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BESINS HEALTHCARE SCIENTIFIC LITERATURE REVIEW – September 2021

Must Read Articles in Men's Health

Hypoactive Sexual Desire Disorder in Women: Physiology, Assessment, Diagnosis and Treatment

Pettigrew J.A. *et al*

Journal Of Midwifery and Women's Health

Pubmed Link: doi:10.1111/jmwh.13283

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Optimizing the Diagnostic Accuracy and Treatment Decisions in Men with Testosterone Deficiency

Bhasin S *et al*

Endocrine Practice

Pubmed Link: https://doi.org/10.1016/j.eprac.2021.08.002

Other Articles of Interest - Men's Health

Clinical efficiency of combination therapy using testosterone replacement therapy, phosphodiesterase 5 inhibitors and Kampo herbal medicine for eugonadal patients with late-onset hypogonadism syndrome	Takeuchi *et al* Experimental and Therapeutic Medicine 2021:22:1173	This study examined the treatment efficiency of combination therapy using TRT, herbal medicine and PDE5i in male patients with late-onset hypogonadism (LOH). 21 patients were enrolled for 12 weeks followed by Diagnostic testing and questionaries. In patients with low FT, the symptoms of LOH syndrome may be improved by aggressive intervention using combination therapy with TRT, herbal medicine and PDE5i.

Pharmacokinetics of Testosterone Therapies in Relation to Diurnal Variation of Serum Testosterone Levels as Men Age	Pastuszak A. W *et al* Andrology	This study aimed to compare pharmacokinetic (PK) profiles of serum T from approved T formulations with endogenous diurnal T variations in young and older men, and to consider whether there may be value in mimicking the diurnal T rhythmicity with exogenous TTh as men age. The results showed that all exogenous T replacement dosing targets an increase in average T levels to within the normal physiologic range and improves symptoms associated with low T, but no single TTh can exactly mimic the normal diurnal T patterns seen in younger men and the blunted circadian T secretion of older men.
Comparison of Testosterone Levels in Patients with and Without Type 2 Diabetes	Kumari *et al* Cureus 2021:13(7): e16288	This study examined testosterone levels in type 2 diabetes patients and the association between duration of diabetes diagnosis and testosterone levels. 200 T2DM patients and 200 controls aged 30-69 were included. Mean total T levels were significantly lower in T2DM patients and androgen deficiency higher compared to controls. A significant decrease in T levels was observed as the duration diabetes diagnosis increased.

Title	Authors	Journal and Issue	Article Type
Hypoactive Sexual Desire Disorder in Women: Physiology, Assessment, Diagnosis and Treatment	**Pettigrew J.A. *et al***	**Journal Of Midwifery and Women's Health**	**Review**

Background:

The International Society for the Study of Women's Sexual Health definition of HSDD:

Female Hypo Sexual Desire Disorder (HSDD) is characterized by deficiency of sexual thoughts, feelings or receptiveness to sexual stimulation that has been present for at least six months, causes personal distress, and is not due to another medical condition.

Aim:

The aim of this publication is to provide a general overview of one of the most prevalent female sexual health complaints HSDD and outline the biopsychosocial assessment and treatment options that exist in the United States currently for HSDD.

Key Messages:

- 43% (N= 31,581) of women surveyed on sexual function in the USA in 2008 reported sexual concerns, the most common concern being low sexual desire.

Dual -Control Model:

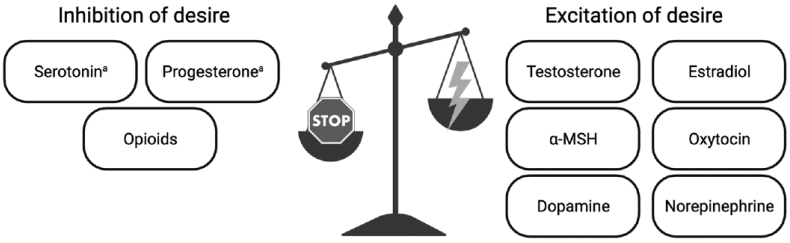


Figure 1. Various Physiologic Substrates and Their Role in Either Exciting or Inhibiting Sexual Desire, Based on the Dual-Control Model

Deficient excitation, excessive inhibition, or a mix of both can contribute to the physiology of hypoactive sexual desire disorder.
[a]Serotonin and progesterone have both excitatory and inhibitory properties, although are usually considered inhibitory. α-MSH, alpha-melanocyte stimulating hormone.
From Bancroft et al, 2009.[15]

- HSDD can result if there is a dysfunction of excitatory or inhibitory signals by preventing adequate excitation or promoting excessive inhibition.
- The Physiology of HSDD consists of interactions between various steroid hormones, peptide hormones and neurotransmitters.

- Clinicians should evaluate HSDD using a biopsychosocial assessment to determine contributing and modifiable factors. Domains in the biopsychosocial assessment include biological, psychological, interpersonal and sociocultural.
- Laboratory assessment should be patient specific and may include blood count, thyroid screening disease, vitamin D and prolactin levels if there is suspicion for underlying disease.
    - Routine sex hormones, particularly testosterone are not recommended in healthy women as it's not useful for establishing a diagnosis of HSDD.

- HSDD treatments consists of education, specific therapeutic interventions such as mindfulness therapy or cognitive behavior therapy and prescription medication.
    - First line therapies are education and counseling.

- In 2015 **Flibanserin** was the first FDA approved treatment for HSDD in premenopausal women.
    - It works type 1A agonist and a serotonin type 2A receptor antagonist.
    - Flibanserin decreases serotonin but raises dopamine and norepinephrine in the prefrontal cortex
- Clinical trials comparing Flibanserin to Placebo in premenopausal women with HSDD demonstrated that patients had increased sexual desire, decreased sexual distress and increased number of satisfying sexual encounters.
- Flibanserin carries a black box warning in the US stating that patients should wait two hours after alcohol consumption to take the drug and that severe hypotension may occur with the use of moderate or strong CYP3A4 inhibitors.
- It is licenced for use in pre-menopausal women, but is used off-label in post-menopausal and there are studies showing efficacy in post-menopausal

- **Vyleesi (bremalanotide)** an injectable α-MSH (analogue melanocortin receptor agonist) was approved for use in the US in June 2019 for premenopausal women with HSDD.
    - Bremalanotide 1.75mg is injected subcutaneously using an autoinjector 45 minutes prior to an anticipated sexual encounter as needed.

  - It is contraindicated in patients with uncontrolled hypertension or known cardiovascular disease.

- Other central nervous system agents have been used off label for the treatment of HSDD, including repurposing of the older anti-depressant drugs Bupropion, Buspirone, Trazodone.

- Estrogen therapy is first line treatment for HSDD in menopausal women who are appropriate candidates.

- The off-label use of testosterone for the treatment of HSDD in postmenopausal women is supported by evidence and several professional societies.
  - No established testosterone cut-off levels have been agreed upon for HSDD.
  - Testosterone dosing in perimenopausal in postmenopausal women is in the range of physiological levels for a premenopausal female.
  - In the absence of an approved female testosterone product clinicians are advised to use male products at $1/10^{th}$ the dose.
  - Follow up testing of free and total testosterone levels should occur after three months of therapy.
  - Monitoring of lipids and ongoing assessment of cardiovascular risk is appropriate.
  - If no improvement is seen within three months, T therapy should be stopped.
  - Contraindications to use of testosterone are similar to those with estrogen (cardiovascular disease, history of clot, stroke, venous thromboembolism, hormone receptor positive breast cancer, history of endometrial cancer).
  - Definitive data are lacking as to whether testosterone therapy affects risk for cardiovascular disease, breast cancer, and thrombotic events.

Practice Points:

- Different approach to treatment of HSDD depending on whether pre or post menopausal. First line in menopausal is estrogen therapy.

- There are two approved therapies for HSDD in the US: flibanserin and Vyleesi (bremalonitide):
- Flibanserin originally developed as an anti-depressant has to be taken daily as a tablet before bedtime (due to somnolence side effect) whereas Vyleesi is a subcutaneous injection that is administered 45 mins before planned sexual activity.

- Testosterone is being used off-label in both pre menopausal and menopausal women at one tenth the male dose with the aim of bringing testosterone levels to physiological levels in a premenopausal woman

Title	Authors	Journal and Issue	Article Type
Optimizing the Diagnostic Accuracy and Treatment Decisions in Men with Testosterone Deficiency	**Bhasin S *et al***	**Endocrine Practice**	**Review**

Background:

- According to the authors, the non-specificity of symptoms; substantial variations in testosterone levels over time due to biological factors; methodological problems in the measurement of total and free testosterone levels; and the suboptimally-derived reference ranges contribute to diagnostic inaccuracy in the evaluation of men suspected of having testosterone deficiency.

Aim:

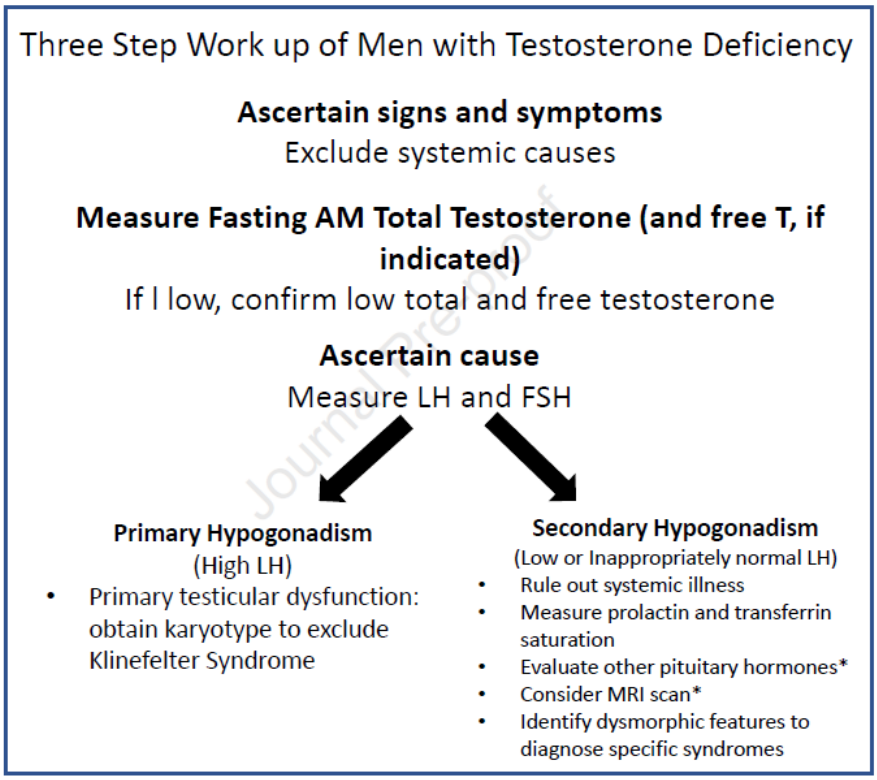
This review offers a guideline-based approach to improving the diagnostic evaluation and treatment decision making in men being assessed for testosterone deficiency.

Key Messages:

Testing for testosterone deficiency should be performed in men who present with conditions that are associated with high risk of testosterone deficiency and in whom treatment might be beneficial such as men presenting with low sexual desire, erectile dysfunction, infertility, gynecomastia, HIV-associated weight loss, osteoporosis or low trauma fracture; men using opioids, glucocorticoids, and androgenic-anabolic steroids; and men treated with cancer chemotherapeutic agents or pelvic radiation

Figure 1: Diagnostic evaluation of men who present with Clinical Symptoms of Testosterone deficiency

Key Message 1, the 3 Step Work Up



*The need for a magnetic resonance imaging and detailed pituitary work-up in men deemed to have secondary hypogonadism should be guided by the severity of testosterone deficiency and the level of suspicion of a pituitary space occupying lesion. The diagnostic yield can be improved by performing a more detailed search for a pituitary lesion in men with baseline total testosterone less than 160 ng/dL or hyperprolactinemia or evidence of mass effect (e.g., headaches or visual field impairment). The evaluation of other pituitary hormones should include measurements of serum IGF-1, TSH and free T4, and screening for hypercortisolism if Cushing's syndrome is suspected

Key message 2:

Table 1. Strategies to reduce the diagnostic inaccuracy in the evaluation of men suspected of having testosterone deficiency

Sources of diagnostic inaccuracy	Steps to minimize diagnostic inaccuracy

Non-specificity of symptoms and signs	• Consider that some clinical features are more strongly associated with testosterone deficiency:
	  ○ Incomplete or delayed sexual development
	  ○ Loss of body hair (axillary and pubic) hair
	  ○ Very small testes (less than 6 mL each)
	  ○ Sexual symptoms (reduced sexual desire, decreased spontaneous erections, and erectile dysfunction)

Biological variation	• Measure early morning testosterone level on 2 or more days • Obtain blood sample in a fasting state • Avoid evaluating testosterone deficiency during an acute illness • Avoid making a diagnosis based on one value

Imprecision and inaccuracy of total testosterone assays	• Chose an accurate assay
	  ○ Choose an LC-MS/MS assay, if available because LC-MS/MS assays have the highest precision and accuracy in the low range.
	  ○ Choose a laboratory that is certified by an accuracy-based benchmark, such as the CDC's HoST Program

Alterations in binding proteins	• Measure free testosterone level when binding protein abnormality is suspected or when the total testosterone levels are in the borderline zone. • Use an equilibrium dialysis method for the measurement of free testosterone level in a reliable laboratory.

Key message 3:

Prescribing Testosterone Replacement Therapy should take a patient centric approach

- Testosterone treatment is indicated in men who have symptomatic testosterone deficiency to induce and maintain secondary sex characteristics and relieve symptoms of testosterone deficiency.
- Only initiate testosterone treatment after discussing with the patient the benefits and uncertainties about the long-term risk of MACE and prostate cancer. Consideration should be given to the potential risks, cost and burden of long-term treatment and monitoring.
- Testosterone treatment should be avoided in men who are planning fertility in the near future and should be avoided in men with prostate or breast cancer, polycythemia thrombophilia, uncontrolled heart failure, untreated severe sleep apnea or men with increased risk of prostate cancer or severe urinary tract symptoms without urological evaluation.
- Consider the patients value and tolerance of the cost burden and uncertainties of long-term benefits and risks.
- Testosterone treatment can be initiated with any of the approved testosterone formulations based on consideration of pharmacokinetics, patient preference, cost and convenience.

Key message 4

Table 5. Monitoring of Testosterone Replacement Therapy

	Baseline	**3 – 6 months**	12 Months	**Annually**
Symptoms	X	X	X	X
Adverse events	X	X	X	X
Testosterone level	X	X	X	X
Hemoglobin / hematocrit	X	X	X	X
PSA / DRE*	X	X	X	X*

Legend: A standardized plan for monitoring of testosterone replacement therapy. Because prostate monitoring has the potential for harm, the decision to screen patients for prostate cancer risk and to institute PSA monitoring should be made jointly by the clinician and the patient. The expert opinions and local practices on PSA screening and monitoring vary. After 1 year of testosterone treatment, prostate monitoring should conform to guidelines for prostate cancer screening, depending on the race and age of the patient.

PSA, prostate specific antigen; DRE, digital rectal examination.

Practice Points:

Guidance information on the following:

- 3 Step Work Up
- Strategies to ensure more accurate diagnosis
- Joint decision making with patient
- Monitoring