Androgen replacement in women

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1. Introduction

Over the past few years female androgen deficiency has climbed onto centre stage, both in the perception of the scientific community and, importantly, of the lay audience. This development comes shortly after the results of the Women’s Health Initiative have brought the concept of postmenopausal estrogen progestin replacement to a stand still [42] and itself had to take a blow when the controversial and widely debated Endocrine Society Guidelines on female androgen replacement became available in early 2006 [50]. Importantly, it is far from certain that the ovary invariably loses its androgenic capacity during the menopausal transition while it is a proven and definitive fact that ovarian estrogen synthesis ceases with menopause. However, facts on female androgen physiology are still not well known and the use of insufficiently or ill-defined terms like ‘female androgen deficiency syndrome’ and ‘hypoactive sexual desire disorder’ have muddied the waters further, provided little help with precise definition of female androgen deficiency. Clinical experience with androgen therapy in women is still limited, in particular with regard to randomized controlled trials. The FDA recently denied approval of an androgen replacement tool for women because of concerns about paucity of long term safety data. This review aims to summarize currently available information on androgen therapy in women, highlighting in particular areas where further studies are required.

2. Androgen biosynthesis in women

In humans, the adrenal glands and the ovaries represent the main source of circulating androgens in women. The adrenal steroid dehydroepiandrosterone (DHEA) represents the crucial precursor of human sex steroid biosynthesis. DHEA and its sulphate ester (DHEAS) are the most abundant steroids in the human circulation. DHEA is mainly released from the adrenal zona reticularis [1] and only desulphated DHEA, but not DHEAS, can be converted downstream toward sex steroids. Recent evidence suggests that hydrolysis of DHEAS to DHEA may have to be restricted to some peripheral tissues including prostate and mammary gland while the rate-limiting step regulating the equilibrium between DHEA and DHEAS will be DHEA sulfotransferase activity converting DHEA to DHEAS [26]. A significant amount of the total androgenic pool derives from androgen synthesis within peripheral target cells of androgen action. In addition, DHEA may serve as a prohormone for ovarian androgen synthesis [27]. Transient adrenal suppression by dexamethasone in healthy young women leads to a 90% decrease in circulating DHEA and DHEAS and also reduces circulating testosterone (T) and dihydrotestosterone (DHT) levels to 30–40% of their respective baseline levels [5]. DHEA, DHEAS and androstenedione do not have androgenic activity unless they are converted to T and DHT, which can both bind and activate the androgen receptor. Therefore, the term “adrenal androgens” is imprecise and should rather be replaced by ‘adrenal androgen precursors’. T can be converted either to DHT, which has a five times higher binding affinity to the androgen receptor or it can be aromatized towards estrogens. DHT cannot be aromatized. Therefore, it is important to realize that an increase in the circulating T pool will invariably be associated with increased estrogen generation within peripheral target tissues of sex steroid action.

In women, significant androgen production physiologically starts during adrenarche, i.e. the increase of adrenal DHEA and DHEAS production from previously non-detectable levels occurring between the 6th and 10th year of age. This leads to an increased conversion of DHEA toward active androgens in peripheral target cells like the skin and characteristically results in the first appearance of pubic hair (‘pubarche’). Adrenarche is independent of the onset of menarche. In girls who do not undergo adrenarche, ovarian maturation and folliculogenesis is not affected, but circulating androgen levels invariably remain low. The intraindividual maximum of DHEA and DHEAS production is reached in early adulthood, followed by a steady decline throughout adult life, eventually decreasing to 10–20% of previous maximum levels by 70–80 years of age [2, 37,38]. This age-associated decrease has been termed “adreno-

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pause,” in spite of the fact that adrenal glucocorticoid and mineralocorticoid secretion rates are maintained without change throughout one’s lifetime. Adrenopause is independent of menopause, and it occurs in both sexes.

The degree to which naturally occurring menopause affects circulating androgen levels has been a matter of debate. Studies in subjects with dexamethasone-induced adrenal suppression indicate that the resulting decrease in serum androgen levels seemed to be more pronounced in postmenopausal [18] than in premenopausal women [5]. This suggests that the ovarian contribution to the total androgenic pool may be lower during menopause. However, DHEA of adrenal origin may still be converted to T within the postmenopausal ovary. Cross-sectional and longitudinal studies during the menopause transition found no evidence of a significant decrease in circulating androgens [16,34]. This was confirmed by a recent study from Australia studying a carefully selected, population based reference sample of 595 women in whom all potential co-founding variables impacting on androgen levels had been excluded [22]. This extremely well designed and adequately powered study describes a gradual but modest decline of circulating androgens (T, free T, Androstenedione and DHEAS) with age [22]. However, menopause did not significantly impact on serum androgens. Thus, the ability of ovarian theca cells to synthesize androgens apparently persists after menopause, despite the loss of estrogen production in granulosa cells. This is also illustrated by the finding that bilateral oophorectomy in postmenopausal women leads to a significant decrease in circulating levels of androgens [22,29].

3. Female androgen deficiency – how to define what

The 2002 Princeton consensus statement issued by an expert panel from the United States and Australia defined “female androgen deficiency syndrome” (FADS) as a state that may be diagnosed in women who meet all of the following three criteria: firstly, impaired well-being or libido, secondly, adequate estrogensation (i.e. either normal ovarian function or established estrogen replacement therapy) and thirdly, serum androgen concentrations below or within the lower quartile of the female normal range [7]. However, this seems to be a rather loose definition as impaired mood and libido are multifactorial in origin and thus cannot be considered specific indicators of androgen deficiency. It does not seem feasible to consider androgen replacement for every woman with self-perceived impaired well-being, who also happens to have serum androgen concentrations within the lower quarter of the normal range.

An even more problematic development is to consider the diagnostic term “Hypoactive sexual desire disorder” (HSDD) as a sufficient justification for the initiation of androgen replacement therapy. According to the consensus of the Sexual Function Health Council of the American Foundation for Urologic Disease (AFUD), comprising 19 experts from five countries, HSDD is defined by the concurrent presence of the following two criteria: firstly, persistent or recurrent deficiency (or absence) of sexual fantasies, thoughts, and/or desire for, or receptivity to, sexual activity; secondly, personal distress caused by the sexual dysfunction described in the first criterion [11]. HSDD is obviously of multi-factorial origin and androgen deficiency is not part of its definition. If we were to base the indication for androgen therapy in women on the presence of HSDD, we would start to treat a large proportion of the general population, with recent figures indicating a 50% incidence of female sexual dysfunction based on the AFUD criteria in gynecologic and uro-gynecologic out-patient cohorts [24]. The presence of HSDD alone is certainly no justification for the initiation of androgen treatment.

However, the field experienced a complete turn around with lots of political repercussions after the Endocrine Society Guidelines on Female Androgen Replacement were published, first online and then later in print in the JCE&M [50]. Surprisingly, the expert panel suggested that at present the diagnosis of androgen deficiency cannot be established due to a lack of data and tools to precisely measure female androgens, with the subsequent conclusion that at present no women should receive androgen replacement therapy. This is a view that is certainly difficult to accept, in particular as the nearly concurrently published androgen replacement guidelines for male patients took a different view [40], based on not many more or even less trials available in the public domain.

In contrast to the view provided in the Endocrine Society Statement on Androgen Therapy in Women [50] there is a wealth rather than a paucity on androgen data in women. Importantly, a recently published cross-sectional study in a large cohort of Australian women (n=1423) found no significant correlation of circulating androgen levels with self-reported perception of sexual desire and sexual satisfaction [19]. Interestingly, though the majority of women with a low DHEAS did not have low sexual function, a low DHEAS (10th percentile) was still significantly associated with higher odds of impaired sexual function [19]. However, no data were provided on circulating levels of biologically active, desulfated DHEA in this cohort. It is well described that circulating DHEAS can be decreased in chronic disease or stress and this may also contribute to the observed decrease in libido in those women. The data from the Australian cohort were further corroborated by the results of the recently published Study of Women’s Health Across the Nation (SWAN) [43] that studied circulating androgens in a community-based cohort of 42- to 52-year-old women (n=2961). Only modest or minimal associations of T with increased sexual desire and DHEAS with functional status and self-reported health were found, but androgens were most strongly associated with markers of metabolic syndrome (body mass index, waist circumference, and waist-hip ratio) [43].

The currently available facts on female androgen physiology clearly suggest that women with significant, near-total depletion of androgens are the most suitable candidates for androgen replacement. Women invariably develop severe androgen deficiency following bilateral oophorectomy, confirming the important role of the ovaries as a source of active androgens. Similarly, women with adrenal insufficiency usually present with significant androgen deficiency due to the pathologic loss or decrease in adrenal DHEA synthesis.
Pharmacologic glucocorticoid treatment, e.g. for asthma or rheumatic diseases, invariably results in suppression of adrenal DHEA synthesis following feedback inhibition of ACTH release and therefore also associated with androgen deficiency. Women with one of these established causes of severe androgen deficiency and concurrent complaints of impaired wellbeing and libido are likely to benefit from androgen replacement therapy. Women with premature ovarian failure of autoimmune origin may also have pathologically decreased androgen levels. However, DHEA production in premature ovarian failure persists [12] and therefore androgen deficiency is less pronounced. Furthermore, premature ovarian failure may in some cases be associated with even increased androgen levels, possibly as a consequence of a considerable variability in the extent of destruction of androgen-producing ovarian theca cells [6]. Women with Turner syndrome may also suffer from significant androgen deficiency [25].

It is important to consider the assays employed for assessment of androgen deficiency, when establishing a diagnosis of severe androgen deficiency based on hormone measurements. Some luminometric assays used for determination of free T levels may be problematic; whereas, radioimmunoassays (RIAs) generally are reliable. Concurrent measurement of total T and sex hormone-binding globulin (SHBG) concentrations may represent an alternative when no RIA for free T is available. T and SHBG levels can be used to calculate the free androgen index (FAI), where FAI = (T nmol/l × 100)/SHBG nmol/l [8]. Importantly, estrogens increase SHBG concentrations, and thus decrease the FAI. Consequently, if assessing androgen deficiency in a woman treated with an oral contraceptive or estrogen replacement therapy, one should always consider first reducing the estrogen dose rather than immediately initiating androgen therapy. Furthermore, the progestin component of oral contraceptives may exert anti-androgenic properties, e.g. cyproterone acetate or drospirenone, and should be exchanged for another progestin if problems like loss of libido occur.

4. Administration of testosterone in women

Androgen replacement therapy is a challenge even when treating men, but adjusting androgen levels to the normal range in women has proven to be even more difficult. Oral T preparations show a broad variability with regard to resorption. Methyltestosterone and T undecanoate have short half-lives and require repeated administration. Their pharmacokinetic properties lead to supraphysiologic androgen levels shortly after resorption, followed by rapid decline. Not surprisingly, some studies in which a single daily dose of methyltestosterone was used for androgen therapy in women did not detect any increase in circulating androgen levels [36]. Subcutaneous T depot implants have the advantage that they only need to be administered every four to six months. However, even the smallest available dose (100 mg) induces supraphysiologic androgen levels for several weeks to several months after implantation [15]. Recently introduced transdermal androgen patches are more convenient to use but may still have some unfavorable pharmacokinetic properties [15], sometimes resulting in supraphysiologic active androgen levels in treated women [46]. Optimization of transdermal delivery system is underway which will include testosterone gel and cream preparations already in use for men and first experiences have been published [10]. However, it is important to keep in mind that none of the currently available options is officially approved for the use in women.

Some studies have used the synthetic testosterone analogue oxandrolone to examine effects of androgen replacement in women with Turner’s syndrome [41]. This synthetic androgen has been previously used to induce growth-promoting effects in Turner syndrome patients. Oxandrolone is a low-affinity androgen receptor agonist with 10–100 times lower activity than T and DHT [28]. Oxandrolone cannot be aromatized, thus its effect is mediated via the androgen receptor only. However, one obvious disadvantage of treatment with synthetic anabolic steroids is that drug monitoring is more difficult as serum testosterone levels cannot serve as a parameter for treatment surveillance.

5. Studies investigating the efficacy of testosterone therapy in women

Most if not all of the studies published to date concentrated on potential effects on female libido and well-being and recorded androgenic skin effects while data on lipids, insulin sensitivity, body composition are much more scare, and often preliminary. When interpreting the results of studies on the effects of androgen treatment in women several methodological issues have to be considered. Firstly, due to the pharmacokinetic properties of available T preparations most published studies focused on the effects of treatments associated with supraphysiologic androgen levels. Secondly, several studies were not carried out in a double-blind fashion, thus precluding proper assessment of the effects of androgens on self-perceived mood and libido. Thirdly, most of the earlier studies in this field compared the effects of conventional estrogen/progesterin HRT with the effects of HRT + androgens in previously untreated, symptomatic postmenopausal women. The effect of initiating estrogen treatment in these women was so dramatic that any additional benefit of androgen treatment was almost non-detectable [35]. Table 1 summarizes the published studies employing T treatment in women.

Results of two studies that employed T implants and oral methyltestosterone in addition to HRT indicated significant beneficial effects on bone mineral density [9,20]. However, the degree to which these effects were due to aromatization, thus representing estrogen rather than androgen effects, is unclear. The effects on body composition are inconsistent, and while mostly a gain in lean body mass was reported [23, 30], there were reports of both a gain [30] and a loss [23] in fat mass. The small number of participants and the lack of longer-term studies currently prevent proper evaluation of effects of testosterone treatment on body composition, bone mineral density or insulin sensitivity. Study results showing androgen effects on lipids are also heterogeneous, but androgens are con-
Table 1
Randomized controlled studies on testosterone treatment in women

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants Description</th>
<th>Design</th>
<th>Duration</th>
<th>Dose</th>
<th>Outcome (measure)</th>
</tr>
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<tbody>
<tr>
<td>Sherwin et al. 1985 [44]; Sherwin et al. 1985 [45]</td>
<td>Women with surgical menopause (N = 53)</td>
<td>Randomized, double-blind, placebo-controlled, crossover study</td>
<td>3 months</td>
<td>Group 1: Estrogen only&lt;br&gt;Group 2: TE 150 mg&lt;br&gt;Group 3: Estrogen + TE 150 mg&lt;br&gt;Group 4: Placebo monthly i.m. injections of TE</td>
<td>Increase in sexual desire, arousal and fantasies</td>
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<tr>
<td>Myers et al. 1990 [36]</td>
<td>Women with physiological menopause (N = 40)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>10 weeks</td>
<td>Group 1: CEE 0.625 mg/d (N = 10)&lt;br&gt;Group 2: CEE + MPA 5 mg/d (N = 10)&lt;br&gt;Group 3: CEE+MPA+MT 5 mg/d (N = 10)&lt;br&gt;Group 4: Placebo (N = 10)</td>
<td>Increased pleasure from masturbation↑, no changes in mood, sexual behavior and sexual arousal↑ (caveat: normal sexual function at baseline, no ERT prior to study)</td>
</tr>
<tr>
<td>Davis et al. 1995 [20]</td>
<td>Women with physiological menopause (N = 34)</td>
<td>Randomized, single-blind, placebo-controlled, parallel study</td>
<td>12 months</td>
<td>Group 1: T implants 50 mg plus estradiol implants 50 mg&lt;br&gt;Group 2: Estradiol implants only, three-monthly s.c. insertion</td>
<td>Bone mineral density (whole body, trochanter, lumbar spine)↑ (DXA); increase in sexual activity, satisfaction, pleasure, and orgasm</td>
</tr>
<tr>
<td>Watts et al. 1995 [49]</td>
<td>Women with surgical menopause (N = 66)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>24 months</td>
<td>Group 1: CEE 0.625 mg/d&lt;br&gt;Group 2: CEE 0.625 mg/d + MT 2.5 mg/d</td>
<td>Bone mineral density (lumbar spine)↑; HDL cholesterol↑, triglycerides↓</td>
</tr>
<tr>
<td>Raisz et al. 1996 [39]</td>
<td>Women with physiological menopause (N = 28)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>9 weeks</td>
<td>Group 1: CEE 1.25 mg + MT 2.5 mg/d&lt;br&gt;Group 2: CEE only (N = 15)</td>
<td>Bone formation markers↑ (osteocalcin, bone alkaline phosphatase, C-terminal procollagan peptide II); HDL cholesterol↑, triglycerides↓ slight but significant improvements in body weight and subjective health status perception (RAND 36-item Health Questionnaire) in the 300 µg dose group; lean body mass→ (DXA) Increase in sexual activity, pleasure, orgasm, fantasies (BISF-W) and self-perceived well-being (PGWB) in the 300 µg dose group</td>
</tr>
<tr>
<td>Miller et al. 1998 [31]</td>
<td>Women with AIDS wasting syndrome (N = 53) (37 ± 1 yrs)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>12 weeks</td>
<td>Transdermal T patches&lt;br&gt;Group 1: 150 µg/d (N = 14)&lt;br&gt;Group 2: 300 µg/d (N = 18)&lt;br&gt;Group 3: Placebo (N = 13)</td>
<td>Increased sexual activity and pleasure (BISF-W, SRS, SIQ); Lean body mass↑, percentage body fat↓ (DXA); body weight↑; lower body strength↑; upper body strength→</td>
</tr>
<tr>
<td>Shifren et al. 2000 [46]</td>
<td>Women with bilateral oophorectomy and impaired sexuality (N = 75) (35–56 yrs)</td>
<td>Randomized, double-blind, placebo-controlled, crossover study</td>
<td>12 weeks</td>
<td>Transdermal T patches&lt;br&gt;Group 1: CEE 0.625 mg + T 150 µg/d&lt;br&gt;Group 2: CEE 0.625 mg + T 300 µg/d&lt;br&gt;Group 3: CEE 0.625 mg + Placebo</td>
<td>Increased sexual activity and pleasure (BISF-W, SRS, SIQ); Increased sexual activity and pleasure (BISF-W, SRS, SIQ); Caveat: normal sexual function at baseline, no ERT prior to study</td>
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<tr>
<td>Dobs et al. 2002 [23]</td>
<td>Women with physiological menopause (N = 36)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>16 weeks</td>
<td>EE 1.25 mg/d (N = 18) vs. EE + MT 2.5 mg/d (N = 18)</td>
<td>Increase in sexual activity and pleasure (BISF-W, SRS, SIQ); Decrease in personal distress (PDS); significant incidence of androgenic skin side effects, no serious adverse events</td>
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<td>Braunstein et al. 2005 [13]</td>
<td>Women with surgical menopause (N = 447)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>24 weeks</td>
<td>Transdermal T patches&lt;br&gt;Group 1: ERT + T 150 µg/d (N = 107)&lt;br&gt;Group 2: ERT + T 300 µg/d (N = 110)&lt;br&gt;Group 3: ERT + T 450 µg/d (N = 111)&lt;br&gt;Group 4: ERT + Placebo (N = 119)</td>
<td>Significantly increased frequency of satisfying sexual activity (SAL) and sexual desire (PFSSF) in the 300 and 450 µg dose groups; increased androgenic skin side effects in the 450 µg dose group</td>
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<tr>
<td>Buster et al. 2005 [17]</td>
<td>Women with surgical menopause (N = 533)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>24 weeks</td>
<td>Transdermal T patches&lt;br&gt;Group 1: ERT + T 300 µg/d&lt;br&gt;Group 2: ERT + Placebo</td>
<td>Significantly increased frequency of satisfying sexual activity (SAL) and sexual desire (PFSSF); decrease in personal distress (PDS); significant incidence of androgenic skin side effects, no serious adverse events</td>
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<tr>
<td>Simon et al. 2005 [48]</td>
<td>Women with surgical menopause (N = 447)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>24 weeks</td>
<td>Transdermal T patches&lt;br&gt;Group 1: ERT + T 300 µg/d&lt;br&gt;Group 2: ERT + Placebo</td>
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<th>Dose</th>
<th>Outcome (measure)</th>
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<tbody>
<tr>
<td>Davis et al. 2006</td>
<td>Women with surgical menopause on transdermal ERT (N = 77)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>24 weeks</td>
<td>Transdermal T patches Group 1: ERT + T 300 μg/d; Group 2: ERT + Placebo</td>
<td>Significantly increased frequency of satisfying sexual activity (SAL) and sexual desire (PFSF);</td>
</tr>
<tr>
<td>Shifren et al. 2006</td>
<td>Women with physiological menopause (N = 549)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>24 weeks</td>
<td>Transdermal T patches Group 1: ERT + T 300 μg/d; Group 2: ERT + Placebo</td>
<td>Significant increase in frequency of satisfying sexual activity and sexual desire (PFSF), decrease in personal distress (PDS);</td>
</tr>
<tr>
<td>Miller et al. 2006</td>
<td>Women with hypopituitarism (N = 51; 19–50 yrs)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>12 months</td>
<td>Transdermal T patches Group 1: T 300 μg/d; Group 2: Placebo</td>
<td>Significant increases in sexual function incl. sexual arousal (DISF-FV), mood (BDI) and quality of life aspects (NHP, PGWB, RAND 36-item Health Questionnaire);</td>
</tr>
<tr>
<td>Barton et al. 2007</td>
<td>Postmenopausal women with a history of cancer and no current evidence of disease</td>
<td>Randomized, double-blind, placebo-controlled, crossover study</td>
<td>4 weeks</td>
<td>Transdermal T cream Group 1: 10 mg T/day; Group 2: Placebo</td>
<td>No improvement in libido (CSFO) despite significant increases of Testosterone into the normal range;</td>
</tr>
<tr>
<td>Miller et al. 2007</td>
<td>Women with hypopituitarism (N = 51; 19–50 yrs)</td>
<td>Randomized, double-blind, placebo-controlled, parallel study</td>
<td>12 months</td>
<td>Transdermal T patches Group 1: T 300 μg/d; Group 2: Placebo</td>
<td>No significant change in markers of cardiovascular risk (fasting glucose, fasting insulin, IRHOMA, QUICKI, hsCRP, VCAM, leptin, Lp(a), apoA1, and homocysteine);</td>
</tr>
</tbody>
</table>

T: testosterone; MT: methyltestosterone; TE: testosterone enanthate; CEE: conjugated equine estrogens; EE: esterified estrogen; MPA: medroxyprogesterone acetate; BISF-W: Brief Index of Sexual Functioning in Women; PGWB: Psychological General Well-Being Index; SRS: Sabbatsberg Revised Sexual Self-Rating Scale; SIQ: Sexual Interest Questionnaire; SAL: Sexual Activity Log; PFSF: Profile of Female Sexual Function; PDS: Personal Distress Scale; CSFO: Changes in Sexual Functioning Questionnaire; DISF-FV: Derogatis Interview for Sexual Function-Female Version; BDI: Beck Depression Inventory; NHP: Nottingham Health Profile.

sistentely reported to induce a decrease in high-density lipoprotein (HDL) cholesterol levels [9,14,30].

Since early on, the effects of androgens on female sexuality has been a main focus of research. Beneficial effects on libido and mood were reported in both double-blind [44,45] and single-blind [20] studies on T replacement in surgically menopausal women, i.e. women with an established cause of significant androgen deficiency. However, in these studies, T administration resulted in supraphysiological serum androgen concentrations. Administration of low-dose oral T did not induce significant additional improvements compared with conventional ERT after 2 years of treatment in oophorectomized women [9]. Shifren et al. conducted a landmark study helping to define the impact of androgens on sexuality [46]. They studied the effects of transdermal T replacement in 75 oophorectomized women who had impaired sexual function at baseline. Results showed that T therapy had statistically significant beneficial effects on various aspects of sexuality. However, these results were only statistically significant for patients in the higher dose group (300 μg/d) associated with circulating androgen levels at or above the upper limit of the normal range [46]. Most recently, three large studies on a transdermal T delivery system in women with bilateral oophorectomy and concurrent sexual desire disorder has been published [13,17, 48]. The study by Braunstein et al. [13] compared 24 weeks of treatment with three doses of transdermal T (150, 300 and 450 μg/d) to placebo and established that 300 μg/d significantly increased frequency of satisfactory sexual activity and sexual desire, while 150 μg/d did not result in significant improvements and 450 μg/d was associated with a significantly higher incidence of androgenic skin effects. Following up on this, Buster et al. [17] and Simon et al. [48] published the results of phase III trials comprising 24 weeks of treatment with transdermal T (300 μg/d) or placebo in two studies with parallel design. These studies included 533 [17] and 562 women [48], respectively, suffering from sexual dysfunction after bilateral oophorectomy. Both studies confirmed the efficacy of 300 μg/d on sexual activity and desire; side effects included an increased frequency of mostly mild skin effects and no serious adverse events were noted. However, in a significant proportion of these women testosterone treatment resulted in supraphysiological serum concentrations of T and DHT. Similar efficacy was yielded by testosterone treatment in women with physiological menopause and impaired libido [21] and in a recent study in women with androgen deficiency due to hypopituitarism [32].

6. DHEA as an alternative option for female androgen replacement

DHEA may represent an elegant alternative tool for treatment of androgen deficiency in women [1,3], as it is a crucial sex steroid precursor and rapidly converted downstream towards androgens [5,51]. Following oral administration of DHEA to women with adrenal insufficiency, who suffer from invariably low or even non-detectable androgen levels [4,34], circulating levels of androgens have increased from subnormal levels to the lower end of the normal range [4,51]. Daily
administration of 50 mg DHEA increases DHEA and androstenedione levels to the mid normal range, while T and DHT only increased to the lower limit of the normal range [4]. However, circulating levels of androstanediol glucuronide (ADG), an androgen metabolite and useful marker of androgen generation within peripheral cells, increased to the upper limit of the normal range [4]. This indicates that DHEA replacement may not affect circulating androgens as much as testosterone administration, but the androgenic effect may be similar subsequent to DHEA conversion within peripheral cells. This review does not provide further details on DHEA replacement in women with androgen deficiency as a separate review in the same issue addresses exactly that topic.

7. Side effects of androgen treatment in women

The FDA has recently denied the approval of a transdermal androgen delivery system for the use in women, based on its concerns about the lack of long-term safety data. Most commonly reported side effects are androgen skin effects (increased sebum secretion, greasy skin and hair, scalp itching, alopecia, hirsutism).

The long term impact of unfavorable changes in cardiovascular risk markers has been investigated in a recently published 12-month study investigating the effects of testosterone replacement in women with androgen deficiency due to hypopituitarism, but replete oestrogen status [33]. This study did not report any adverse effects on metabolic markers of cardiovascular risk (Table 1).

However, there is certainly still need for clinical studies exceeding the 12-month period to further document the safety of this treatment. Also, it is very important to take physiology into account again. A recently published study on testosterone treatment in female cancer survivors with low libido who were estrogen replete found no beneficial effect of testosterone treatment [10]. This illustrates how important a sufficient estrogen supply is for normal sexual function. However, more importantly it highlights a safety issue as testosterone administered to these women can certainly be aromatized to bioactive estrogen by widespread expression of aromatase (CYP19) in peripheral tissues including the breast. Caution is important here and in these patients groups it might be wiser to choose non-aromatizable androgens like oxandrolone or dihydrotestosterone.

8. Conclusion

Choosing both a convenient and efficient mode of androgen administration in women remains a challenge and currently none of the available preparations is officially approved for the use in women, though this is likely to change in the near future. It will be key to achieve a more precise diagnostic consensus for female androgen deficiency and to give answers to the questions “whom to treat why, when and for how long”. Androgen replacement is a promising option for the treatment of women established causes of severe androgen deficiency including surgical menopause or adrenal insufficiency, if they concurrently suffer from symptoms of impaired mood and libido. In addition, the therapeutic potential of androgen replacement in women receiving chronic pharmacological glucocorticoid treatment and women with Turner’s syndrome may deserve further exploration. Importantly, impairment of libido is multifactorial in origin and in the majority of cases not associated to evidence of androgen deficiency. Therefore, the diagnosis of hypoactive sexual desire disorder does not automatically lead to justification of androgen replacement, as androgen deficiency not necessarily associated with this condition. It is important to acknowledge, that physiological menopause in women with intact ovaries is not associated with a sudden loss of androgen synthesis, unlike the steep drop in ovarian estrogen production. Therefore, the average healthy postmenopausal woman does not routinely require androgen replacement. More long-term studies in larger cohorts of women with severe androgen deficiency are needed to comprehensively assess both potential beneficial and adverse effects. However, we should also not paralyse ourselves by issuing guidelines that interfere with the clinical management of patients who really need androgen replacement. Future research will hopefully solve these problems.

Acknowledgements

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Miller KK, Biller BM, Beauregard C, et al. Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a random-