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Male Hypogonadism and Infertility

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Objectives

1. Review signs/symptoms of low testosterone
2. Review the hypothalamic-pituitary-gonadal axis
3. Discuss how to evaluate the finding of low serum testosterone
4. Realize the importance of determining if the etiology is 1° (testicular) or 2° (hypothalamic/pituitary)
5. Review the differential diagnosis of male hypogonadism
6. Review the risks and benefits of testosterone replacement therapy (TRT)
7. Review the various modes of TRT
8. Review male infertility

Definition

"Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis"
The Endocrine Society Clinical Practice Guidelines
Two parts to the diagnostic evaluation:

1. Ascertainment of signs and symptoms
2. Ascertainment of low testosterone levels

Signs & Symptoms of Low Testosterone

Clinical Findings of Male Hypogonadism

Physical	Sexual	Emotional/Psychiatric
Fatigue	Decreased libido	Depression
Muscle weakness	Erectile dysfunction	Anxiety
Sparse body hair	Oligospermia	Irritability
Decreased bone mineral density		Insomnia
Fat distribution		Memory Impairment
Impaired hematopoiesis		Cognitive dysfunction
Osteoporosis		

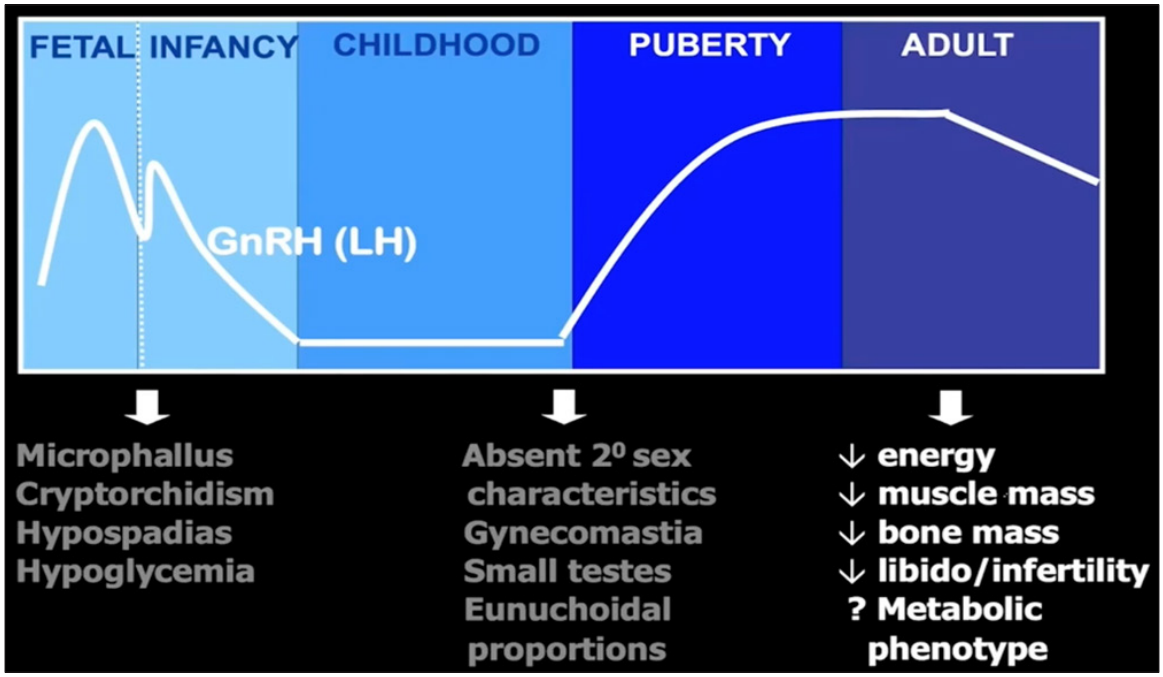
Symptoms and Signs with Higher Specificity

- Incomplete or delayed sexual development
- Loss of body hair (axillary and pubic) hair
- Very small testes (less than 6 mL)

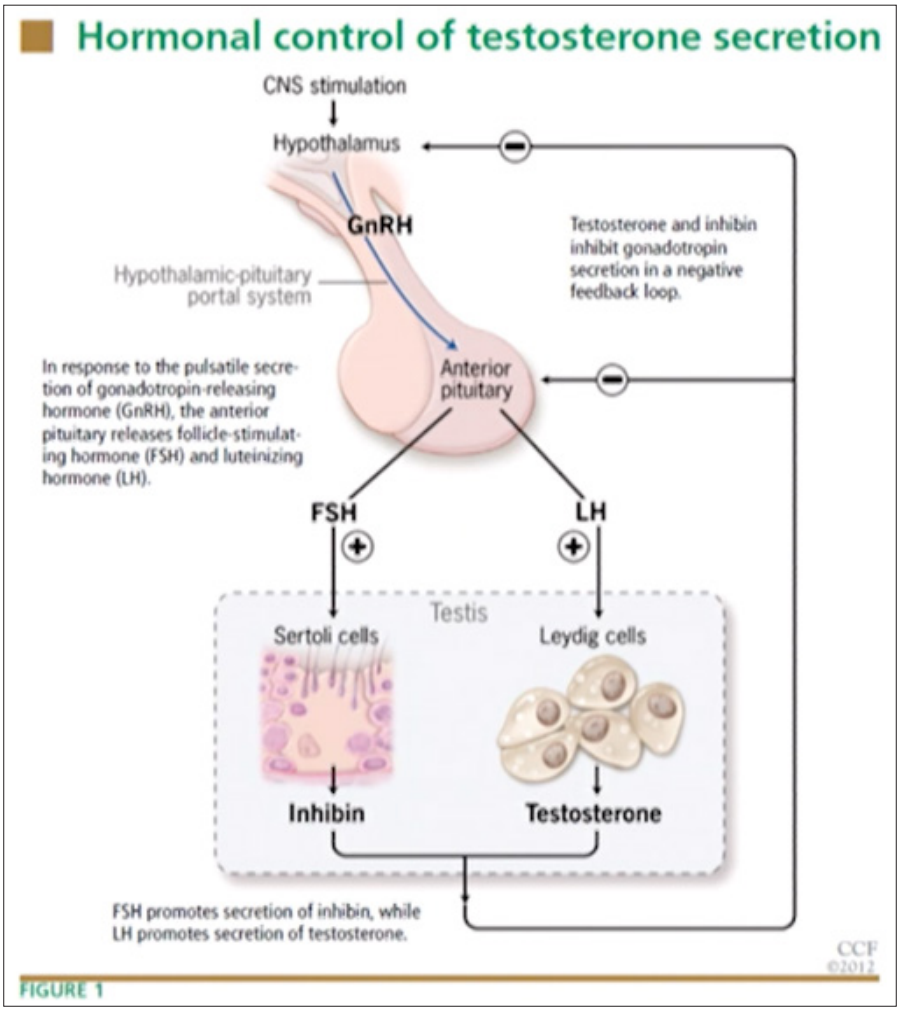
Sexual symptoms

- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Erectile dysfunction

Clinical Presentation of Hypogonadism



Hypothalamic-Pituitary-Gonadal Axis



Diurnal Rhythm

Testosterone is highest near 8 am

- check for deficiency when level should be highest

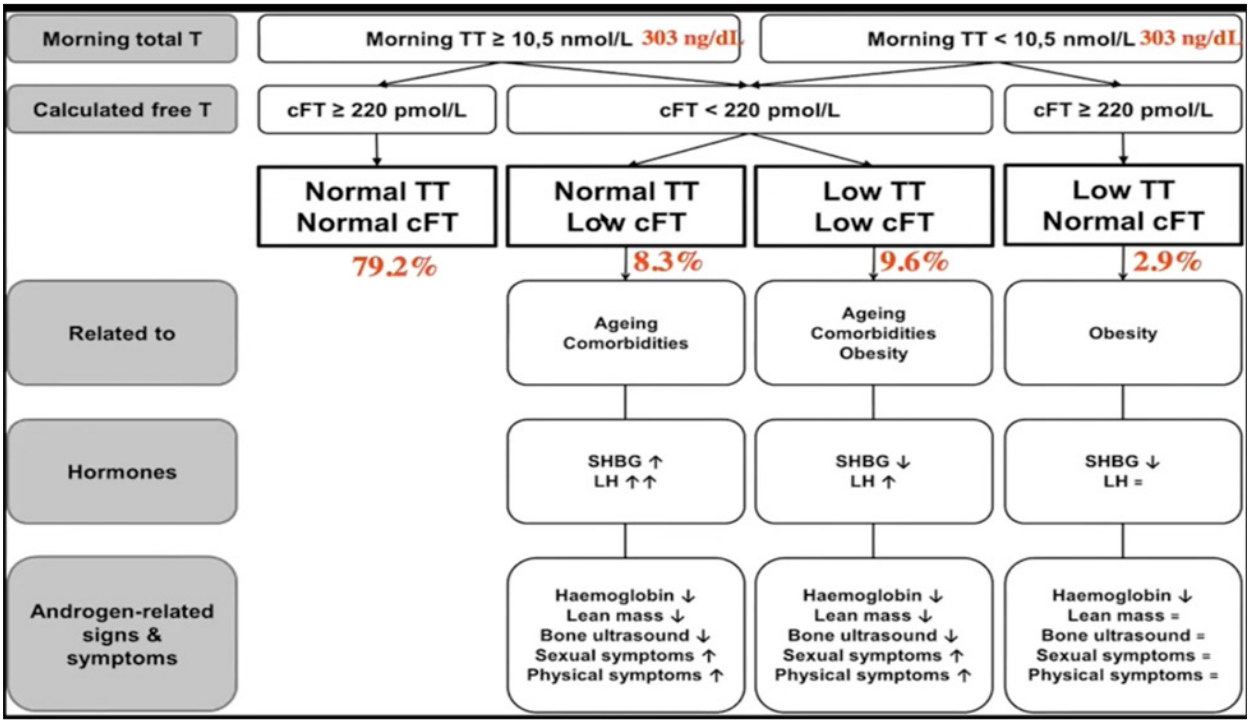
Confirm the finding

- At least one confirmatory measurement
- early morning specimens should be obtained near 8 am
- Acute effect of stressful illness may result in a transient lowering of testosterone levels

Low Testosterone

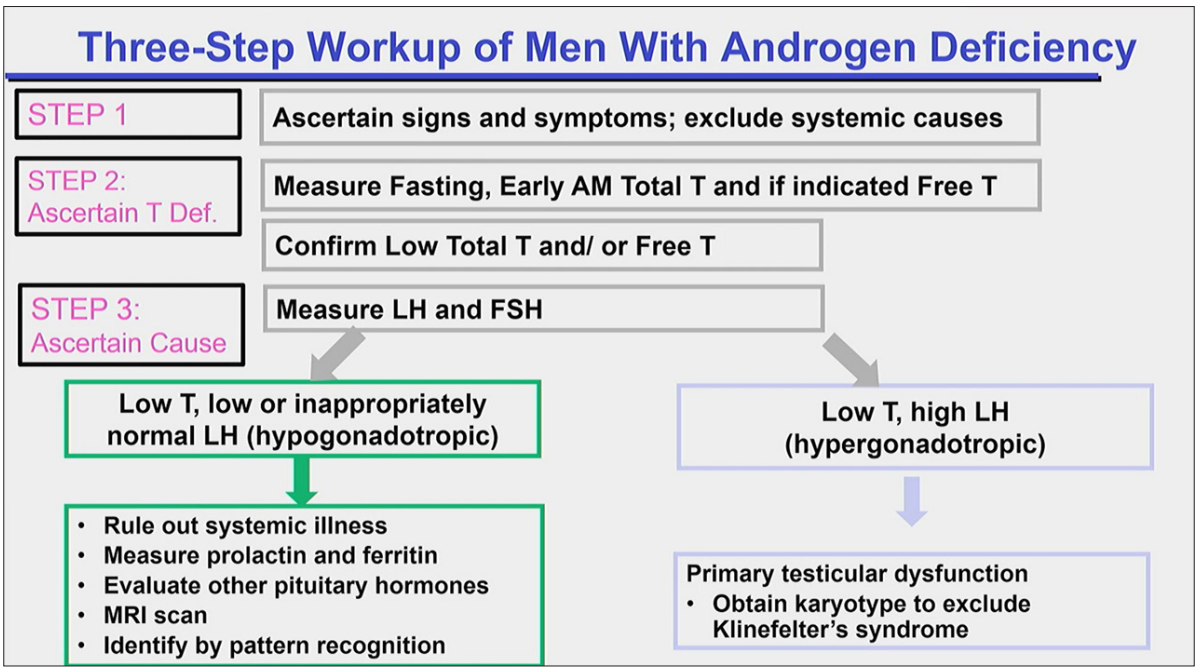
- Confronted with the finding of a low serum testosterone level, physicians should not jump to the diagnosis of hypogonadism and treat with testosterone supplementation
- Confirmation and thorough evaluation are warranted prior to making a diagnosis and/or starting therapy

Importance of Free Testosterone - Data From EMAS-



In Obesity, Free testosterone (FT)is normal. There are no sexual symptoms. 4 types of hypogonadism have been described - Primary hypogonadism, secondary hypogonadism, congenital, etc. There are Sexual symptoms in both. With Testosterone(T), there is improvement of the sexual symptoms. Compensated hypogonadism- High Luteinizing hormone(LH) and low normal Testosterone. There are Physical, not sexual, symptoms with this type of hypogonadism. Physiological hypogonadism- Obesity- Free Testosterone(FT) is normal, Total Testosterone(TT) is low. Do not give T initially. With weight loss, TT improves. If it does not and symptoms persist- then treat with T.

T is contraindicated if metastatic Prostatic cancer, breast cancer, or hematocrit above 50%.Testosterone improves in primary and secondary hypogonadism the sexual symptoms, anemia, and Bone mineral density(BMD). Does not decrease osteoporotic fractures(OP FX), increases in Traverse trial all types of FX, not osteoporotic ones. Venous thromboembolism (VTE) – do not give T if there is thrombophilia. But incidence DVT/PE has not increased significantly in recent studies. If history of DVT - do not use Testosterone in the first 6 months post-DVT. Not anymore black box warning for T for CVD. Also refer to urologist if AUA-SI above 19, PSA above 4 ng/ml, or 3 ng/ml with certain races- African-Americans, first-degree relatives with prostatic cancer, etc., or increases with more than 1.4 in a year post-treatment or on Digital Rectal examination(DRE), there is a nodule [1].



MRI

Secondary Hypogonadism

- The yield of pituitary-hypothalamic imaging in older men is fairly low in the absence of other pituitary hormone abnormalities/deficiencies
- There are limited data regarding appropriate criteria for performing pituitary imaging studies
- Cost-effectiveness to exclude pituitary and/or hypothalamic disease is unknown

Guidelines/experts recommend imaging in patients with secondary hypogonadism when:

- The total testosterone level is very low (<150 ng/dL)
- There are abnormalities of multiple hypothalamic-pituitary axes panhypopituitarism
- Persistent hyperprolactinemia
- If clinical signs/symptoms warrant imaging
- Visual field deficits, cranial nerve palsy, etc.

Day-to-Day Variability in T Levels During Repeated Testing

VISIT 1	VISIT 2		
ng/dL	≤300 ng/dL	> 300 ng/dL	TOTAL
≤300	16	5	21
> 300	7	93	100
TOTAL	23	98	121

The diagnosis of androgen deficiency should not be based on a single testosterone measurements.

Reversible Causes of Hypogonadotropic Hypogonadism

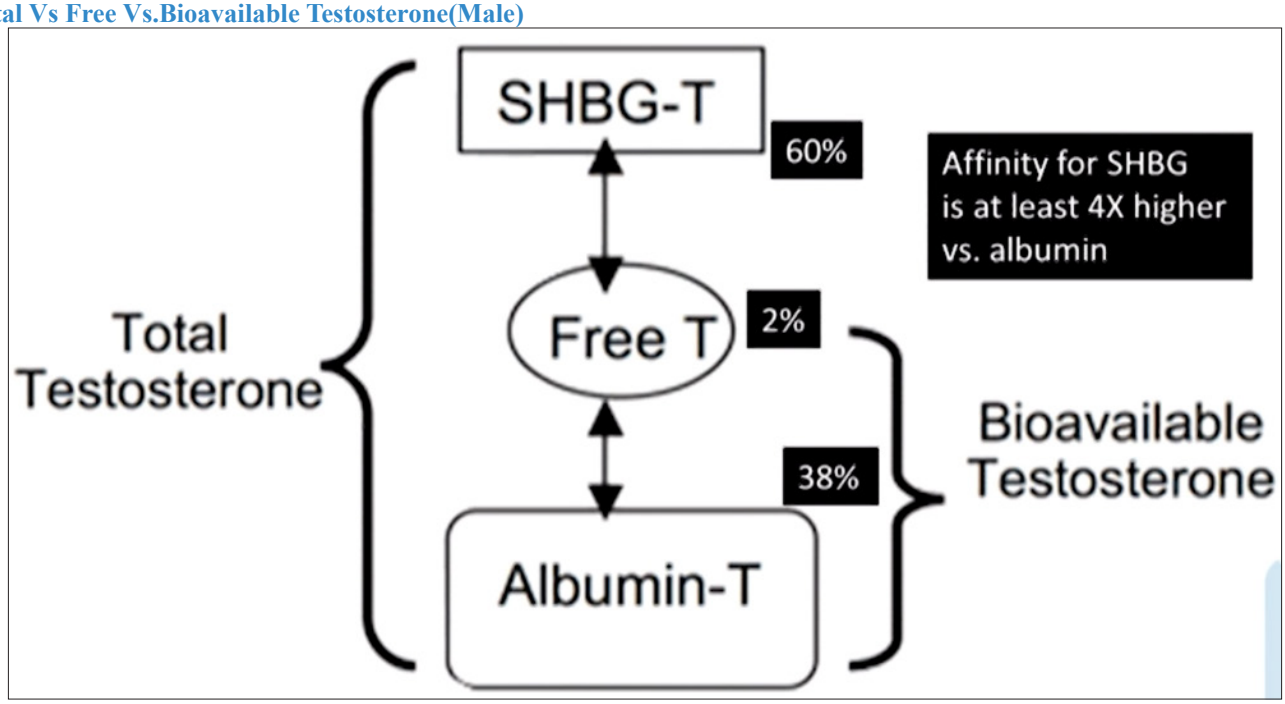
Systemic illness/recent surgery

- Medications
- Opioids
- Glucocorticoids
- GnRH analogs
- Drugs that cause hyperprolactinemia:

anti-psychotics, anti-emetics, anti-hypertensives - tyrosine kinase inhibitors e.g. crizotinib

- Eating disorders
- Excessive exercise

Total Vs Free Vs.Bioavailable Testosterone(Male)



Reduction in the Level of Sex Hormone Binding Globulin

- Results in low total serum testosterone levels
- Seen in patients with obesity and/or DM-2 states of insulin resistance

Also seen in other conditions such as

- Acromegaly Hypothyroidism
- Nephrotic syndrome
- Therapy with glucocorticoids, progestins, and androgenic steroids

In these settings, checking the level of free testosterone and/or bioavailable testosterone may be more appropriate

Conditions with increased SHBG[2]

1. HIV
2. Hyperthyroidism
3. Estrogens, OCP'S, Pregnancy
4. Anti seizure medications
5. Congenital
6. Aging
7. Chronic liver disease
8. Anorexia nervosa
9. GH deficiency

Reducing Measurement Error by Using Accurate Assays Certified by Accuracy-based Standardization Programs

Measure T using an accurate assay.

- LC-MS/MS assays, or immunoassays that are certified by an accuracy-based benchmark.

Certification by an Accuracy Benchmark such as the CDC's HoSt Program or the CAP Surveys:

- The participating assays are bench-marked to a higher order reference method and calibrator.
- Total T levels by LC-MS/MS in CDC-certified laboratories are similar.

Methods for Assessing Free Testosterone (FT) Levels

Two ways of assessing FT levels

Direct Measurement

- Equilibrium dialysis (reference method)
- Tracer analog methods
- Ammonium sulfate precipitation

Calculated FT (CFT)

- Calculation based on linear binding models
- Empirically-derived equations

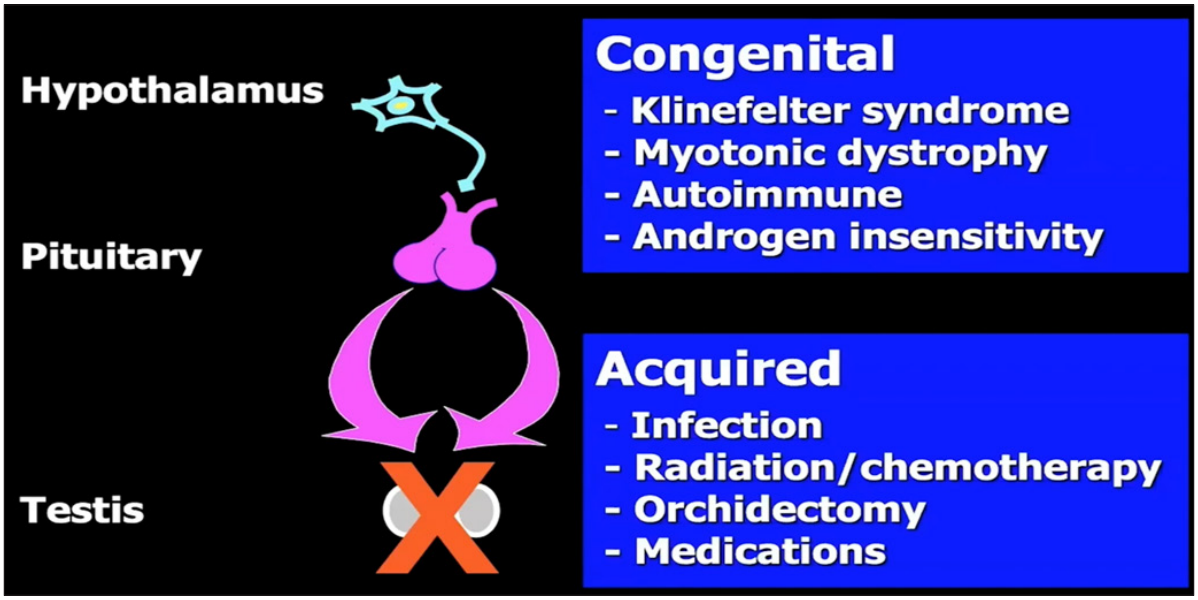
The Endocrine Society's Expert Panel suggested:

"the calculation of free testosterone from reliably measured total testosterone and SHBG using mass action equations provides the best approach for the estimation of free testosterone..."(Rosner et al 2007).

Primary Hypogonadism

- Toxin exposure (chemotherapy)
  Congenital defects
- Anorchia, cryptorchidism Karyotype abnormalities
  Klinefelter Syndrome (47 XXY)
- Orchitis (mumps, autoimmune)
- Testicular trauma or infarction
- Hemochromatosis
- Increase in temperature of testicular environment
  Varicocele, large panniculus
- Medications which inhibit androgen synthesis Ketoconazole

Primary Hypogonadism



Klinefelter Syndrome

47, XXY karyotype: nondysjunction during meiosis; 46, XY/47,XXY) more common

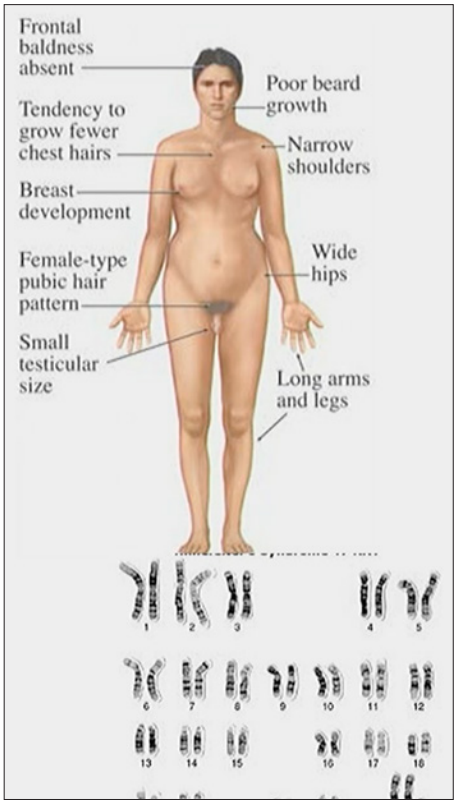
Approx. 1 in 500 males

Presentation

- Childhood: behavioral and learning problems -
- Adulthood: Infertility or androgen deficiency

Phenotype

- Normal pubertal development
- Very small testes, eunuchoidal proportions, gynecomastia
- Normal performance IQ, but low verbal IQ



Excess Morbidity and Mortality in Klinefelter's Syndrome

KS patients are at increased risk for:

- Overall mortality
- Breast cancer
- Certain types of non-Hodgkin's lymphomas
- Lung cancer
- Autoimmune diseases

Lower risk for prostate cancer

Men with KS should undergo periodic screening for breast cancer.

Secondary Hypogonadism

↓ or normal LH/FSH in the setting of testosterone

Congenital Disorders

- Inherited/Genetic defect

Acquired

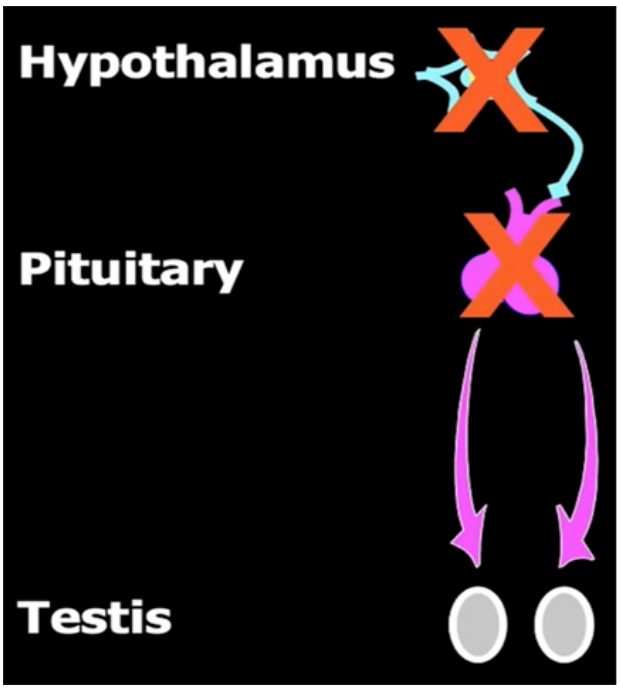
- Damage to gonadotrophs
- Suppression of gonadotrophs

Secondary Hypogonadism

Congenital - Genetic

Normosmic hypogonadotropic hypogonadism (HH)

Kallmann syndrome (HH + anosmia)



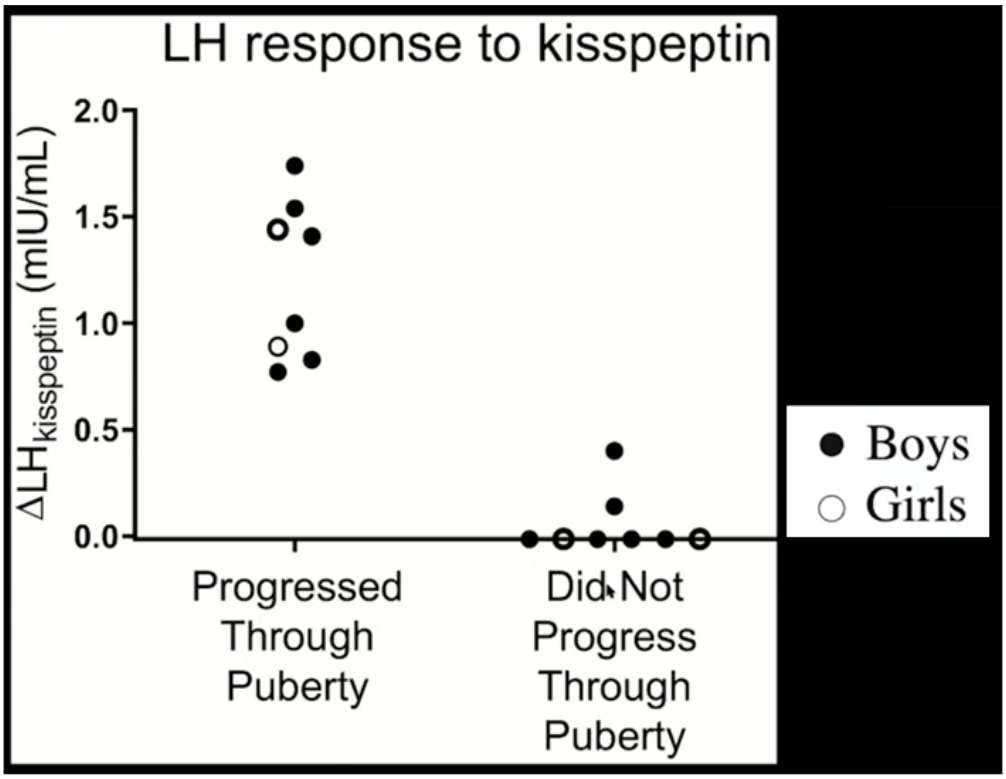
Congenital Disorders

Kallmann syndrome

- Anosmia and GnRH deficiency
- Additional findings: cleft lip and/or palate, syndactyly, unilateral renal agenesis, and cryptorchidism
- KAL1 X-linked inheritance
- FGFR1, PROKR2, and PROK2 autosomal dominant Mutation/Deficiency of the GnRH receptors
- Genetic mutations associated with pituitary hormone deficiencies (PROP-1 mutation)

Distinguishing Hypogonadism from Constitutional Delay of Puberty

- Family history
- Short stature
- Anosmia, cryptorchidism, microphallus
- Other congenital anomalies
  - -synkinesia
  - - cleft lip/palate
  - - digital anomalies



Acquired Damage to Gonadotrophs

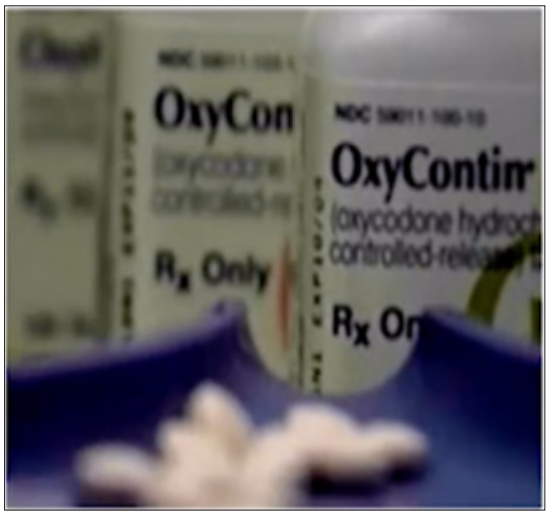
- Sellar mass/cysts
- pituitary adenomas, craniopharyngioma, Rathke cleft cyst, meningioma
- Infiltrative lesions
- lymphocytic hypophysitis, Langerhans cell hystiocytosis, sarcoidosis, hemochromatosis, infection
- Metastatic lesions (breast, renal cell, lung)
- Trauma (head injury)
- Radiation exposure/Surgery to sellar region
- Pituitary apoplexy
- Stalk severance

Acquired Suppression of Gonadotrophs

Medications (opioids, corticosteroids)
Obesity, insulin resistance
Type 2 diabetes mellitus
Obstructive sleep apnea
Aging
Hemochromatosis
Hyperprolactinemia
Estrogen excess
Anabolic steroid abuse
Anorexia nervosa
Acute illness
Human immunodeficiency virus infection
Chronic medical conditions
Alcohol abuse
Severe primary hypothyroidism
Pubertal delay

Medications

Chronic therapy with common medications such opioids and/or corticosteroids can result in secondary hypogonadism



GnRH analogues (leuprolide)
used in the treatment of prostate cancer

Opioid-Induced Hypogonadism

- Due primarily to inhibition of GnRH secretion
- Observed in:
  - heroin addicts
  - patients on methadone maintenance Rx (less so with buprenorphine)
  - patients with chronic pain receiving oral, transdermal or intrathecal opioids
- Low T levels may increase pain perception and limit analgesic efficacy of opiates

Insulin Resistance/DM-2

Insulin resistance

- Low total testosterone but normal free testosterone
- Reduction in SHBG
- Low levels of free testosterone can also be observed, particularly in morbid obesity, but the cause remains unclear
- Decrement is proportional to the degree of obesity

Testosterone levels have been reported to be lower in obese men with diabetes than in those with obesity alone

- Decrement comparable in magnitude to the effects of other chronic diseases
- Suggests that low testosterone **may simply be a marker of poor health**

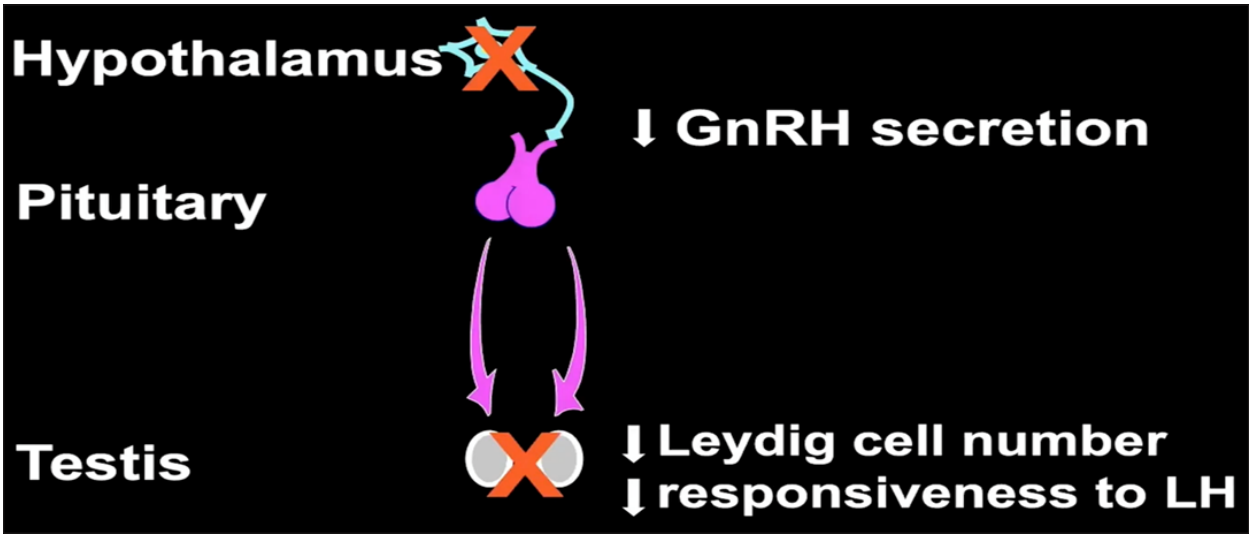
Hyperprolactinemia

- Approximately 50% of men with macroprolactinomas remain hypogonadal and require TRT
  - -Either from residual prolactin elevations secondary to dopamine agonist resistance or damage to gonadotrophs
- Testosterone is aromatizable to estrogen (estradiol)
- Estradiol can stimulate prolactin secretion and lactotroph growth (increase in tumor size)
- Aromatase inhibitors (or SERMS) may prevent a secondary rise in prolactin and potential enlargement of the macroprolactinoma

Obstructive Sleep Apnea

- Disturbances in the sleep cycle, regardless of the underlying cause, can result in decreased serum testosterone
- Often, correction of the underlying sleep disturbance can result in normalization of serum testosterone levels
- Caution must be used, and a thorough evaluation for sleep apnea should take place in high-risk individuals (obese)
- Testosterone replacement therapy can adversely affect ventilatory drive and induce or worsen obstructive sleep apnea!

Again Causes Dual Defects in HPG AXIS



Acute Illness

Gonadotroph Sick Syndrome

- Hypogonadism is a relatively common finding in any critical illness
- Analogous to euthyroid sick syndrome with respect to the hypothalamic-pituitary-thyroid axis
- It is transient, and resolves with resolution of the underlying medical condition
- sepsis, myocardial infarction, etc.

Exogenous

Excess Estrogen

- Exposure to estrogen containing contraceptives/creams

Endogenous

Testicular or adrenal estrogen-secreting tumors

- Sertoli/Leydig cell tumors (often visible on U/S)
- HCG secreting testicular tumors

↑E, T,↔ ratio favors estrogen

Rare syndrome of aromatase excess

- Persistent gynecomastia since adolescence, short stature, elevated SHBG
- Low Testosterone (suppression of HPG axis by elevated estrogens)
- Robust rise T&E to IM HCG

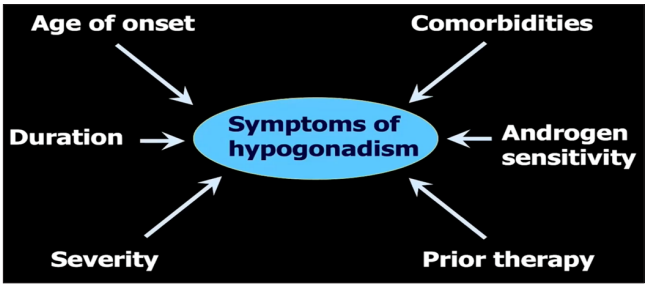
AAS Withdrawal Hypogonadism

- After prolonged use of large doses of AAS, the recovery of HPT axis may be incomplete or may not occur at all leading to AAS Withdrawal Hypogonadism.
- In some men's health clinics, AAS withdrawal hypogonadism has emerged as important cause of androgen deficiency.

Hormone Profile with Anabolic Steroid use

Steroid regimen	LH	T	E_2
Synthetic androgens only	↓	↓	↓
Synthetic androgens plus testosterone	↓	↑	↑
Synthetic androgens plus T plus aromatase inhibitor	↓	↑	↓

AAS(Anabolic Androgen Steroids)- induced hypogonadism[3]1. During the withdrawal phase2. Absent libido3. Impaired erections4. Symptoms of depression5. AAS users exhibit HPT(Hypothalamus-pituitary-testicular) suppression with secondary hypogonadism/azoospermia persisting for many months even more than one year6. Treatment- besides stopping AAS restoration of HPT Function with GnRH, SERM(Selective estrogen receptor modulators)-clomiphene or HCG(Human Chorion Gonadotropin). Not always success. Some despite Clomiphene citrate and increased LH and FSH- low Testosterone - irreversible damage to Leydig cells and some even with nl Testosterone -downregulation of the Testosterone receptors which might be irreversible with clinical signs of hypogonadism.



Challenges in Diagnosing Hypogonadism

- Debate as to threshold T level for dx
- Variability in T levels due to circadian rhythms, medications, co-morbidity, assay methodology
- 30% men with low testosterone levels have normal levels on repeat testing
- Greater likelihood that co-morbid illness is contributing to non-specific symptoms of hypogonadism in older men

Indications for TRT

Key Points

- Testosterone measurements should occur near 8 am
- A low serum testosterone value should always be confirmed by a reliable reference laboratory
- The definition of a low testosterone level varies from lab-to-lab
- In general, values <200-250 ng/dL are clearly low in most
- laboratories, and values between 250-350 ng/dL may be considered borderline low
- Determine if the etiology is primary (testicular) or secondary (hypothalamic/pituitary)
- Acute illness and treatment with opioids, anabolic steroids, or corticosteroids can cause hypogonadism

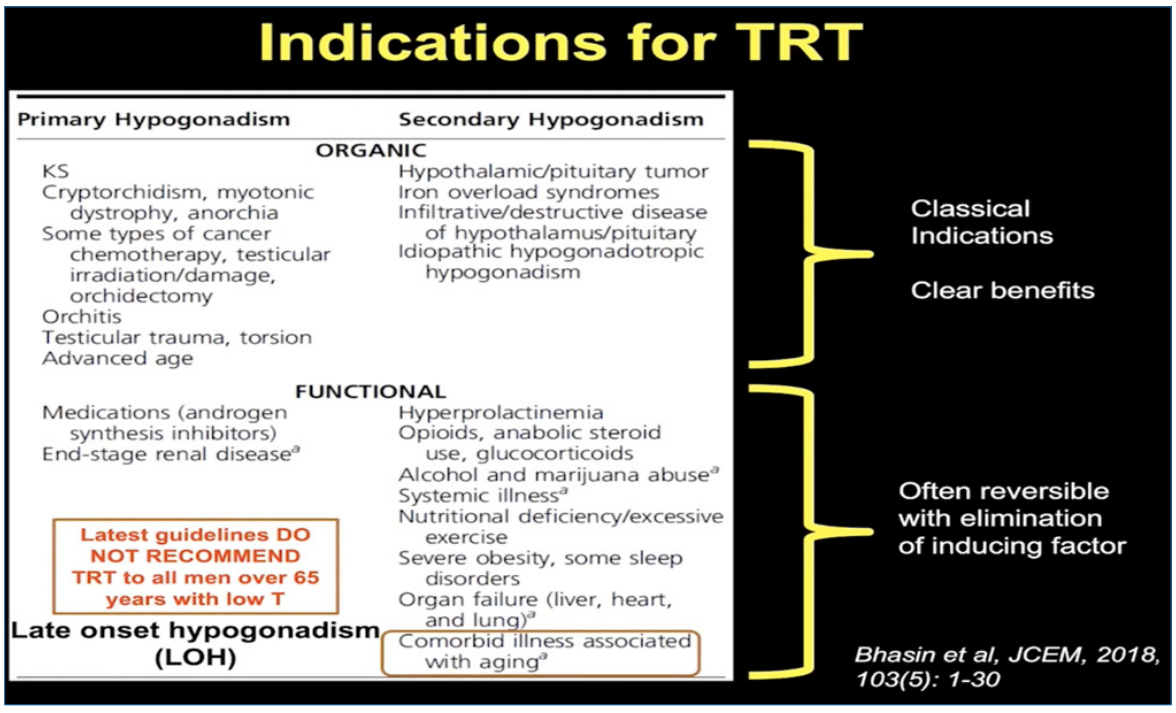
Risks/Benefits/Alternatives of Treatment

Discuss the R/B/A of treatment

- This conversation between the physician and patient should include dialogue regarding the uncertainty of the risks and benefits of testosterone supplementation in the older male population
- Treatment is only recommended in patients with clinically significant symptoms of androgen deficiency
- simply treating low T values is not recommended
- Recent guidelines suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations
- Treat the underlying cause, if one can be found

Testosterone Therapy and Alternatives

Below there is a discussion of different indications, side effect, as well as risks/benefits of testosterone therapy and alternative treatments, as well as comparisons between different treatments. Also, fertility issues and treatments are discussed [4,5,6,7,8,9,10,11].



Treatment goals for Male Hypogonadism

STEROIDOGENESIS

- Normalization of serum testosterone and obtain symptomatic improvement in men with both primary and secondary hypogonadism

SPERMATOGENESIS

- Induction of spermatogenesis in secondary (hypogonadotropic) hypogonadism
- Retrieval of sperm in primary (hypergonadotropic) hypogonadism

TRT: Expanding Choices

Widely used:

- Injectable short acting T esters (enanthate/cypionate/ mixture of esters)
- Injectable long acting T ester (undecanoate) [Nebido®: outside USA]
- Topical gels/solutions (1%, 1.62%, 2%)
- Topical patches
- Testosterone implantable pellets

Sparsely used:

- Buccal testosterone
- Oral testosterone (undecanoate)

Testosterone Undecanoate

2 loading doses 750 mg IM at 1 week and at 4 weeks
F:
+ every 10 weeks thereafter
Approved by FDA in 2014, the drug is available, with restrictions, through the Aveed® Risk Evaluation and Mitigation Strategy (REMS)
Under the REMS, prescriber education and certification will be required and distribution of the product will be limited
Aveed®-testosterone undecanoate injection 750mg/3mL
3 mL (750 mg) at the start of treatment, at 4 weeks, and then at 10 week intervals After each injection, patients are observed for symptoms of pulmonary microembolism (POME) or anaphylaxis for 30 minutes in the physicians office clinic, or hospital, the only places where the drug can be administered

Recently approved preparations

Oral testosterone undecanoate (Jatenzo®)

- Oral twice-daily administration
- Starting dose: 237 mg twice daily
- Monitor by serum T levels drawn 6 hours post ingestion (after at least one week of starting therapy/dose adjustment)

CAUTIONS:

- Boxed warning: Increase in BP; risk of CV events
- Assess CV risk and BP control prior to starting medication
- Only approved for genetic/structural etiologies of hypogonadism; not approved for <18 years of age

Treatment Goals Mid-normal Serum Testosterone Levels

- Transdermal preparations
- mid-normal range
- approximately 400-600 ng/dL
- IM testosterone cypionate or enanthate
- approximately 400-700 ng/dL midway between injections - some advocate trough of 300-350 ng/dL
- Subcutaneous pellets
- within the normal range at the end of the dosing interval

Treatment

- Make decision on individual basis
- You prescribe the testosterone, you do the f/u testing and monitoring!
- HCT
- ??? PSA and/or DRE
- Baseline, and at 3 to 12 months, and then annually

Prostate Cancer Monitoring

Hypogonadal men 55 to 69 years old with life expectancy > 10 years

- Guidelines suggest discussing the potential R vs. B of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring.
- For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone.
- Hypogonadal men being considered for testosterone therapy who are 40 -69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer), guidelines recommend discussing prostate cancer risk with the patient and offering monitoring options

Endocrine Society Guidelines 2018

Treatment goals for TRT

- To induce and maintain secondary sexual characteristics in hypogonadal men
- Correct symptoms of testosterone deficiency

Clinical Monitoring Endocrine Society Guidelines

At 3-6 months assess

- Improvement in sexual function, libido
- Improvement in muscle strength
- Improvement in body composition

Contraindications

According to the most recent Endocrine Society Guidelines, testosterone therapy is not recommended in patients with

- Breast or prostate cancer
- Palpable prostate nodule or induration or PSA > 4 ng/ml without further urological evaluation
- PSA > 3 ng/ml in individuals at high risk for prostate cancer African Americans
- Men with 1st degree relatives who have prostate cancer Erythrocytosis (hematocrit > 50%)
- Untreated obstructive sleep apnea
- Severe lower urinary tract symptoms
- Class III or IV heart failure (uncontrolled or poorly controlled) Myocardial infarction or stroke within the last 6 months Thrombophilia
- Those desiring fertility in the near-term

Stop Therapy and Consult Urology

- Verified serum or plasma PSA concentration > 4.0 ng/ml at any time
- An increase in serum or plasma PSA concentration greater than 1.4 ng/ml within any 12-month period of testosterone treatment
- Detection of a prostatic abnormality on digital rectal examination
- Substantial worsening of LUTS

Stop therapy

If HCT should rise to greater than 54%

- Cessation of testosterone therapy should occur until HCT decreases to a safe level
- Evaluate the patient for hypoxia and sleep apnea
- If indicated, therapy should be reinitiated at a reduced dose

Role of anti-estrogen therapy in the treatment of low serum testosterone

- Although the use of anti-estrogen therapy (Clomiphene) or aromatase inhibitors for the sole purpose of raising serum testosterone is endorsed by some, this is not a common practice in the United States and it is generally discouraged by most specialists
- However, these medications may be warranted in the setting of infertility where their utility is beyond that of merely increasing the levels of serum testosterone

Testosterone formulation	Dosing regimen	Rate of hematocrit elevation >50%
Testosterone cypionate or enanthate [53] (short-acting injectable)	100-200 mg IM every week	67%
Testosterone undecanoate [54] (long-acting injectable)	1000 mg, first interval 6 weeks, followed by intervals of 12 weeks	7%
Transdermal gel [53]	Testosterone 50-100 mg every day(sachets) Testosterone 20-80 mg every day (dosing pump)	13%
Pellets [53]	Crystalline testosterone 75 mg/ pellet implanted, 10-14 pellets every 3-6 month	35%

Effects of TRT

- In the aging, overweight male with type 2 diabetes and subnormal testosterone levels, treatment should be first directed toward lifestyle measures such as weight loss and exercise
- May raise testosterone and provide multiple health benefits
- Simply providing testosterone supplementation may alter body composition in a metabolically favorable manner, but changes are modest and have not consistently translated into reductions in insulin resistance or improvements in glucose metabolism
- May actually cause more harm than good

What Have We Learned from large RCTs about Testosterone's Effects on Sexual Function?

Sexual Function

- No beneficial effects in men who have normal T levels and no symptoms
- TRT improves overall sexual activity, sexual desire, erectile function, and satisfaction with erections in older men with unequivocally low T levels and decreased libido.
- TRT does not improve ejaculatory function or erectile response to PDE5ls.

Effects of Testosterone on Muscle Mass, Strength and Physical Function in Older Men

- TRT improves muscle mass, strength, self-reported physical function, and stair climbing power. The gains in muscle mass and strength are dose-related.
- Improvements in gait speed are small and their clinical meaningfulness remains unclear.
- Testosterone's long-term safety and efficacy in improving health outcomes disability, fractures, falls - remains unknown.

Effects of TRT on Other Outcomes in Older Men

Anemia

- Improved unexplained anemia of aging as well as anemia of known causes

Cognition

- No significant effect on cognition

HRQOL: No overall effect on HRQOL

- Improvement in self-reported physical function

Fatigue

- No meaningful improvement in fatigue

Depression

- Small improvement in mood; no improvement in clinical depression

Adverse Events Associated with Testosterone Therapy

Adverse Events for which there is Evidence of Association

- Acne, oiliness of skin
- Erythrocytosis
- Testicular atrophy and infertility
- Increasing the risk of detection of prostate events
- Increasing the growth of metastatic prostate cancer
- Some formulations-specific adverse events, such as local skin reactions

Adverse Events for Which there is Weak or Inconclusive Evidence of Association

- Gynecomastia
- Prostate cancer
- Obstructive sleep apnea
- Lower urinary tract symptoms
- Cardiovascular events

Testosterone and Erythropoiesis

Erythrocytosis the most frequent AE associated with T therapy (Calof et al, 2005)

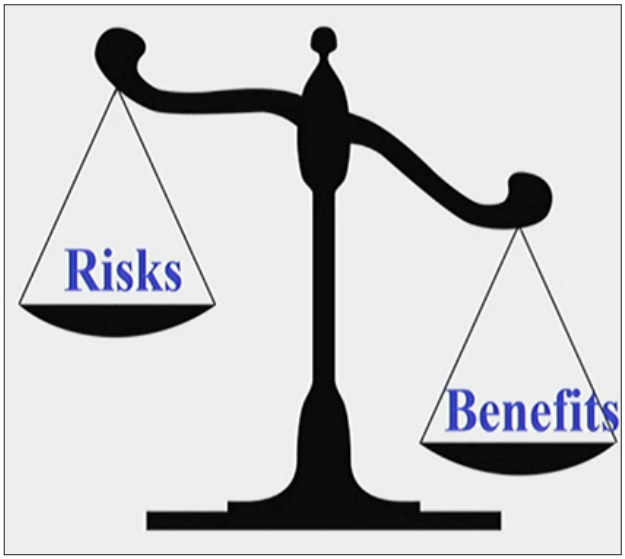
- Effects are related to T dose and concentrations
- Greater increments in older men

Mechanisms

- T stimulates erythropoiesis
- Suppresses hepcidin and increases iron availability
- Increases Epo
- Resets epo:Hb set-points
- Effects on RBC survival

Synthesis and Conclusions

- Important to distinguish between classical hypogonadism and age-related decline.
- In young men with classical hypogonadism, TRT improves symptoms with low AE frequency.
- In older men with unequivocally low T and symptoms, TRT improves sexual function, anemia, bone density and quality, muscle mass, strength and some measures of function, but long-term benefits in improving hard outcomes and long-term risks remain unknown.



Infertility

DEFINITION : Failure of conception after 1 year of unprotected intercourse

PREVALENCE: 15% in 1 year 6% in 2 years
(10% of couples seek medical attention)

INFERTILITY CAUSES

1982-5 W.H.O. multicenter study

Male	20%
Female	38%
Both	24%
Idiopathic	15%

MALE INFERTILITY

ROLE OF THE ENDOCRINOLOGIST

- Identify untreatable causes (e.g. Klinefelter (?), anorchia) and convey information empathetically
- Counsel such patients re: alternatives (A.I.D.; adoption) Initial evaluation to exclude systemic / endocrine diseases
- Identify and treat certain abnormalities (gonadotropin deficiency; hyperprolactinemia; retrograde ejaculation)
- Be aware of underlying genetic disorders (screen & counsel)
- Refer as necessary for assisted reproductive technologies

(modified from Bhasin, 1997)

MALE INFERTILITY ETIOLOGY

PRE-TESTICULAR'

- Endocrine (hypogonadotropism; others)

TESTICULAR

- Genetic (Klinefelter; Y deletions)
- Congenital cryptorchidism
- Orchitis
- Toxic (heat; drugs; irradiation)
- Vascular (torsion, varicocele)
- Idiopathic

POST-TESTICULAR

- Obstructive (congenital - absent vasa deferentia [cystic fibrosis]; infective; vasectomy)
- Epididymal hostility
- Cilial defects (zero motility)
  a) Kartagener syndrome
  b) Young syndrome
- Immunologic (idiopathic; post-vasectomy)

ERECTILE/EJACULATORY DYSFUNCTION

INTRACYTOPLASMIC SPERM INJECTION (ICSI)

- since 1993
- accumulated experience pregnancy rate
- > 20% cycle (vs. normal 30%)
- sperm source - semen, epididymis or testis (biopsy or needle aspiration)
- concern re: transmission of genetic disease (?prescreening)
- minor increased risk of sex chromosome anomalies
- remember the female at risk from ovulation induction/egg harvesting

MALE INFERTILITY - WHAT'S NEW?

Y chromosome microdeletions

- Many map to the Yq11 region of the chromosome, that is named azoospermic factor (AZF)
- 10-20% of males with azoospermia or severe oligospermia
- Most with small testes (<15 ml)

Complete deletions of the AZFa or AFZb regions lead to azoospermia and Sertoli cell only syndrome.

- Sertoli cell only syndrome: a condition of the testes in which only Sertoli cells line the seminiferous tubules
- Usually have normal secondary male features

- Generally speaking, testosterone and LH levels are normal, but due to lack of inhibin, FSH levels are increased
- Partial deletions AZFa or AZFb or complete deletion of the AZFc regions result in a variable phenotype varying from hypospermatogenesis to Sertoli cell only syndrome and present with severe oligozoospermia or azoospermia.

Sperm Stimulation

hCG stimulates the Leydig cells

- Concentration of intratesticular T↑ 80-100X fold higher than in serum, crucial for spermatogenesis
- In post-pubertal men who develop secondary hypogonadism, hCG alone is usually sufficient, even if testes have undergone some atrophy

FSH stimulates spermatogenesis by acting on Sertoli cells of seminiferous tubules

- FSH in combination with hCG is generally necessary in those men who develop pre-pubertal hypogonadism, have small testicular size (< 8mL), or have history of cryptorchidism

GnRH-requires intact pituitary

SERMS

- Clomiphene (estrogen receptor antagonist, hypothalamic)
- Requires intact hypothalamus and pituitary

Aromatase Inhibitors

- Aromatase inhibitors (lower estradiol levels)
- Requires intact hypothalamus and pituitary

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