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Leading Article

Androgen Therapy for Postmenopausal Women; What is New?

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Physiology of Androgens

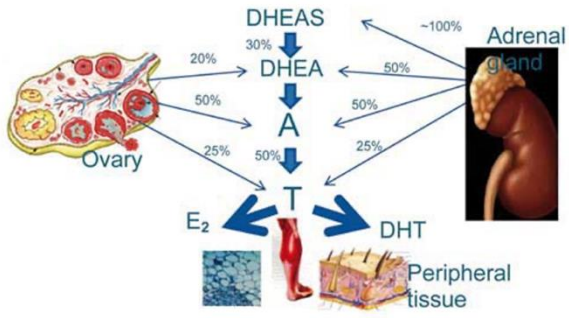
Androgen metabolism includes the synthesis, secretion, transport, tissue uptake, peripheral transformation, and excretion of C-19 steroids. Evolving knowledge of androgen metabolism has widened the concept of the function of steroid more than just inactivation and excretion. Metabolic transformation androgens produce steroid by-products with variable effects; some are oestrogens.

The major androgens in women in decreasing order of magnitude are dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, androstenediol, testosterone, and dihydrotestosterone (DHT) (Fig 01).

Adrenarche is characterized by the maturation of the adrenal zona reticularis, leading to the onset of adrenal androgen production. In premenopausal women, androgens are produced in near equal amounts in the adrenal glands and ovaries. Testosterone is the most abundant ovarian androgen, and DHEAS is the most abundant adrenal androgen.

The androgen levels start to steadily decline when women are in their mid-thirties, with no clinically significant additional decrease in androgen levels during the menopausal transition. All androgen levels continue to decline throughout the postmenopausal years, and by the seventh decade of life,

Figure 01 – Steroidogenesis in the ovaries, adrenal glands and peripheral tissues of the principal hormones related to female sexual function.



E2 – estradiol, DHT – dihydrotestosterone, DHEA – dehydroepiandrosterone, DHEAS – dehydroepiandrosterone sulphate, A – androstenedione, T – testosterone

androgen production is about 10%–20% of its peak levels (Fig.2).

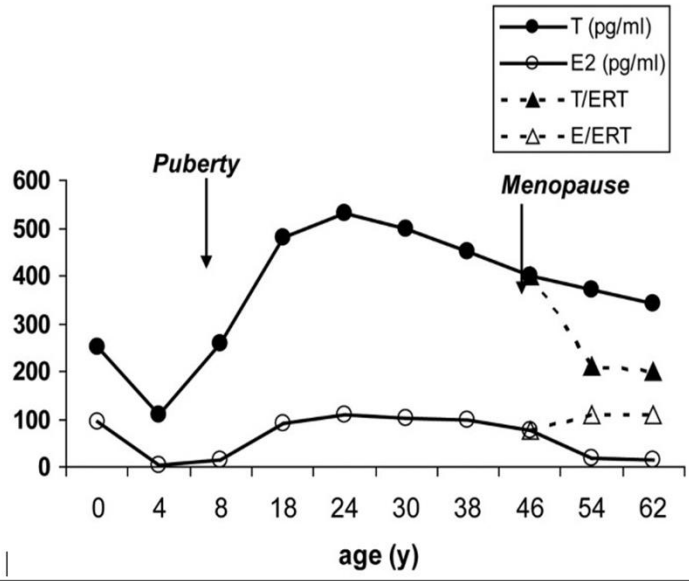
The most commonly measured androgen in women is testosterone. Most of the previously used assays for testosterone were based on a radioimmunoassay and had low accuracy, reliability, and reproducibility. Currently, many laboratories use tandem mass spectrometry, coupled with liquid chromatography - mass spectrometry (LC-MS), which is a more sensitive assay and is considered the gold standard for testosterone measurement. Most laboratories provide reference ranges for premenopausal and postmenopausal women. Regardless of improvements in testosterone assay, the interpretation of testosterone levels in women creates extra challenges.

Serum testosterone levels do not correlate to testosterone synthesized in peripheral target tissues and the individual variability in the sensitivity of androgen receptors. The clinical effects of androgens are tissue specific and not totally related to serum levels. They are influenced by the tissue level and activity of aromatase and 5-alpha reductase enzymes in each individual and are influenced by other factors that can cause alterations in cellular and membrane receptor activity.

Clinicians must be extra careful when interpreting low testosterone levels in women due to these physiological alterations and variations in each woman.

Impact of Androgens in Postmenopausal Women

Figure 2 - Laboratory assessment of serum androgen levels in women.



Androgens have an important biological role in health and well-being mainly related to sexual health. Peripheral aromatization to oestrogen act as main source of oestrogen in menopause. Many of other benefits are indirect effects of oestrogen derived from androgen aromatization. Body composition, anabolic effects of muscles and bones and osteoblast effects of bones linked to reduced fragility fractures in women. This effect is profound when free testosterone is high in women. Effects of androgens on lipids and CVS have a protective role in atherosclerosis and endothelial vasodilation.

Effects of Androgen on Breast Tissues – Are complexed and breast tissues have abundant aromatase activity generating high local oestrogen level linked to indirect proliferative action.

Effects of Androgen on Endometrium – Aromatization and paracrine effect of local oestrogens are minimal, thus minimal or no endometrial hyperplasia risk by androgens.

Effects of Androgen on Sexual Health – Androgens improve sexual wellbeing, libido and sexual arousal in women through its effect on the central nervous system.

Controversies Linked to Androgens in Women

Studies of the association between androgen levels and female sexual function have yielded mixed results mostly due to variation in studies. Female sexual function is complex, and it is influenced by numerous variables, including relationship status, physical health, and psychosocial well-being. The impact of androgen levels on female sexual function is considered modest.

Aziz et al (2005) explained that regardless of 50% decline of serum androgen level following oophorectomy, it was unable to demonstrate consistent correlation between hormone levels and sexual functions in women. Although higher free-testosterone levels have linked to lower fracture rates in older women, a clear benefit of androgen therapy on bone mass and fracture risk has not been shown in limited studies. At present available data is insufficient to make conclusions. Therefore, clinicians recommend against the use of androgens for prevention or treatment of osteoporosis in postmenopausal women.

Limited observational data favours that low endogenous androgen levels in women are associated with increased risk of atherosclerosis. Population-based Rotterdam study showed that higher testosterone levels in postmenopausal women were not associated with increased cardiovascular risk. However, emerging data from recent Multi-ethnic Study of Atherosclerosis showed that a higher ratio of endogenous total testosterone to oestrogen was linked to an increased incidence of CVD and heart failure events in post-menopausal women.

Diagnosis of Androgen Deficiency in Women

Laboratory assessment for testosterone was based on a radioimmunoassay and the test itself showed low accuracy, reliability, and reproducibility. Furthermore, physiologically low testosterone levels in women (compared with men) made accurate measurement even more challenging.

Currently, there is no bio-chemical criteria to diagnose androgen deficiency in menopause. Low androgen levels do not reliably reflect clinical symptoms and findings. Serum testosterone levels are not independent predictors of female sexual functions as well. Overall, there is no well-defined clinical syndrome and age based normative data for testosterone concentrations. Difficulty in diagnosis made androgen use less popular in women after menopause.

Indication for Testosterone Use in Postmenopausal Women

According to Global Consensus Position Statement on the use of testosterone therapy for women published in 2019, Hypoactive

Sexual Desire Disorder (HSDD) is the only indication for testosterone use in postmenopausal women and it has mild to moderate clinical efficacy.

Testosterone/Androgens should not be prescribed for reasons like

- Improving bone or muscle mass/bone health
- Treating vasomotor symptoms or cardiac benefits
- Improve the patient's sense of well-being/cognitive functions

As there is no clinically proven benefits of androgen therapy for particular reasons.

Hypoactive Sexual Desire Disorder

Hypoactive sexual desire disorder/dysfunction (HSDD) and female sexual arousal disorder (FSAD) are two distinct conditions that should be categorized separately when considering the impact of androgens on their clinical presentation and response to treatment. Although HSDD and FSAD overlap, they have distinct aetiologies, risk factors, clinical features, and responses to psychological and biological interventions. HSDD has been the most common sexual health problem in women. Its prevalence is 10% in American and European adult women. HSDD is defined as persistent or recurrent lack or absence of sexual fantasies and desire for sexual activity, associated with marked distress or difficulty in the relationship, which is not accounted for by a medical or psychiatric condition. This definition has been replaced by DSM-V as "female sexual interest/arousal disorder.

Latest expert opinion on diagnosis of HSDD in clinical practice suggests that it should be based on thorough clinical assessment guided by available diagnostic criteria such as the International Society for the Study of Women's Sexual Health or the International Classification of Diseases. However, many studies were based on older definition; therefore, former classification is still accepted by professionals.

This condition is related to complex neuro-hormonal activity in body and both premenopausal and postmenopausal women are affected. Diagnosis requires minimum 6 months symptoms that cannot be related to any other psycho-somatic cause. It is never made with biochemical testing as associations between endogenous androgen concentrations and sexual function in women remain uncertain because of issues relating to the sensitivity and specificity of androgen assays and no cut-off blood level can be used for any measured circulating androgen to differentiate women with and without sexual dysfunction. However, only available treatment option-androgen is only considered in post-menopausal age group.

Treatment Options

Apart from psychotherapy, counselling, anxiolytics like multimodal options, proven benefit is there for androgen therapy.

Options

1. Testosterone transdermal patches
2. Low dose compounded testosterone creams/gels/ointments.

Compound oral testosterones are not recommended due to side effects and lack of safety data. Topical preparations are also advised not to apply over upper body to avoid absorption to breast lymphatics and to avoid transfer to other individuals by body-to-body touch. When applying transdermal patches, 2 to 3 times per week application is sufficient. Pre-treatment

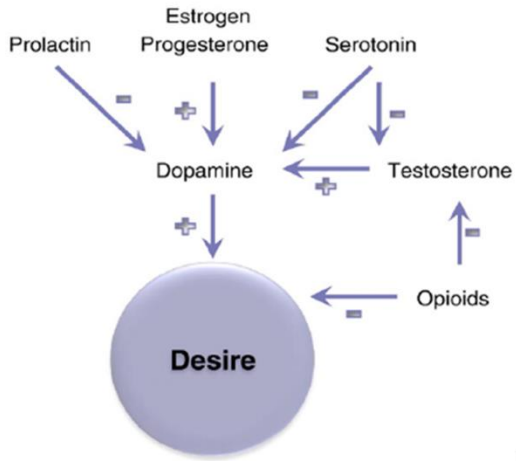
baseline testosterone level should be checked. Repeat the testosterone level 3-6 weeks after commencing the therapy. Patient should be clinically assessed for effective response and side effects. Every 6 months serum total testosterone level assay is compulsory to screen over use of therapy. If no benefit noted in first 6 months, stop the treatment.

Patient Counselling

This is essential before commence treatment and patient should be clearly advised for following details.

- Women should try safe and effective alternatives before considering a trail of testosterone.
- Testosterone therapy takes several weeks to be effective.
- Treatment should not be continued for longer than 6 months if no clinical improvement is noted.
- After testosterone therapy is initiated, frequent clinical and laboratory monitoring is required.
- Goals of therapy are to achieve clinical improvement while maintaining testosterone levels within the physical range.

Figure 03 – Demonstrates connection between CNS and Endocrine System in sexual desire/arousal-Excitatory role of Oestrogen, Progesterone and Testosterone is exerted via Dopamine release.



- All testosterone products currently offered to women are prescribed off-label.
- Limited testosterone formulations are available to women.
- Long-term safety data of testosterone therapy are currently unavailable.
- High placebo response rate is seen in trials of testosterone therapy.

Androgen Therapy; How effective and safe?

Many early studies for HSDD used oestrogen and testosterone combination therapy. But subsequent studies showed testosterone alone is effective as combination regimens. Most of these studies are RCTs and they showed promising results with testosterone use. Despite of modest efficacy shown by

statistics, patients' experience of at least one additional satisfying sexual intercourse. And this finding was clinically important when considering patient complains.

APHRODITE Study: A Phase III RCT-Research, A Study of Female Sexual Dysfunction in Women on Testosterone Patch without Oestrogen Conducted over 52 weeks. Women with natural or surgical menopause were randomized to one of three study arms placebo, 150 mcg TTP, or 300 mcg TTP. Study showed a modest, but meaningful improvement in sexual function, a 52% response rate with 300 mcg TTP (Vs. placebo 32%). Most women in the treatment group noticed only minor adverse effects. All aspects of satisfying sexual act in women (desire, arousal, lack of stress, pleasure and orgasm) were improved.

Adverse Effects

Androgenic side effects are dose dependent. Hirsutism, seborrhoea, scalp oiliness or itching, androgenic alopecia, behavioural changes such as anger or aggression, deepening of the voice, and Clitoromegaly. Hirsutism is the most frequent among these and it accounts for 10-15% of side effects. Clitoromegaly and deepening of voice may be irreversible. Many of these findings are from studies of Danazol, a potent synthetic androgen.

DHEA Therapy in Women

Lack of efficacy and safety data has limited its clinical use. But Vaginal DHEA has promising results against moderate to severe dyspareunia in older women. This effect only noted in local application. But no beneficial effects over HSDD or any other sexual dysfunction.

Conclusion

Testosterone therapy in women is not currently well established because of the lack of long-term data regarding efficacy and safety. However, low-dose TTP is a promising option for selected postmenopausal women with HSDD after other contributors to sexual dysfunction have been appropriately addressed. Patients should receive detailed counselling regarding the lack of long-term safety data, and they should be monitored closely to avoid supra-physiological dosing. Intra-vaginal DHEA is used for management of genitourinary syndrome in postmenopausal women, and it has no effect on HSDD.

Author Disclosure Statement
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