aspects of sexual functioning.

2.6. Assessment of women with sexual problems

2.6.1. Consultation

Studies suggest that less than 30% of female patients with sexual problems will discuss treatments with their general practitioner [27] and that only a third of these are likely to accept medication [28]. In particular, women are unlikely to raise HSDD as a primary problem [29]. A study designed to determine physicians' attitudes and practices regarding HSDD in the primary care setting found that 90% of respondents had little confidence in making a diagnosis of HSDD and that 90% had not screened a patient for HSDD [30]. These results are consistent with an earlier international survey of people aged 40–80 years, which found that only 8–10% of respondents had been asked about their sexual health during a routine visit to their doctor [31].

Contraceptive and sexual health clinics, cervical screening, postnatal and menopausal assessments represent useful opportunities for patients and clinicians to mention the subject. It should be remembered that a patient will often have more than one sexual problem. Although, as indicated above, sexual difficulties are more prevalent in older women, the distress and relationship difficulties they cause are generally greater and more frequent among younger women (the older women are more accepting of these difficulties than are their younger counterparts) [29].

Health-care professionals need to be careful that they use terms such as sexual 'problems', 'concerns', 'difficulties' and 'dysfunctions' appropriately [7,32]. Labelling the patient as suffering from a dysfunction may lead to over-medicalisation, whereas classifying a severely distressed patient as having a 'concern' may be equally unsatisfactory for the patient.

2.6.2. Initial assessment

Physicians should allow adequate time for a full history [32] and consider the use of questionnaires in the assessment. The assessment should cover the following:

1. Sexual history
   - Sexual problems, pregnancies, postpartum complications, sexual abuse.

- Localisation of any pain or discomfort.
- Current sexual functioning and practices.

2. Medical history
   - Co-morbid medical conditions that affect sexual desire and arousal.
   - Bilateral oophorectomy, POF.
   - Cardiovascular disease.
   - Diabetes.
   - Depression.
   - Thyroid disease.
   - Medications that can affect sexual function, particularly antidepressants, antipsychotics, antihypertensives, corticosteroids and hormones (including oral contraceptives and hormone replacement therapy).
3. Questionnaires
   - The DSDS (Decreased Sexual Desire Screener) is a short diagnostic aid [33,34].
   - The BISF-W (Brief Index of Sexual Functioning for Women) is a more comprehensive inventory but is more complex [35].
   - The PFSF (Profile of Female Sexual Function) is a patient-based instrument for measuring loss of sexual function in menopausal women with low libido [36].
   - The FSFI (Female Sexual Function Index) is a detailed questionnaire to assess desire, arousal, lubrication, satisfaction and pain; it is used mainly as a research tool [37].

2.6.3. Detailed investigation: laboratory diagnosis

Laboratory testing [38,39] is indicated to rule out concomitant medical conditions such as diabetes and thyroid disease which may affect sexual function. This should include a full blood count, fasting glucose, thyroid function, urea and electrolytes, creatinine and liver function tests.

Hormone assays (total and free testosterone levels, SHBG, FSH, LH, prolactin) may be indicated in women with amenorrhoea or oligomenorrhoea to establish a diagnosis. The current methodological limitations of testosterone measurements discussed above make it difficult to make correlations between levels and HSDD in women and thus are not routinely recommended. Women with a SHBG level above 160 nmol/l are unlikely to benefit from testosterone therapy [40].

2.6.4. Making the diagnosis

Once the patient has been assessed, the following information should be available:

- the nature of the problem(s) (see Table 1);
- its duration;
- whether it is primary or secondary;
- whether it is situational or generalised.

In addition, the physician should have established:

- whether there are any relationship problems;
- whether there is a disparity of desire between partners;
- whether there are stressors, such as family difficulties, exacerbating the problem;
- whether there are sexual problems in the partner (e.g. erectile dysfunction, premature ejaculation, HSDD—see below on sexual disorders in men);
- whether the woman has a history of physical, emotional or sexual abuse.

2.7. Treatment of female sexual problems

2.7.1. Types of interventions and treatments

The complexity of sexual function in women indicates that all patients reporting a problem of a sexual nature should be offered the opportunity for psychosexual and/or couples counselling or sex therapy [41]. Many psychological interventions can be proposed by clinicians who have not undergone detailed psychotherapy training as part of an integrated treatment package [42]. A number of pharmacological options are evolving which may form part of the treatment plan alongside any 'talking therapy' recommended to a woman [43].

The Third International Consultation on Sexual Medicine (Paris 2009) summarised the scientific evidence supporting mechanisms by which hormonal changes associated with ageing and endocrine disorders contribute to sexual dysfunction in women [44]. Natural and surgical menopause and endocrine disorders that alter estrogen and androgen precursors may affect female sexual function. However, hormones are only one component of the many factors that contribute to normal sexual function in women (see above).

Several trials have shown that testosterone therapy improves sexual desire and different routes of administration have been evaluated, including (more recently) patches [45]. Androgens may also be used by those women who are hypogonadal as a result of pituitary problems in the premenopause. However, although supra-physiological doses of androgens can enhance genital engorgement [46], community-based and clinical studies with a total of nearly 5000 women suggest there is no consistent correlation between sexual functioning and levels of androgens (free and total testosterone, androstenedione, dihydroepiendrosterone and SHBG) across a wide age range [24,25,47]. In any one woman, changes in androgens may or may not be relevant to her sexual functioning [46].

With these caveats in mind, a more detailed summary of the effects of androgens on women's sexual function is presented below, by type and route of administration of androgen. The evidence presented here was derived from a Cochrane review [48] and a PubMed review by the present authors in which relevant articles were retrieved after inputting the terms 'androgen', 'testosterone' and 'women'. The presentation here is mainly, but not exclusively, restricted to double-blind, randomised androgen treatment trials ('level 1' evidence).

2.7.2. Oral treatments

2.7.2.1. Testosterone. The Cochrane review [48] presented studies using either methyl-testosterone or testosterone undecanoate combined with oral estrogens versus estrogen-alone therapy [49–54]. Two of these studies [49,51] were undertaken with women who had had hysterectomies/oophorectomies. One showed a non-significant increase in sexual interest [49] and the other a significant increase in sexual interest, satisfaction with sexual frequency, and enjoyment of sex [51]. The larger study [49] involved 311 women and used methyl-testosterone; the smaller study involved 44 women and used testosterone undecanoate [51]. Three out of the four other studies of postmenopausal women showed statistically significant increases in sexual interest, satisfaction and frequency in the combined androgen/estrogen arms compared with estrogen alone [50,52,53]. The remaining study [54] had mixed results seen with different sexual function questionnaires.

2.7.2.2. Dehydroepiandrosterone (DHEA). DHEA and its sulfate, DHEAS, are physiologically secreted by the adrenals and are converted into potent androgens and estrogens in peripheral tissues. DHEAS levels in men and women are up 500 times higher than that of testosterone and up to 10,000 times higher than estradiol levels [55]. The peripheral conversion takes place at intracellular level,

according to local enzymatic control and needs. Overall, DHEA is preferentially transformed into androgens rather than into estrogens [56].

Clinical trials of the use of DHEA for improving sexual function in women have been reviewed by Panjari and Davis [57]. The authors identified seven randomised controlled trials, in which the dosages were highly variable (50 mg up to 1600 mg per day) and treatment lasted between 2 weeks and 12 months. All the studies were placebo controlled and the majority of participants were postmenopausal. Two studies included pre- and perimenopausal women. A positive effect on female sexual function was reported in only three studies. The reviewers commented that these trials were characterised by small sample size, inadequate study power and measurement of sexual functioning by non-validated instruments.

Overall, then, the more recent randomised controlled trials do not support a benefit of oral DHEA therapy for women. A possible benefit that has emerged, though, is that vaginally administered DHEA may improve vaginal atrophy, with concomitant improvements in sexual function in women who are estrogen deficient due to menopause [58].

DHEA can be bought over the counter in the US as a 'dietary supplement'. It is available via the Internet in the UK. A quality control study in 1998 looking at a number of brands of this product concluded that for only 7 of 16 preparations was the quality of the product as stated on the manufacturer's label [59].

2.7.2.3. Tibolone. Tibolone is a synthetic steroid; it is inert but, on absorption, is converted *in vivo* into metabolites with estrogenic, progestogenic and androgenic actions. It is used in postmenopausal women who do not wish to have withdrawal bleeds. It is classified as hormone replacement therapy (HRT) in the UK *British National Formulary*. It is used to treat vasomotor, psychological and libido problems. The daily dose is 2.5 mg. It conserves bone mass, and reduces the risk of vertebral and non-vertebral, but not hip, fracture.

A recent multicentre, double-blind, randomised, clinical trial compared over 24 weeks the efficacy on sexual function of tibolone (2.5 mg) and that of continuous combined transdermal estradiol (E2)/norethisterone acetate (NETA) (50 μg/140 μg) in naturally postmenopausal women with sexual dysfunction [60]. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) and the frequency of satisfying sexual events (daily diaries) were assessed. In total 403 women (mean age 56 years) were included. Both therapies improved sexual function as assessed by the FSFI. In the per protocol analysis, but not in the intent-to-treat analysis, the increase in FSFI scores was significantly larger in the tibolone group than in the E2/NETA patch group at week 24. The frequency of satisfying sexual events increased from three to four times per 28 days at week 24, but with no difference between groups. The FSDS score decreased significantly (indicating clinical improvement) from baseline in the two treatment groups.

Previous studies have also supported a beneficial effect of tibolone on libido; however, these used questionnaires developed before the international classification of sexual problems was put forward [61].

2.7.3. Parenteral treatments

2.7.3.1. Testosterone implants. Four blinded studies have been reported of testosterone plus estrogen versus estrogen-only implants, involving a total of 111 postmenopausal women [62–65]. All women reported loss of or low libido before the study. In one study women specifically seeking therapy for low libido were excluded from randomisation [64] as it was considered unethical for them to be randomised to the estradiol-only group and deprive such women of testosterone. In the three other studies there were significant improvements in sexual interest and responsiveness [62,63,65] (two used analogue scales and the other a validated inventory to measure this).

2.7.3.2. Intramuscular testosterone. A placebo-controlled study of 53 oophorectomised women showed that an intramuscular testosterone/estrogen combination resulted in significantly greater sexual desire and arousal than estrogen alone or placebo over 3 months [66].

2.7.4. Transdermal treatments

2.7.4.1. Transdermal testosterone patches (TTP). Five large placebo-controlled studies have examined the use of TTP for the treatment of low sexual desire (one study) or HSDD (three studies) in oophorectomised women taking estrogen replacement and naturally postmenopausal women not taking systemic estrogen (one study).

An initial crossover phase II study used an optimal dose of 300 μg per day and showed a broad increase in all sexual parameters, compared with placebo [67].

A larger phase II placebo-controlled parallel-dosing study using validated inventories with 318 such women confirmed the optimal daily dose to be 300 μg [68]. Women treated with 300 μg of testosterone per day had a statistically significant increase from baseline of 0.58 satisfying episodes per week, representing an increase of 79% from the baseline mean, compared with a 43% change from baseline in the placebo group. No statistically significant differences in the number of satisfying episodes were observed for the groups on 150 μg/day or 450 μg/day compared with placebo. Women treated with testosterone at 300 μg/day also experienced statistically significant increases in the total number of sexual events and the total number of orgasms at week 24 compared with women receiving placebo.

Two phase III studies, INTIMATE 1 and 2 [69,70], of 300 μg TTP per day versus placebo for 24 weeks showed statistically significant increases in the number of satisfying sexual acts per month and in sexual desire, as well as decreases in distress over that time compared with placebo. The two studies had 1094 participants in total. Looking at the results in more detail, the mean number of satisfying sexual acts rose to 5 from 3 (at baseline) in the TTP group and to 4 from 3 in the placebo group. Critics have suggested that an increase of one sexual act per month compared with placebo may not be clinically meaningful. An 'anchoring' study, however, has shown that those respondents who felt they had a meaningful response to TTP had 4.4 satisfying sexual acts per month compared with 0.5 in those who felt their response not to be meaningful and that 85% of the former group would wish to continue TTP [71].

A placebo-controlled dose-ranging study of TTP (150 μg and 300 μg) in 814 naturally postmenopausal women not taking systemic estrogen (HRT) found a modest but meaningful increase in sexual functioning in the 300 μg group compared with placebo [72].

2.7.4.2. Transdermal gels. A placebo-controlled randomised crossover study tested 10 mg testosterone gel per day in 53 postmenopausal women with low libido who were already taking estrogen–progestogen HRT. Addition of the gel increased a wide range of sexual functions, including desire [73].

A small placebo-controlled study in premenopausal women showed that testosterone gel used 4–8 h prior to sex significantly increased sexual arousal in the short term [74].

Androgens may also be used by those women who are hypogonadal as a result of pituitary problems in the premenopause.

2.8. Safety of exogenous androgens in women

This issue has been comprehensively discussed by Braunstein, initially in 2007 and subsequently with Shufelt [75–77]. He con-

ducted a MEDLINE literature review, cross-referencing published data, and reviewed the transcripts of the US Food and Drug Administration on this issue. He pointed out that although some retrospective and observational studies have provided long-term safety data, most prospective studies spanned two years or less. In addition, with the exception of high-dose testosterone given in isolation to female-to-male transsexuals, most other studies give testosterone with estrogens plus or minus progestogens, thus confounding their interpretation.

The major side-effects of androgens are hirsutism and acne. These are related to both the dose and the duration of treatment but are generally reversible when the androgen is discontinued. Up to 36% of women receiving oral methyl-testosterone have noted hirsutism [78]. The rates in women receiving implants, pellets or intramuscular injections may be as high as 20% and their frequency also appears to be dose related [75].

Hirsutism was reported overall in 7% of women receiving testosterone patches, versus 5% for controls, over a period of 24 weeks [68–70]. Corresponding rates for acne in these studies over 24 weeks were 9% in the 300 μg group and 7% for placebo patches [68–70]. Up to 45% of women receiving methyl-testosterone have developed significant acne. The rates for women receiving testosterone pellets or implants have been significantly lower [75].

Braunstein [75] concludes that testosterone rarely causes virilisation, that oral but not parenteral or transdermal androgens may lower HDL cholesterol, and that there appears to be no increase in cardiovascular risk through alterations in blood pressure, vascular reactivity, blood viscosity, haemoglobin concentrations, coagulation factors or insulin sensitivity. He further states that the data on endometrial cancer are too sparse to interpret and that giving androgens may in fact lower rates of breast cancer.

However, the Nurses' Health Study [79] found that the risk of breast cancer associated with current use of estrogen and testosterone therapy was significantly greater than that with estrogen-only therapy and marginally greater than that with estrogen and progesterone therapy. Women receiving hormone therapy with testosterone had a 17.2% (95% confidence interval 6.7–28.7%) increased risk of breast cancer per year of use.

The Women's Health Initiative Observational Study [80] found that estrogen plus testosterone (E + T) therapy (esterified estradiol plus methyl-testosterone) had a non-significant impact on the risk of invasive breast cancer. The most commonly used E + T preparation, Estratest, was, though, associated with a significant elevation in invasive breast cancer. However, rates of breast cancer were lower in longer-term E + T users than in shorter-term E + T users.

In a double-blind, placebo-controlled, 52-week trial, 814 postmenopausal women with HSDD not taking estrogen were randomly assigned to receive a patch delivering 150 or 300 μg testosterone per day or placebo. Breast cancer was diagnosed in three women in the testosterone groups between 4 and 12 months after treatment initiation, one of whom reported in retrospect a bloody nipple discharge before randomisation [72].

In the UK, data from the General Practice Research Database and the Health Improvement Network showed no major increase in the risk of cardiovascular diseases or breast cancer in women using testosterone (implants, tablets or injections) [81].

With regard to DHEA there is little good documented evidence for toxicity, although it seems likely its adverse effect profile is similar to that of other androgens [57,82].

Clinical studies suggest that the adverse event rate with low-dose transdermal testosterone therapy is similar to that with placebo, with mild localised skin reactions occurring in over 30% of women given active and placebo patches [71]. There is inadequate evidence from studies in premenopausal women to suggest any adverse effect on fertility [83].

There is no evidence to suggest a risk of liver disease with transdermal low-dose testosterone used for women [83]. There is an established relationship between increased risk of metabolic syndrome and type 2 diabetes in women with the naturally high androgen levels associated with polycystic ovarian syndrome but no evidence has been reported from published studies of low-dose transdermal testosterone [84].

A US Endocrine Society task force advised against the generalised use of testosterone by women, because of inadequate indications and lack of long-term data [46]. This advice has been updated with regard to postmenopausal hormone therapy, including the effect of estrogen, testosterone, DHEA and tibolone therapy on sexual function [40].

The North American Menopause Society in 2005 [85] concluded that:

> 'postmenopausal women with decreased sexual desire associated with personal distress and with no other identifiable cause may be candidates for testosterone therapy. When evaluating a woman for testosterone therapy, recommendations are to rule out causes not related to testosterone levels (e.g. physical and psychosocial factors, medications) and to ensure that there is a physiologic cause for reduced testosterone levels (e.g. bilateral oophorectomy). Laboratory testing of testosterone levels should be used only to monitor for supraphysiologic levels before and during therapy, not to diagnose testosterone insufficiency. Monitoring should also include subjective assessments of sexual response, desire, and satisfaction as well as evaluation for potential adverse effects. Transdermal patches and topical gels or creams are preferred over oral products because of first-pass hepatic effects documented with oral formulations.'

The Society's 2010 position statement [86] concluded that recent data support the initiation of hormone therapy around the time of menopause for either or both of two indications: to treat menopause-related symptoms; or to treat or reduce the risk of certain disorders, such as osteoporosis or fractures, in select postmenopausal women. The benefit–risk ratio for menopausal HRT is favourable for women who initiate it close to menopause but decreases in older women and with time after menopause in previously untreated women.

It must be noted that testosterone implants, which produce hormone levels that exceed those achieved with transdermal patches, have been used in the UK for nearly three decades [87]. At the time of writing no safety concerns with regard to these implants and breast cancer risk have been documented.

2.9. Monitoring and long-term care

It is unclear whether any routine monitoring is needed with long-term testosterone therapy. In addition to asking about side-effects, it would be good practice to measure fasting lipid and glucose levels after 6 months of therapy, if clinically indicated (e.g. by diabetes or hyperlipidaemia). If these are abnormal, a decision should be made as to how to improve them. If lifestyle changes or lipid-lowering drugs are inadequate, it may be prudent to consider stopping testosterone therapy.

A recent review of testosterone and SHBG and their relationship to cardiovascular disease and risk factors has been published [88]. Increased androgenicity, characterised by high testosterone and low SHBG levels, is associated with an adverse risk factor profile for cardiovascular disease in postmenopausal women. However, evidence for an association with cardiovascular events is lacking and it is uncertain whether the observed associations with androgynous testosterone have clinical implications regarding the use of postmenopausal testosterone therapy.

In the absence of adequate long-term data about the risk of testosterone on breast cancer, women should be encouraged to continue routine breast screening for the duration of testosterone therapy, and for the rest of their life. There is, though, no indication for increased frequency of breast screening. Neither is there a need for increased frequency of cervical cancer screening.

2.10. Androgens and female fertility

Androgens are the precursors of estrogens, into which they are converted by the enzyme aromatase (CYP19A1), most importantly in the granulosa cells of the growing ovarian follicle, and in adipocytes. Interest in androgens for women of reproductive age has focused on two main areas: their role within the ovary in the regulation of follicular growth; and the effects and implications of hyperandrogenaemia in polycystic ovarian syndrome. Additionally, the weak androgen DHEA may have beneficial effects in women with adrenal failure [89] and its potential as an adjunct in assisted conception has also been investigated [90], although it has not yet been subject to rigorous testing.

Investigation of the role of androgens within the ovary has often produced confusing results. This may partly reflect their role as precursors of estrogens. This has been partially avoided by the use of dihydrotestosterone (DHT), a non-aromatisable androgen, but DHT itself can be metabolised into substrates for the estrogen receptor beta subtype, complicating and potentially confounding interpretation. Nonetheless, it does appear that androgens contribute to the initiation and the early stages of follicle growth. At later stages, androgen receptors are expressed by granulosa cells and these also appear to promote follicle development and oocyte maturation. However, androgens are also involved in the regulation of granulosa cell death and hence follicular atresia; thus local concentration may be critical in determining whether the effect is positive or negative [91,92]. These and other mechanisms underlie the arrested follicular development characteristic of the hyperandrogenism of polycystic ovarian syndrome.

2.10.1. Treatment

Treatment of women with androgens to enhance fertility is rarely indicated. The woman with adrenal insufficiency may benefit from androgen replacement to improve symptoms such as loss of interest in sex, but this should be used with caution and discontinued immediately after pregnancy is achieved. The placenta has a very high level of aromatase activity, which normally protects the fetus from maternal androgens, but this is not established until the second trimester [93].

DHEA has also been investigated as an adjunct to *in vitro* fertilisation, especially where the woman has a reduced ovarian reserve, but this is not supported by the results of randomised controlled trials [90].

3. Men

Much of this section is based on three authoritative sources: current guidelines produced by a number of andrological societies and the International Society for the Study of the Aging Male (ISSAM) [94]; updated guidelines from the Endocrine Society [95]; and the Third International Consultation on Sexual Medicine (Paris 2009) in collaboration with the Standards Committee of the International Society of Sexual Medicine (ISSM) [96]. The level and grade of the supporting evidence (which is better established for men than it is for women) is noted where relevant.

3.1. Androgens and male physiology

The role of androgens in maintaining well-being in men is well established [97]. An increasingly common problem encountered by clinicians is late-onset hypogonadism (LOH), also referred to as age-associated testosterone deficiency syndrome (TDS). This is a clinical and biochemical syndrome associated with advancing age; it is characterised by a deficiency in serum testosterone levels (below the young healthy adult male reference range) [94,98]. This condition may greatly reduce quality of life and may adversely affect the function of multiple organ systems. Common symptoms include fatigue, reduced well-being, depression, loss of concentration, hot flushes and sweats, reduced muscle mass and weakness and reduced body hair. The sexual symptoms usually associated with testosterone deficiency include low sexual libido, erectile dysfunction and ejaculatory dysfunction. LOH was recently defined by Wu et al. as the presence of poor morning erection, low sexual desire and erectile dysfunction, a total testosterone level of less than 11 nmol/l and a free testosterone level of less than 220 pmol/l [99].

3.2. Laboratory measurements of androgens in men

Since the clinical features of hypogonadism are relatively non-specific, it is essential to establish the diagnosis by the documentation of low serum total testosterone. There are no generally accepted lower limits of the normal range for testosterone, however. There is, though, general agreement that a total testosterone level above 12 nmol/l (350 ng/dl) does not require replacement. Similarly, based on data from younger men, there is consensus that patients with serum total testosterone levels below 8 nmol/l (230 ng/dl) will usually benefit from testosterone treatment. If the serum total testosterone level is between 8 and 12 nmol/l, repeating the measurement of total testosterone with sex hormone binding globulin (SHBG) to calculate free testosterone, or free testosterone by equilibrium dialysis, may be helpful (see below) (level 2b, grade A).

For total testosterone determination (level 2a, grade A) blood should preferably be taken at 9 am and certainly between the hours of 7 and 11 am, without fasting.

The reference method for testosterone is isotope dilution gas chromatography mass spectrometry (ID-GCMS). Methods based on mass spectrometry are more accurate and precise [100] (level 2b, grade A) and are increasingly recognised as the method of choice for serum testosterone measurement in men but they are currently not widely available.

Equilibrium dialysis is the gold standard for free testosterone measurement. Assays of free testosterone based on analogue displacement immunoassays are widely available but do not give an accurate measurement and so should not be used [101].

Alternatively, measuring serum SHBG and albumin levels together with a reliable serum total testosterone level provides the data necessary for calculating free testosterone levels (level 2b, grade A) (a free on-line calculator is available at www.issam.ch), and calculated free testosterone levels correlate well with those determined by equilibrium dialysis. Clinicians should be aware that there are various formulae for deriving free testosterone, using different binding constants to Vermeulen's, and giving different values and ranges [102].

Determination of the salivary testosterone level has been shown to be a reliable substitute for free testosterone measurements, but cannot be recommended for general use because the methodology has not been standardised and adult male ranges are not available in most hospital or reference laboratories [103] (level 3, grade B).

Measurements of serum levels of luteinising hormone will assist in differentiating between primary and secondary hypogonadism, and a determination of serum prolactin level is indicated when the serum testosterone is lower than 5.2 nmol/l (150 ng/dl) [104–107] or when secondary hypogonadism is suspected [108–110] (level 3, grade B).

Since the various methods for the measurement of testosterone (both platform-based immunossays and mass spectrometry) are known to produce different results, it is imperative that health professionals use reliable laboratories and are acquainted with the reference ranges established by their local laboratory from healthy volunteers [111,112] (level 2b, grade A). Currently, international efforts are under way to harmonise testosterone measurements and cross-calibration against reference standards and methodologies between laboratories will be required in the near future.

3.3. Epidemiology of sexual problems in men

Problems of sexual function are relatively common in men, but persistent problems are much less so. One study reported the prevalence of the latter – sexual problems lasting at least 6 months in the previous year – as 6.2% and the most common was premature orgasm [113]. The Baltimore Longitudinal Aging Study reported that 8.4% of men between the ages of 50 and 79 years were hypogonadal [114]. Studies of the prevalence of testosterone deficiency in men with erectile dysfunction (ED) have reported rates in a range from less than 3% to around 12% [115,116]. The prevalence of repeatedly low testosterone in men with ED increases with age (4% before age 50 years and 9% among those 50 years or older) [117].

3.4. Risk factors for male sexual dysfunction

Risk factors for hypogonadism in older men include: chronic illnesses (including diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic, renal and HIV-related diseases), obesity, prolactinoma, excessive alcohol consumption, metabolic syndrome and haemachromatosis [108]; and chronic opiate therapy and androgen deprivation therapy (for prostate cancer). Such chronic conditions should be investigated and treated (level 4, grade A).

3.5. Assessment of men with sexual problems

3.5.1. Consultation

The most common presentation of hypogonadism arises from screening investigations for patients presenting with erectile dysfunction and/or reduced sexual desire. The demand of the patient to achieve a satisfactory sexual response is a major driver for testosterone therapy, either alone or in conjunction with erectogenic therapy.

Increasingly, men with type 2 diabetes are being screened as part of NICE guidance, as the prevalence of erectile dysfunction in this population is over 75% and low testosterone is associated with insulin resistance and impaired diabetes control [118,119].

3.5.2. Initial assessment

At present, the diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency, as well as biochemical evidence (level 3, grade A) [94,108]. The symptom most associated with hypogonadism is low libido. Other manifestations of hypogonadism include: erectile dysfunction, delayed ejaculation, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood. None of these is specific to the low-androgen state but may raise suspicion of testosterone deficiency. The initial assessment of all men with erectile dysfunction and/or diminished libido should therefore include determination of serum testosterone (see above on laboratory methods). These dysfunctions, with or without a testosterone deficiency, may also be related to co-morbidities, such as diabetes mellitus, hyperprolactinaemia, metabolic syndrome, bladder outlet obstruction and peripheral vascular disease, or they may be a side-effect of medication (level 2a, grade A) [120].

Clinical assessment should be made in person by the consulting physician and not reliant on non-specific unvalidated questionnaires.

3.5.3. Detailed investigation: laboratory diagnosis

In patients at risk of or suspected of having hypogonadism, a thorough physical and biochemical work-up is necessary (level 4, grade A). Transient decreases in serum testosterone levels, for example as a consequence of acute illness, should be excluded by careful clinical evaluations and repeated hormone measurement. Hypogonadism (primary or secondary) can occur at all ages, including in elderly men.

The free androgen index (total testosterone divided by SHBG, $\times 100$) is of limited value in men.

Measurement of free or bioavailable testosterone (see above) should be considered when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in obese men. There are no generally accepted lower limits of normal for free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 225 pmol/l (65 pg/ml) can provide supportive evidence for treatment with testosterone [5] (level 3, grade C). Threshold values for bioavailable testosterone depend on the method used and are not generally available [5].

The prolactin level should be measured to avoid missing a prolactinoma.

Alterations in other endocrine systems occur in association with ageing (i.e. estradiol, GH and DHEA) but the significance of these changes is not well understood. Determinations of estradiol, thyroid hormones, cortisol, DHEA, DHEAS, melatonin, GH and IGF-I are not indicated unless other endocrine disorders are suspected, based on the clinical signs and symptoms of the patient [108] (level 2, grade A).

3.5.4. Treatment of male sexual problems

Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy (level 2a, grade A). An inadequate response to testosterone treatment requires reassessment of the cause of the erectile dysfunction.

Hypogonadal men restored to the eugonadal state with testosterone replacement may experience [121,122]:

- a general improvement in sexual function, particularly ejaculation, orgasm and penile sensation;
- improved erection;
- restored or enhanced responsiveness to PDE5 inhibitors [123].

The last is an important indication for androgen replacement, especially if restoration of erectile function is a priority for the patient. This issue is particularly relevant to men with type 2 diabetes, where response to PDE5 inhibitors alone may be little more than 50%.

In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short therapeutic trial (e.g. up to 6 months) of testosterone may be justified. An absence of response calls for discontinuation of testosterone. The aim of therapy should be a total testosterone level of at least 15 mmol/l to ensure symptomatic improvement [121–127]. A satisfactory response may be generated by placebo, and so continued assessment is advisable before long-term treatment is recommended [128] (level 2a, grade B).

Age is not a contraindication to testosterone treatment. Individual assessment of co-morbidities (as possible causes of symptoms)

and of the potential risks versus benefits of testosterone treatment is particularly important in elderly men (level 2a, grade A). The situation is clearer in younger men, where hypogonadism is usually associated with specific clinical diagnoses.

The diagnosis of hypogonadism should be confirmed before any androgen therapy is initiated. Once patients are on therapy, it is useful to monitor their levels of total testosterone and SHBG (or bioavailable or free testosterone) to ensure normal serum testosterone concentrations are being achieved.

Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety. For the present time, serum testosterone levels in the middle to lower normal range of young adult males seem appropriate as the therapeutic goal [129]. Sustained supraphysiological levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels (level 3, grade B).

Obese men are more likely to develop adverse effects [129,130] (level 2b, grade B).

3.5.5. Types of interventions and treatments

Preparations of natural testosterone should be used for substitution therapy. Intramuscular, subdermal, transdermal, oral and buccal preparations of testosterone are safe and effective (level 1b, grade A). The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation should be a joint decision of an informed patient and physician [130].

Because any adverse events during treatment (especially elevated haematocrit or prostate carcinoma) [131] require rapid discontinuation of testosterone substitution, short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with late-onset hypogonadism (level 4, grade C).

There is evidence of therapeutic synergism with the combined use of testosterone and phosphodiesterase-5 inhibitors (PDE5i) in hypogonadal or borderline eugonadal men [122] (level 1b, grade B). The combination treatment should be considered in hypogonadal patients with erectile dysfunction who fail to respond to either treatment alone. It is suggested that men with hypogonadism and erectile dysfunction should be treated with testosterone prior to the introduction of a PDE5i.

Preparations of 17-a-alkylated androgens such as 17a-methyltestosterone are obsolete because of their potential liver toxicity and should no longer be prescribed (level 2b, grade A).

There is not enough evidence to recommend substitution of dihydrotestosterone in ageing men; other non-testosterone androgen precursor preparations such as DHEA, DHEAS, androstenediol or androstenedione are not recommended (level 1b, grade A).

Human chorionic gonadotropin (hCG), also known as chorionic gonadotrophin, stimulates the testosterone production of Leydig cells, albeit at a lower rate in older than in younger men. It may be self-administered subcutaneously two or three times weekly, which some men may find more convenient than an intramuscular injection. However, because insufficient information exists about the therapeutic and adverse effects of hCG treatment in older men (a rise in estradiol levels and gynaecomastia) and its relatively high cost, this treatment cannot be recommended in late-onset hypogonadism, except when fertility is an issue (see below on male fertility) (level 1b, grade B). Furthermore, hCG may be self-administered subcutaneously two or three times weekly, which some men may find more convenient than an intramuscular injection.

Anti-estrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels (level 2b, grade B) but there is inadequate evidence to recommend their use. Selective androgen receptor modulators are in clinical development but not yet available. Many of these compounds are non-aromatisable and the risks of long-term use are unclear.

3.6. Safety of replacement testosterone in men

Men with significant erythrocytosis (haematocrit > 50%) (level 3, grade A), untreated obstructive sleep apnoea (level 3, grade B) or untreated severe congestive heart failure (level 3, grade B), breast or prostate cancer should not be started on treatment with testosterone without appropriate treatment of these co-morbid conditions [130,132].

3.6.1. Risk analysis: prostate cancer and benign prostatic hyperplasia

The risk, if any, of prostate pathologies in men on long-term testosterone therapy is currently unknown.

There is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or benign prostatic hyperplasia (BPH) [133–136]. There is also no evidence that testosterone treatment will convert sub-clinical prostate cancer to clinically detectable prostate cancer (level 4, grade C).

Currently, adequately powered and optimally designed long-term studies of prostate disease are not available to determine whether there is any additional risk from testosterone replacement.

Hypogonadal older men should be counselled on the potential risks and benefits of testosterone replacement before treatment and be carefully monitored for prostate safety during treatment (level 3, grade A).

In men over the age of 40 years, prior to therapy with testosterone, the risk of prostate cancer must be assessed using digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA). However, the pre-treatment assessment can be improved by incorporating other risk predictors, such as age, body mass index, family history and ethnicity/race. If the patient and physician feel that the risk is high – PSA > 4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African-Caribbean or men with first-degree relatives who have prostate cancer) – further urological assessment may be desirable [137,138] (level 2a, grade B). However, pre-treatment prostate ultrasound examinations or biopsies are not recommended as routine requirements.

After initiation of testosterone treatment, patients should be monitored for prostate disease at 3–6 months, 12 months, and at least annually thereafter (level 3, grade C). Confirmed PSA increments >1.4 ng/ml during any 1-year period after initiation of testosterone therapy or a PSA velocity >0.4 ng/ml per year during sequential PSA measurements for periods of more than two years should warrant a urological evaluation and more intensive future surveillance for prostate cancer. The combined application of PSA and digital prostate examination improves the prostate cancer detection rate over either test alone.

Severe symptoms of lower urinary tract symptoms (LUTS) – evident, for example, by a high score (over 19) on the International Prostate Symptom Scale (IPSS) – due to benign prostate hyperplasia represents a relative contraindication (although there are no clear data to suggest that testosterone treatment causes exacerbation of LUTS or promotes acute urinary retention) (level 3, grade C). After successful treatment of lower urinary tract obstruction, this contraindication is no longer applicable (level 4, grade C).

Men successfully treated for localised prostate cancer through appropriate treatment such as radical prostatectomy or radiotherapy and suffering from confirmed symptomatic hypogonadism are potential candidates for testosterone substitution, after a prudent interval (at least two years), if there is no clinical or laboratory evidence of residual cancer [139–141]. As long-term outcome data

are not available, clinicians must exercise their clinical judgement, together with adequate knowledge of advantages and drawbacks of testosterone therapy in this situation (level 2b, grade C). The risks and benefits must be clearly discussed with and understood by the patient and the follow-up monitoring must be particularly careful, with serial PSA estimations. The use of testosterone in patients with locally advanced or metastatic prostate cancer is absolutely contraindicated.

3.7. Monitoring and longer-term care

For monitoring, the timing of serum testosterone measurements varies with the preparation that is used. The 'trough' serum testosterone should be measured before injections in men receiving parenteral testosterone enanthate, Sustanon or testosterone undecanoate and the total testosterone value should be at the lower end of the physiological range. The frequency of injection should be decreased or the dose reduced if higher values are obtained.

Serum testosterone can be measured at any time in men who are using a transdermal preparation. Peak values occur 6–8 h after application of a patch. If a gel is used, concentrations fluctuate, but not in a predictable way. This means that at least two measurements should be made at any dose of gel (any time after the first week of treatment) and the time of measurement does not appear to matter. The value should be within the mid-normal range (17–20 nmol/l). Men receiving pellets should have the measurement taken at the end of the dosing interval.

Erythrocytosis can develop during testosterone treatment, especially in older men treated with injectable testosterone preparations. Haematological assessment is indicated before treatment, then at 3–4 months and 12 months, and annually thereafter. To keep the haematocrit below 52–55%, dose adjustments and/or periodic phlebotomy may be necessary [108,130,142] (level 3, grade A).

Assessment of treatment outcome and decisions about continuing therapy should be based on improvement in signs and symptoms of testosterone deficiency. Failure to benefit within a reasonable time interval (up to 6 months is adequate for libido and sexual function, muscle function and improved body fat) should result in discontinuation of treatment. Further investigation for other causes of symptoms is then mandatory (level 1b, grade A).

3.8. Androgens and male fertility

Assessment of male fertility is based principally on semen analysis, but supplemented with physical examination and laboratory testing of hormones and karyotype where appropriate. Semen analysis should be performed by an accredited laboratory, using methods based on the current WHO manual [143]. It should, however, be recognised that there is limited evidence from prospective studies linking specific aspects of the semen analysis with fertility. While many men with classical hypogonadism will be azoospermic, men with later-onset and partial degrees of testosterone deficiency may remain fertile, with normal or near-normal semen analysis, and even a severe degree of oligozoospermia cannot be taken to indicate sterility. It is therefore important to discuss fertility and contraceptive use with all men with hypogonadism, as unexpected fertility may result in unplanned and unwanted pregnancy.

3.8.1. Treatment

Treatment to enhance fertility will depend on the underlying condition and particularly whether there is primary (i.e. hypergonadotrophic) or secondary (hypogonadotrophic) hypogonadism. Azoospermia with elevated gonadotrophins indicates testicular failure and treatment with gonadotrophins is not indicated. Fertility in apparently azoospermic men can be achieved in some cases of primary hypogonadism (e.g. Klinefelter syndrome) with testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI). While published data appear encouraging, it is likely that this reflects publication bias to some extent and the patient's expectations should be managed appropriately.

It is possible that surgical biopsy of the small testis of men for TESE with Klinefelter's syndrome may hasten the onset of testosterone deficiency.

Treatment of secondary hypogonadism will be primarily that of the underlying condition (such as pituitary tumour), with subsequent assessment of the need for gonadotrophin treatment if fertility is required. Endogenous testosterone production can readily be restored to normal in most men with twice-weekly injection of 2000–5000 IU hCG. In some, this can be sufficient to restore spermatogenesis. If, however, the patient remains azoospermic after 6 months with normalised testosterone production, FSH should also be administered. This is often given in 150 IU doses three times a week. Addition of FSH will be required in almost all men who have not gone through spontaneous puberty [144,145]. Treatment duration relates to pre-treatment testis volume, but treatment may be required for more than two years. Many men will not achieve a normal semen analysis, but those who have not gone through spontaneous puberty and do not have any testicular pathology (e.g. Kallmann's syndrome) will often become fertile, with markedly oligozoospermic semen analysis [146]. A less expensive, though unlicensed, option, which may be appropriate for men with mild primary hypogonadism wishing to preserve fertility, is the daily administration of 25–50 mg clomiphene [121].

Once pregnancy has been achieved, the possibility of cryopreservation of sperm to allow subsequent pregnancy should be discussed and arranged if requested. Reversion to conventional testosterone replacement should occur after the first trimester of pregnancy, that is, from 12 weeks' gestation.

3.9. Involvement of androgens in other conditions in men

3.9.1. Metabolic syndrome

Many of the components of the metabolic syndrome (obesity, hypertension, dyslipidaemia, impaired glucose regulation and insulin resistance) are also present in hypogonadal men. Further, epidemiological studies have established a close relationship between obesity and low serum testosterone levels in healthy men. For instance, Kalyani and Dobs [147] found that 20–64% of obese men have a low serum total or free testosterone level. The metabolic syndrome and type 2 diabetes mellitus are associated with low plasma testosterone [118,119,148,149]. These associations are predominantly cross-sectional and the directionality of the relationships are unclear [150]. Serum testosterone should be measured in men with type 2 diabetes mellitus who have symptoms suggestive of testosterone deficiency (level 2b, grade A).

The effects of testosterone administration on the glycaemic control of men with diabetes mellitus are uncertain. It is premature to recommend testosterone treatment for the metabolic syndrome or diabetes mellitus in the absence of laboratory and other clinical evidence of hypogonadism. In men with hypogonadism and diabetes and/or the metabolic syndrome, testosterone treatment for traditional hypogonadal symptoms may have other unproven benefits on their metabolic status (level 2a, grade B).

3.9.2. Body composition

Testosterone administration improves body composition (decrease of fat mass, increase of lean body mass) in men with hypogonadal testosterone levels [151] (level 1b, grade A). Secondary benefits of these changes of body composition in relation to strength, muscle function, metabolic and cardiovascular dys-

function are suggested by available data but require confirmation by large-scale studies.

3.9.3. Bone density and fracture rate

Osteopenia, osteoporosis and fracture prevalence rates are greater in hypogonadal men at any age. Bone density in hypogonadal men of all ages increases under testosterone substitution [152] (level 1b, grade A). Fracture data are not yet available and thus the long-term benefit of testosterone requires further investigation. Serum testosterone measurements should be obtained in all men with osteopenia and osteoporosis [153,154]. Serial assessment of bone density may help in the monitoring of response to and compliance with testosterone replacement in hypogonadal men.

3.10. Summary of recommendations

Women:

- Consideration should be given to routinely asking women if they have any sexual concerns, especially those at high risk. These include women who have premature surgical menopause, urogenital atrophy, depression or a history of sexual abuse.
- Biochemistry assays of testosterone are of limited value and are not routinely recommended.
- Assessment may be undertaken over several consultations and may involve the use of validated questionnaires.
- Treatment should be based upon clinical symptoms and may be long term.
- Treatment of women with sexual desire and arousal problems should be individually tailored and may include psychosexual therapy, estrogen, testosterone or tibolone.

Men:

- Consideration should be given to routinely asking men if they have any sexual concerns, especially those at high risk. These include men with diabetes, osteoporosis (fragility fractures), chronic opiate therapy, cardiovascular disease, erectile dysfunction and depression.
- The diagnosis of hypogonadism is based upon appropriate symptoms combined with reliable measurement of testosterone in the morning on more than one occasion.
- Assessment may be undertaken over several consultations and should not be reliant on questionnaires.
- Treatment should be based upon the presence of clinical symptoms and not on hormone levels alone.
- Frequently, diagnosis and the decision to treat are not clear cut, so that short-term therapeutic trials (of 3–6 months) and continuing assessment of response, with review of diagnosis, are helpful.
- Men receiving testosterone replacement require regular medical review, including surveillance of prostate pathologies and polycythaemia in those over the age of 40 years.
- Treatment of men with sexual desire, arousal and ejaculatory problems should be individually tailored and may include psychosexual therapy, testosterone and erectogenic agents.

Contributors

The authors contributed equally to the production of this guideline.

Competing interest

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