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Medicine, Nursing and Health Sciences

Testosterone for women, who when and how much?

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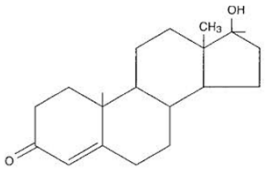
Potential conflicts of interest to report

Research support from Lawley Pharmaceuticals
Consultant to Trimel Pharmaceuticals
Speaker for Abbott Australia

I will be discussing testosterone treatment of women.
There is no approved testosterone product for this purpose in USA

Presentation aims

1. Review female androgen physiology
2. The reasons for low testosterone in women
3. Androgen action in women
4. When and how to treat women with testosterone



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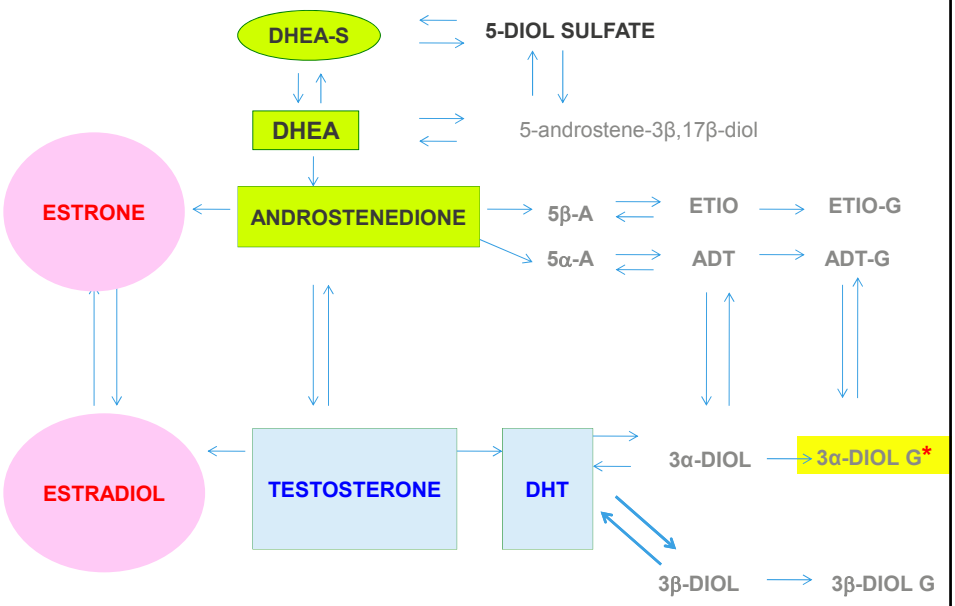


ADT—androsterone
ETIO-etiocholanone

*marker of total androgen exposure

FROM Davis et al JCEM 2011

TOTAL testosterone in the circulation:

SHBG binding affinity:
DHT > Testosterone > Estradiol > Estrone > DHEA

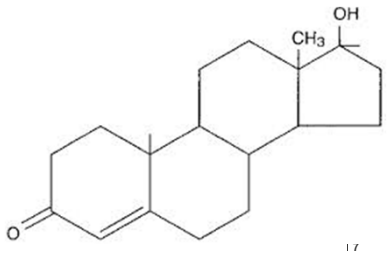
DHEAS IS NOT SHBG BOUND

- Very low SHBG (as in obesity and insulin resistance) will result in underestimation of actual testosterone exposure.

LOW SHBG

- INDEPENDENT marker of insulin resistance
  Worsley et al Menopause 2013
- Predicts high risk of future type 2 diabetes
  Ding EL NEJM 2009
- Relationship between SHBG and insulin resistance /diabetes INDEPENDENT of testosterone and estrogen Worsley et al Menopause 2013

Conditions associated with lowered testosterone



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2. Androgen action in women

- Normal ovarian function and ovulation
- Musculoskeletal health
- Cardiovascular function
- Cognitive performance
- Sexual function
- Vaginal health

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Androgens and female sexual function

Research challenges:

- Imprecision of assays at low levels seen in women
- Wide range of what is normal vs abnormal for individual women
- Dynamic nature of sexual function
- Complexity of female sexual function: testosterone is not a sole determinant
- Imprecision of measuring FSD

Measurement of androgens of interest in women

1. Measurement of testosterone in women only accurate with highly sensitive and specific methodology:
   - Free testosterone kit assays unreliable
   - Measurement of free testosterone by equilibrium dialysis requires accurate measurement of total T
   - BEST OPTION : a reliable total testosterone measure by high quality RIA or LCMS
   - SHBG and calculation of free testosterone by the Sodergard eq
   - the “free androgen index” is not clinically useful
2. Measurement of DHEAS and SHBG is robust

Androgens and Female Sexual Function: OLDER STUDIES

Low T associated with

- Desire disorder in premenopausal women
- Low desire and reduced coital frequency

A positive relationship seen between free T and ratings of sexual desire in women aged 60-70yrs

"female androgen insufficiency"

- **There is no diagnostic cut off** level **for any of the androgens** that identifies a woman with low sexual function as having "female androgen insufficiency syndrome".

- So why measure an androgen profile at all ?
  - To avoid treating women with androgen who have relatively high levels
  - To avoid treating women with elevated SHBG
  - To add caution in treating women with low SHBG

TREATING FEMALE SEXUAL FUNCTION WITH ANDROGENS

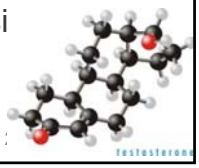
1. TESTOSTERONE
2. DHEA

The overall effect of FSD on quality of life is similar in magnitude to that of chronic back pain and urinary incontinence

EFFICACY OF TESTOSTERONE FOR HYPOACTIVE SEXUAL DESIRE-AROUSAL DISORDER DEMONSTRATED IN LARGE RCTS:

- surgically postmenopausal women on estrogen
- naturally postmenopausal women on estrogen + progestin
- postmenopausal women on no hormone therapy
- premenopausal women aged 35-45 years

Studies consistently show benefits of transdermal testosterone vs placebo for sexual satisfaction, desi arousal, pleasure AND orgasm



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DHEA

- Putative DHEA receptor never isolated
- Primary action is by conversion to estrogen or testosterone
- Can act directly on ERs and AR- action is weak
- (+) effect on trabecular bone probably ER mediated (Engdahl et al Endocrinology 2014).

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The benefits and harms of systemic DHEA in postmenopausal women with normal adrenal function: A Systematic Review and Meta-analysis

Elraiyah et al JCEM 2014 Oct;99(10):3536-42.

- DHEA use was NOT associated with significant improvement in libido or sexual function
- NO significant effect of DHEA on serum lipids, serum glucose, weight, BMI or BMD

Androgens and vaginal health

Daily vaginal DHEA alleviates postmenopausal VVA

- Evidence supported a study conducted of 218 postmenopausal women treated with daily intra-vaginal testosterone (3 doses) vs placebo.
  - *J Sex Med. 2014 Jul;11(7):1766-85.
  - *Climacteric. 2011 Apr;14(2):282-8.
  - *Gynecol Endocrinol. 2010 Jul;26(7):524-32.
  - *Menopause. 2009 Sep-Oct;16(5):897-906.
  - *Menopause. 2009 Sep-Oct;16(5):907-22.
  - *Menopause. 2009 Sep-Oct;16(5):923-31.

Pilot study

Labrie F et al J Steroid Biochem Mol Biol. 2008 Sep;111(3-5):178-94.

Primary indication for testosterone therapy for women:

Treatment of persistent low libido that profoundly impairs quality of life

- testosterone improves sexual desire, arousal and sexual satisfaction in premenopausal and postmenopausal women presenting with loss of sexual desire
- NOTE- substantial overlap between desire and arousal in women

Who fits this category?

- Women late reproductive years and beyond who say
  - they have experienced a distinct change
  - they don't like not feeling sexual / interested
- Women with the following conditions who seek help for loss of libido
  - Surgical menopause
  - Premature ovarian failure
  - Adrenal insufficiency (including glucocorticosteroid therapy)
  - On SSRI /SNRI therapy
- There is no upper age limit

Initial steps

- Management of psychosocial issues
- Review medications (anti-depressants)
- Treatment of vaginal atrophy
- Tibolone (where available)
- Androgen therapy
- Counseling/sex therapy

Contraindications

- androgenic alopecia/ hirsutism/acne
- hormone dependent malignancy
  - potential contraindication
- very low SHBG levels- need to be very judicious in dosing

NOT RECOMMENDED

- TRANSDERMAL MALE FORMULATIONS
- INJECTABLES
- TESTOSTERONE UNDECANOATE
- COMPOUNDED TROCHES (oral) / CREAMS
- DHEA

Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline

Wierman et al JCEM on line 2014

- 1. We suggest a 3- to 6-month trial of a dose of T for postmenopausal women who request therapy for properly diagnosed HSDD and in whom therapy is not contraindicated resulting in a mid-normal premenopausal value in a reference assay to avoid pharmacological T administration
- 2. If T therapy is prescribed, we suggest measuring T levels at baseline and after 3–6 weeks of initial treatment to assess patient overuse
- 3. In cases of ongoing T therapy, we suggest reviewing T levels every 6 months to monitor for excessive use and signs of androgen excess.
- 4. We suggest cessation of T therapy for women who have not responded to treatment by 6 months. No safety and efficacy data for T therapy are available after 24 months

Testosterone implants

- **50mg implants** used for decades in Australia and UK to treat women with FSD. APPROVED BY REGULATORS FOR THIS INDICATION
  - No adverse effects on body composition/lipids
- **75mg testosterone implants** FDA APPROVED FOR MEN. USE IN WOMEN IS OFF-LABEL
  - Usual dose for men 8-10 implants
  - One implant for a woman will last about 6mths
  - Do NOT insert a new implant without first checking testosterone level
  - Side effects are rare with this dose but are common at higher doses.

Testosterone side effects?

- Not seen if women are treated with
  - A dose appropriate for women
  - Transdermal, not oral therapy
- Physiological transdermal testosterone does not adversely effect
  - cardiovascular function,
  - body composition,
  - Endometrium
  - Breast safety remains contentious but most studies do not show an adverse effect on the breast.

International Menopause Society Guidelines

- There is no diagnosis of “androgen sufficiency syndrome”
- There is evidence that testosterone therapy will improve sexual outcomes for women diagnosed with hypoactive sexual desire disorder (HSDD)
- Women can be considered candidates for a trial of treatment after full clinical assessment
- Testosterone formulations for men should NOT be used
- Compounded testosterone not advisable
- There is no evidence for a benefit of DHEA in women with intact adrenal function (adrenal fatigue is not a diagnosis)

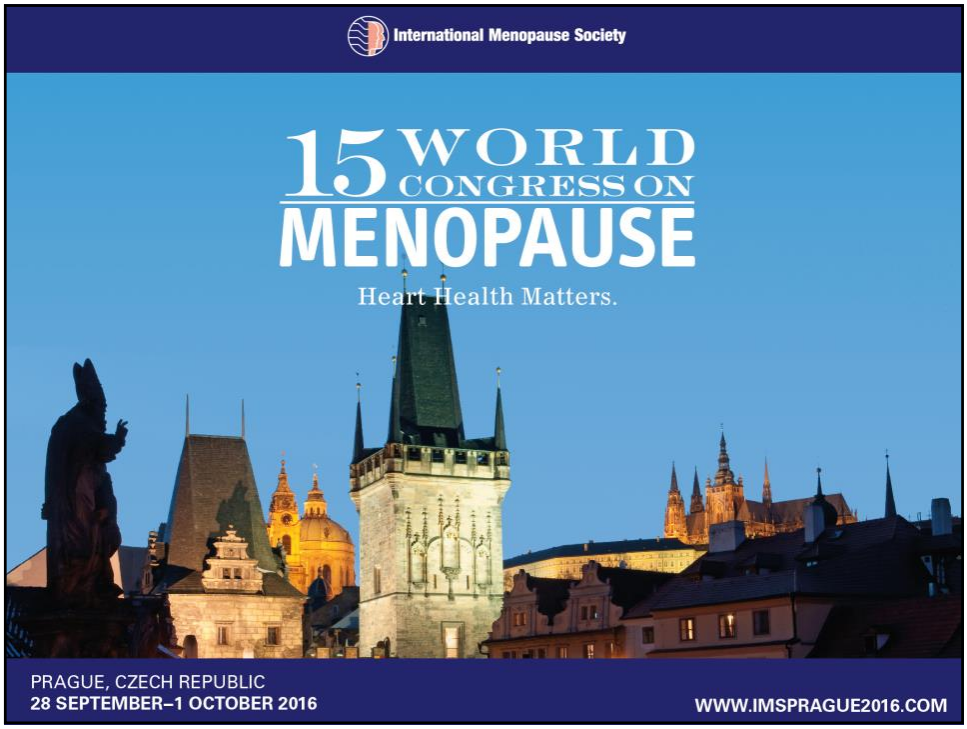
De Villiers TJ et al Climacteric 2013

T for women-where are the road blocks?

- Testosterone has been used to treat women with HSDD for decades with no evidence of emergent adverse events
- RCTs in women show no evidence of serious adverse events
- Regulators cannot agree on what endpoints are meaningful in terms of both efficacy and adverse effects
- Physicians are forced to resort to prescribing either compounded testosterone or modifying doses of testosterone formulated for men
- Compounded hormone therapy completely unregulated and regulators do not care- beyond their jurisdiction
- Regulators are neglecting the needs of women in the community by their approach to this field

International Menopause Society You TUBE - for your patients

https://www.youtube.com/playlist?list=PLAjwoYultHS-4jvjL6gJgM7o-vpr0PVk6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PRAGUE, CZECH REPUBLIC
28 SEPTEMBER–1 OCTOBER 2016
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