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Clinical Investigation and Laboratory Analyses in Male Hypogonadism

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Disclosures

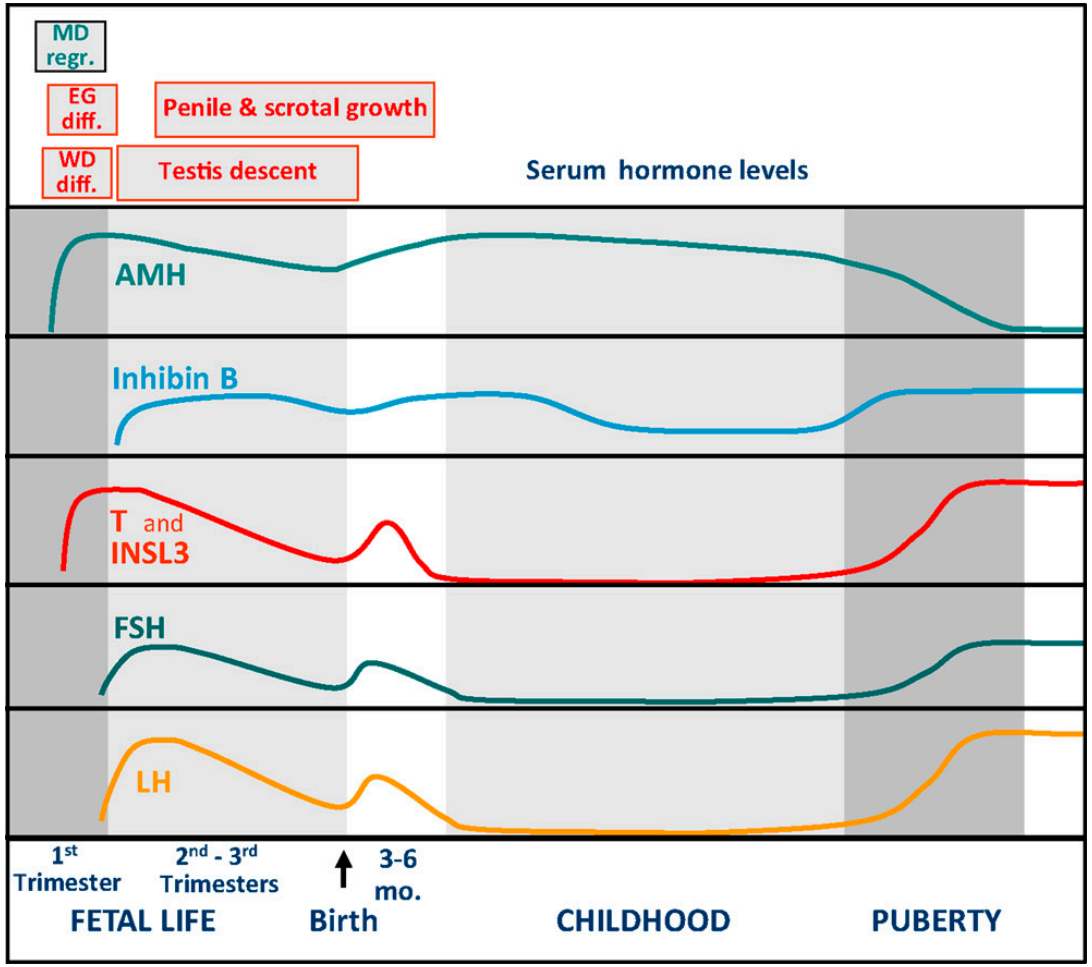
Drs. Sadri and Howards have *no financial disclosures or conflicts of interest* to report relevant to this presentation.

Learning objectives

After this presentation, the learner should be able to:

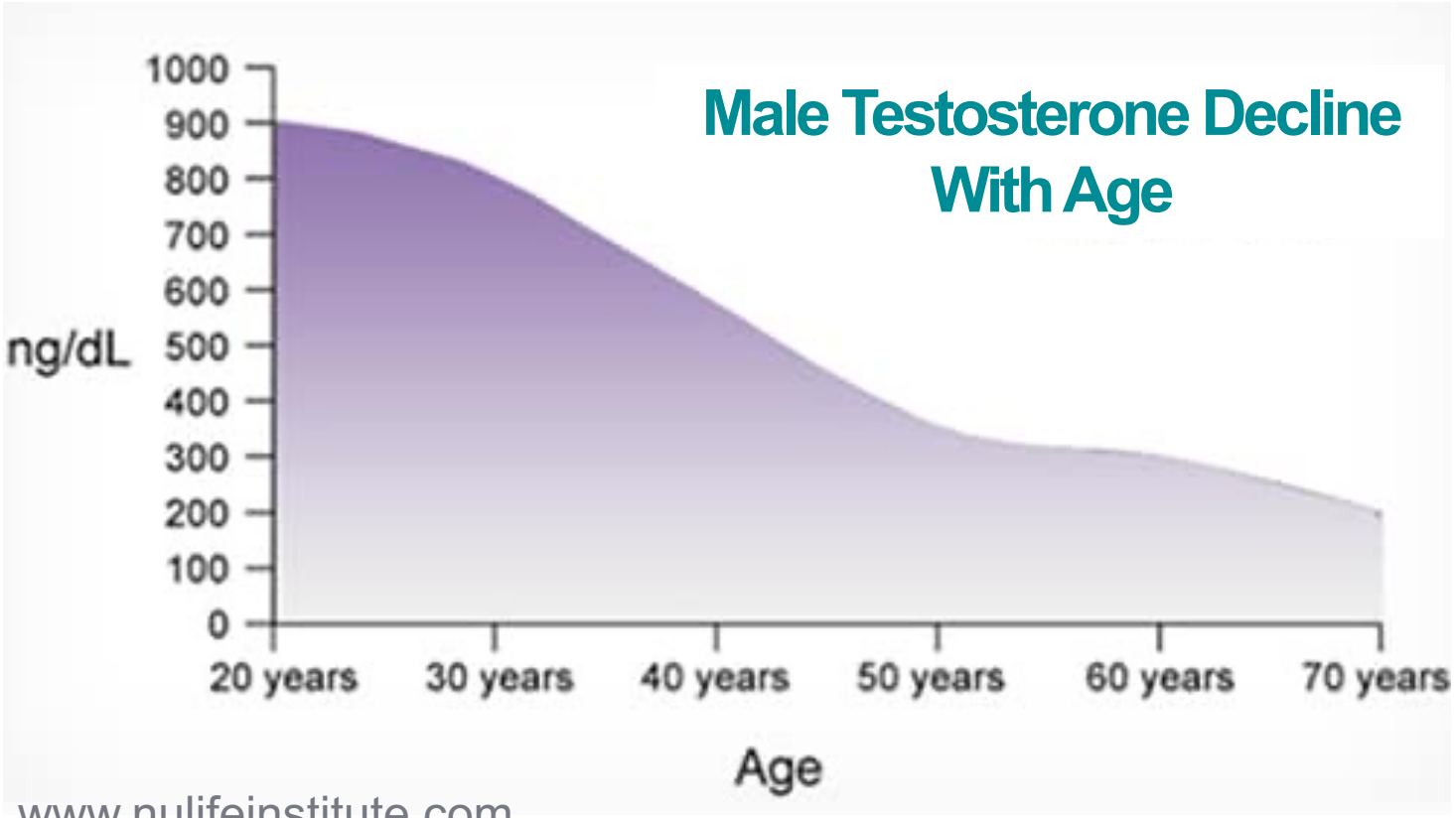
- Understanding the definition and classification of male hypogonadism
- Identify the etiologies and different categories of male hypogonadism
- Apply the latest recommendations of AUA on evaluation and management of male hypogonadism

The pituitary–testicular axis hormone levels and of sexual differentiation and development of male internal and external genitalia



Front. Endocrinol., 07 May 2014 | https://doi.org/10.3389/fendo.2014.00051

Male Testosterone Decline With Age



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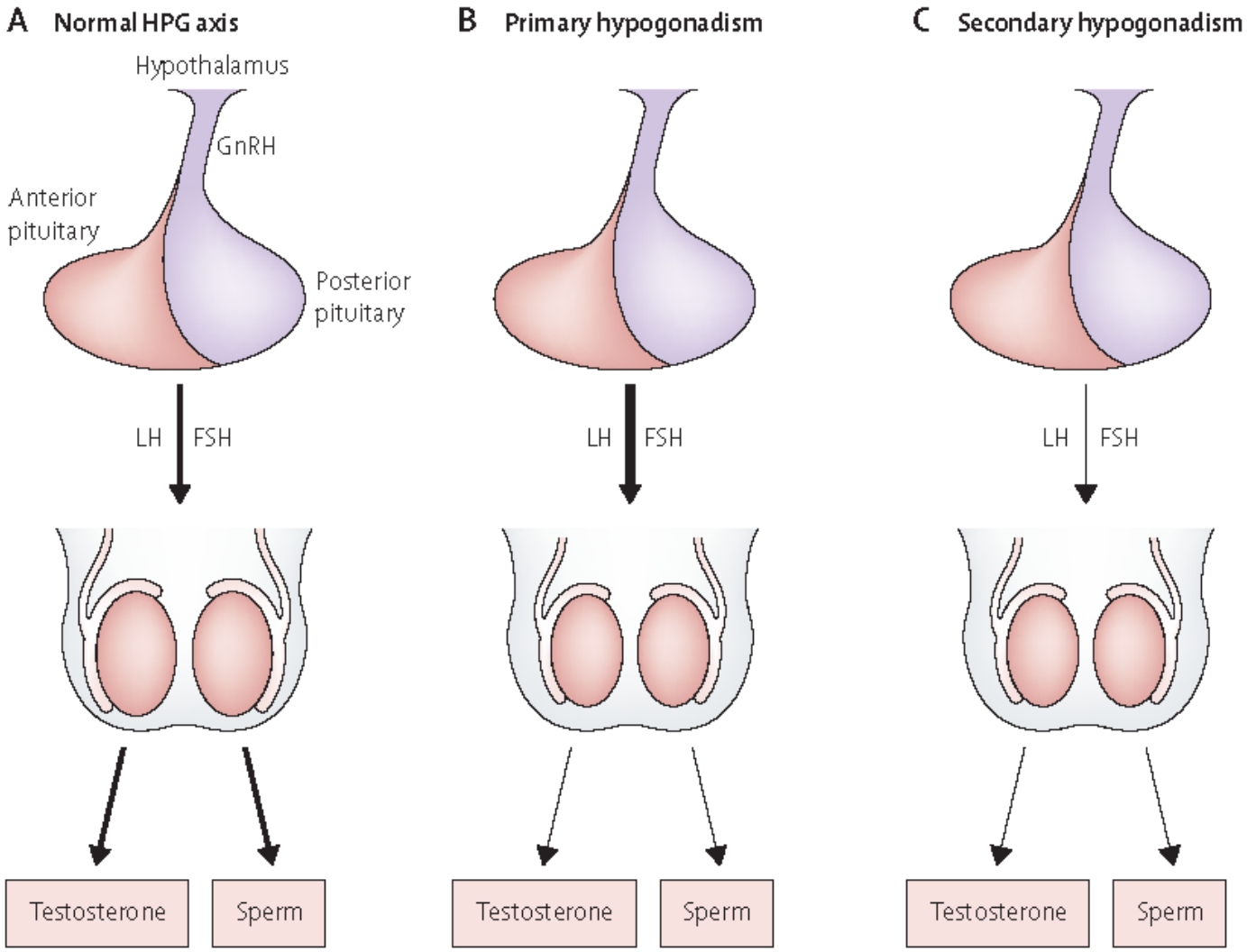
Andropause

DEFINITION OF MALE HYPOGONADISM

Impairment/lack of either (or both) of the two main functions of the testes: testosterone secretion and/or sperm formation.

- . Testicular failure can result from
  - The disease of the testes (**primary** hypogonadism)
  - The disease of the pituitary or hypothalamus (**secondary** hypogonadism).

Hypothalamic-pituitary-gonadal axis



Lancet 2014; 383: 1250–63

Causes of Primary Hypogonadism

Testicular diseases (↑ gonadotrophins +/- ↓testosterone)

Congenital

- **Klinefelter syndrome (1:500 male new borns)**
- Defects of testosterone biosynthesis (STAR, 20–22 desmolase 3β-HSD, 17α-HSD, 17–20 desmolase, 17β-HSD: rare)
- Pure gonadal dysgenesis (46 XX and 46 XY, rare)
- Congenital anorchia (rare)
- Leydig cell hypoplasia (including type I and II for LH/hCG receptor mutations, rare)
- Myotonic dystrophy (including type I and II)
- **Cryptorchidism (1:100 male new borns)**
- Germinal aplasia (Del Castillo syndrome, sertoli-cell only syndrome)
- **Y Chromosome microdeletions (from 5 to 15: 100 in azoospermic and severely oligozoospermic males)**
- **Autosomal translocations (1:100 severely oligospermic males)**
- Follicule stimulating hormone receptor (FSHR) mutations (rare)
- Adrenoleukodystrophy

Acquired

- Orchitis (including mumps and autoimmune disorders), bilateral torsion trauma
- Chemotherapy (alkylating agents, metotrexate) and testicular irradiation
- Inhibitors of testosterone synthesis (ketoconazole, aminoglutethimide, mitotane metyrapone)
- **Varicocele (15:100)**
- **General diseases (including renal failure, liver cirrhosis, diabetes mellitus)**
- **Aging**

Causes of Secondary Hypogonadism

A) Hypothalamic diseases (↓ gonadotrophins, ↓ testosterone)

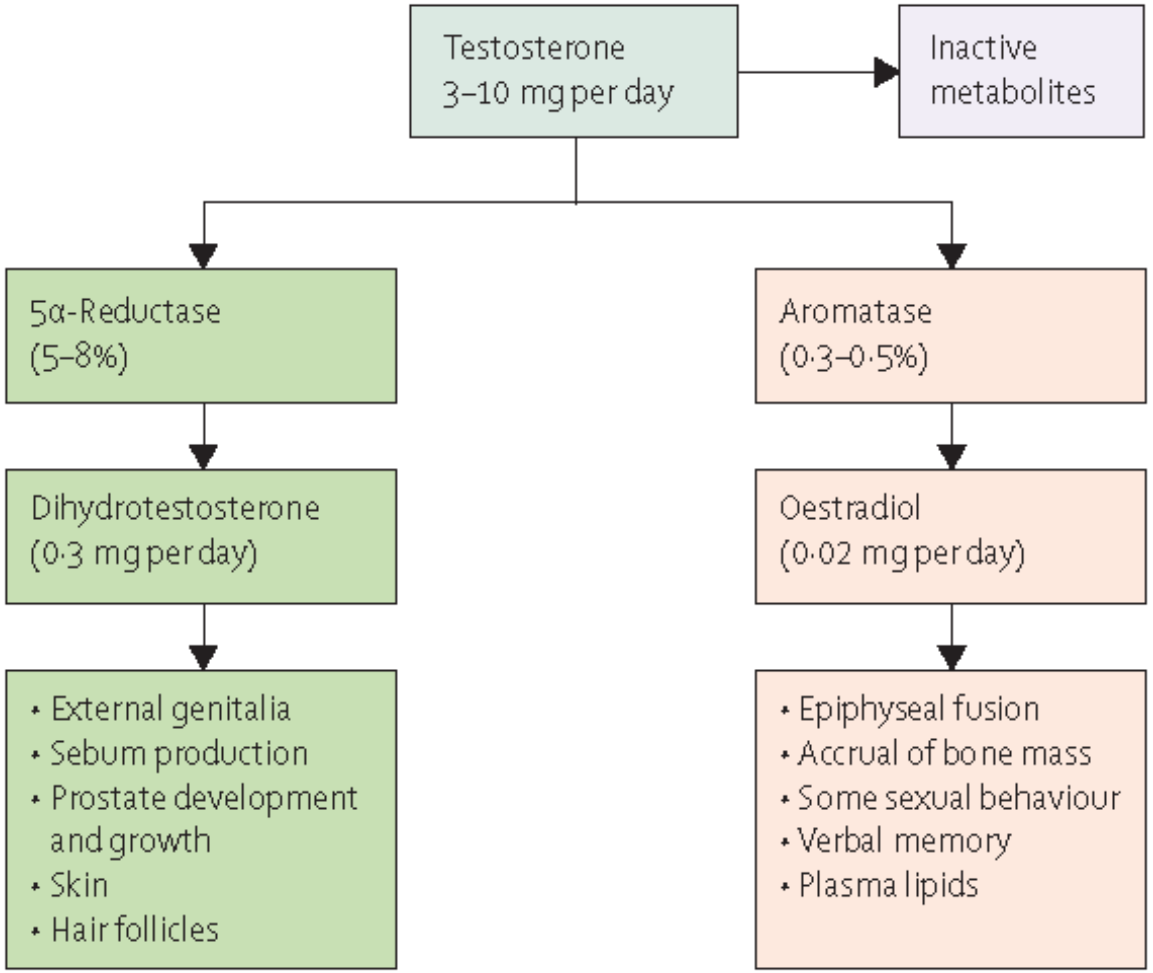
- **Congenital (1:10000 male new borns)**
  - Kallmann syndrome (including KAL 1, FGFR1, PROK2, PROKR2 mutations)
  - Leptin and Leptin receptor mutation
  - GPR-54 mutation
  - DAX-1 mutation
  - SF-1 mutation
  - Prader–Willi syndrome
  - Laurence–Moon syndrome
  - Bardet–Biedl syndrome
- Acquired (rare)
  - (a) Hypothalamic tumors (germinomas, gliomas, astrocytomas, craniopharyngiomas, meningioma, metastases)
  - (b) Infiltrative and infective disorders (rare)
    - Langerhans' histiocytosis
    - Sarcoidosis and tuberculosis, syphilis
    - Encephalitis
  - (c) **Head trauma (10–15% of men after traumatic brain injury)**
  - (d) Idiopathic
  - (e) **Functional disorders**
    - **Hyperprolactinemia (prolactinoma, hypothyroidism, antidopaminergic and serotonergic drug–induced, opiates-induced)**
    - Nutritional
    - Critical illness
    - Excessive exercise (rare)
    - **Diabetes mellitus (30:100 of men with type 2 diabetes)**
    - **Metabolic syndrome (20–30:100 of men in western countries)**
    - **Aging**
    - Cushing disease (rare)
  - (f) Drugs (estrogens, anabolic steroids, progestogens)

Causes of Secondary Hypogonadism

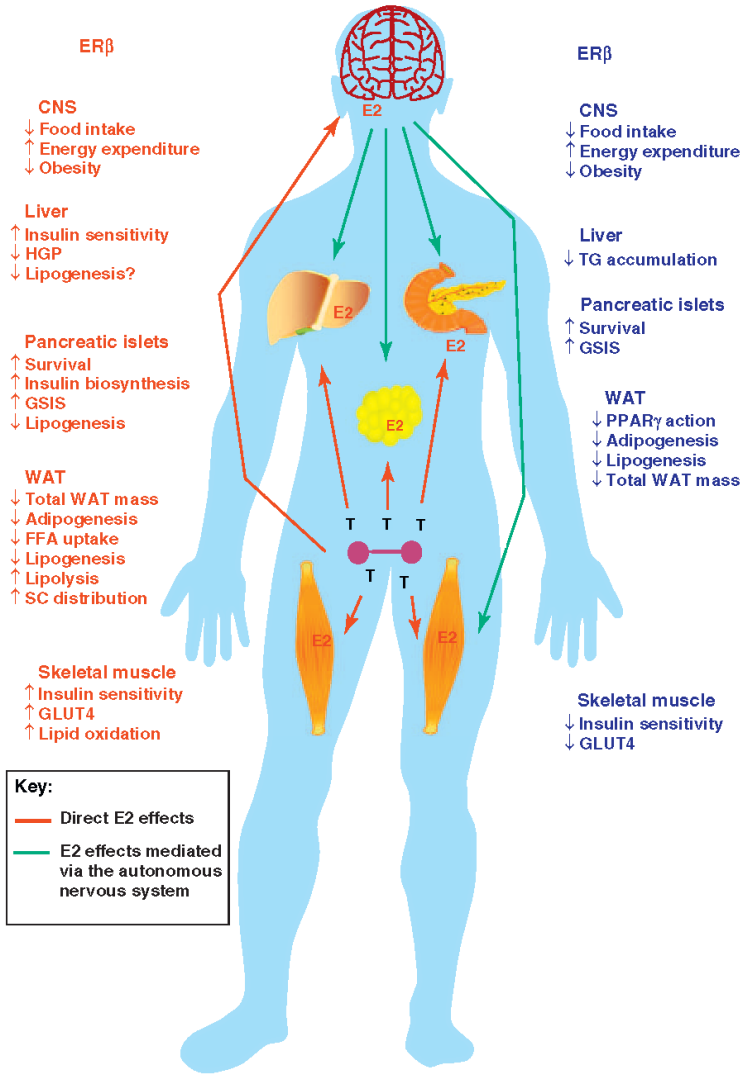
B) Pituitary diseases (↓ gonadotrophins, ↓ testosterone)

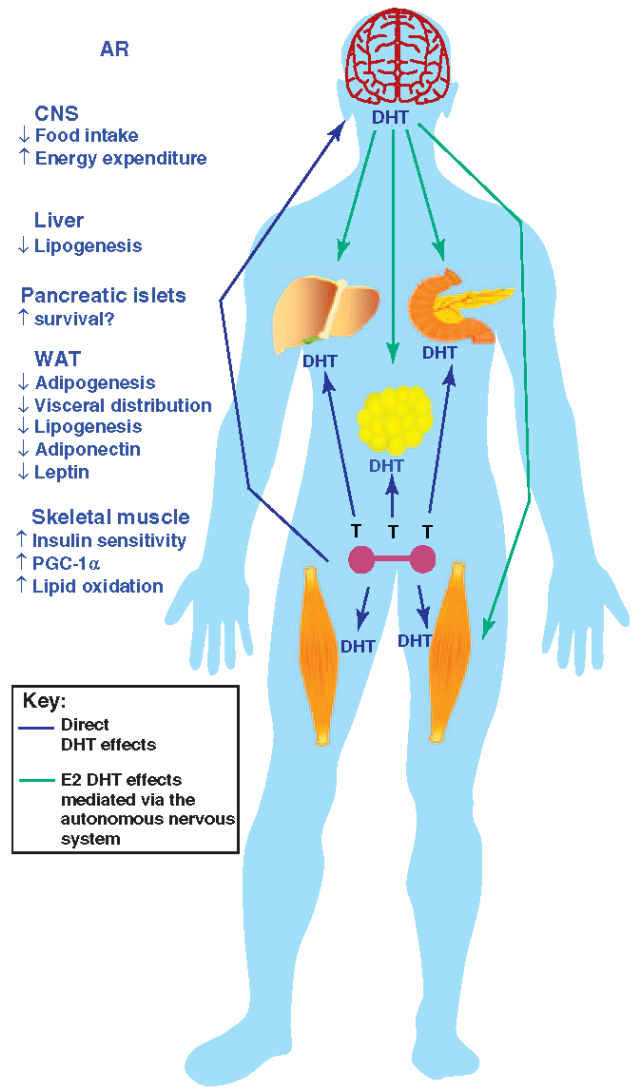
- Congenital
- Multiple hormone deficiency (including Prop1, DAX-1 mutations, rare)
- GnRHR mutations
- FSHβ and LHβ mutations
- Pituitary aplasia or hypoplasia
- Hemochromatosis
- Acquired
  - (a) Pituitary tumors (functional and nonfunctional adenomas, craniopharyngiomas, metastases)
  - (b) Infiltrative and infectious diseases (primary hypophysitis, sarcoidosis, tuberculosis, syphilis, parasites, and fungal)
  - (c) **Head trauma**
  - (d) Empty sella
  - (e) Vascular
  - (f) Drugs (GnRH agonists and antagonists), estrogens, anabolic steroids, progestogens
  - (g) X-irradiation

Production and metabolism of testosterone into its active metabolites



Estrogen and Androgen Receptors





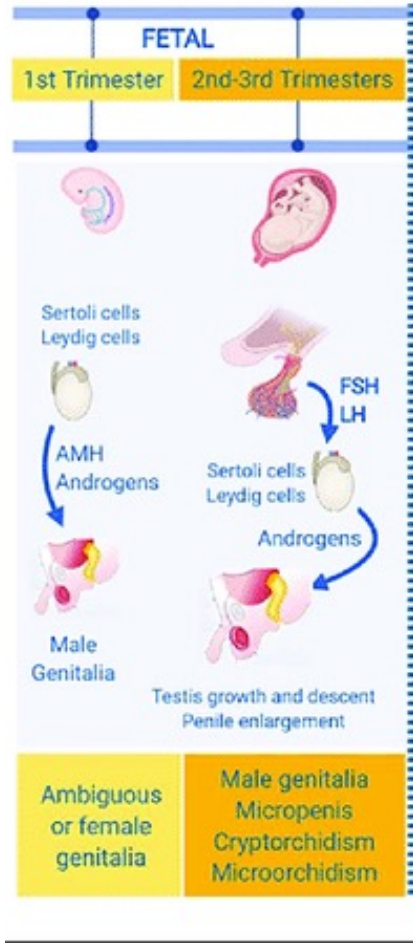
CLINICAL FEATURES OF MALE HYPOGONADISM

- Fetal hypogonadism (very early hypogonadism)
- Prepubertal and peripubertal hypogonadism (early hypogonadism)
- Adult hypogonadism
- Late onset hypogonadism (LOH)

Fetal hypogonadism (very early hypogonadism)

- Ambiguous or completely feminine genitalia can be observed in a male infant:
  - Normal karyotype 46XY
  - Defective secretion/action of testosterone during the first trimester of fetal life usually because of genetic disorders, most commonly the androgen insensitivity syndrome (AIS)
  - These patients are rare and are usually seen by pediatricians.
  - In boys with ambiguous external genitalia, urologists can be consulted for surgery on external genitalia for sex assignment or reassignment.

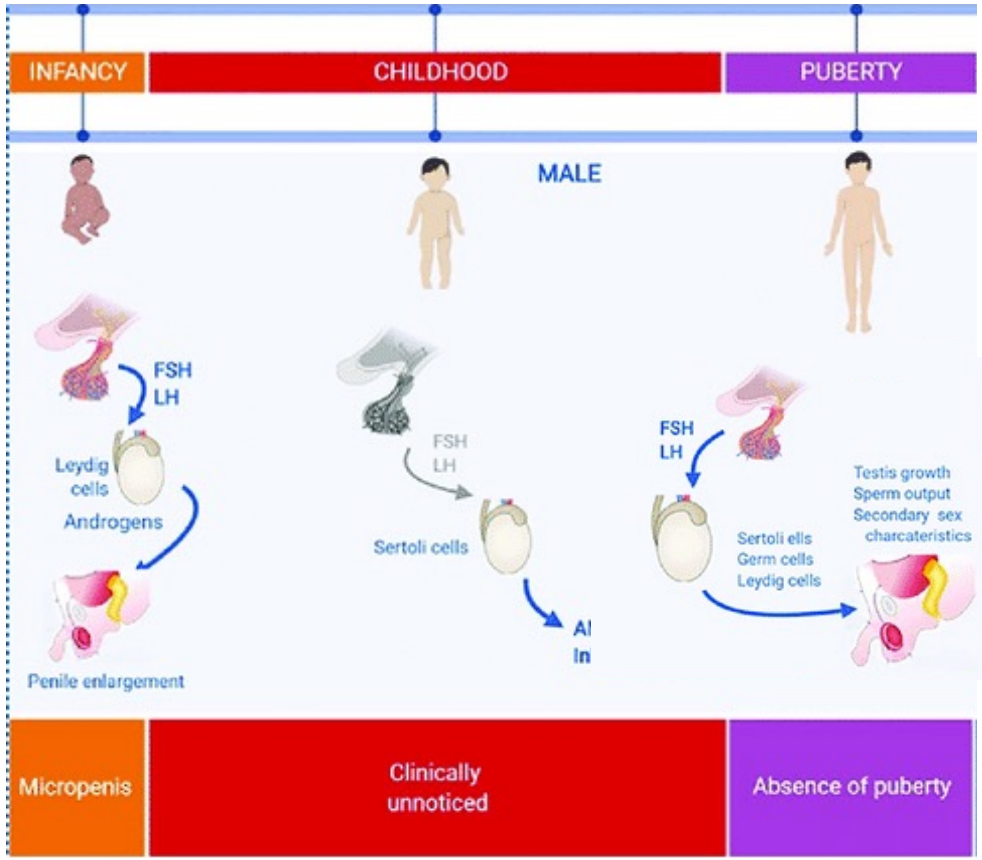
- The subjects with complete AIS having 46,XY karyotype but fully feminine external genitalia can be referred, **at the age of puberty**, either to a gynecologist or to an endocrinologist because of primary amenorrhea.
- Another typical cause of referral for these subjects is **uni or bilateral inguinal hernia**, which is uncommon in Chromosomally normal females.
  In the AIS subjects, the hernia is caused by abnormal localization of the testes.



American Journal of Men's Health, Ray and Grinspon 2020

Prepubertal and peripubertal hypogonadism (early hypogonadism)

- If hypogonadism occurs in infancy (e.g., because of vanishing testes, bilateral testicular torsion, sequelae of some types of cancer-–for example, a craniopharyngioma that destroys the pituitary gonadotrophs, leukemia with testicular infiltrates) or is due to congenital causes (for instance, the Klinefelter syndrome (KS) or congenital hypogonadotropic hypogonadism) very few clinical symptoms can be observed, as infancy is a condition characterized "per se" by substantially quiescent testes.
- According to the different causes and severity, occurrence of Leydig cell dysfunction in the peripubertal age induces a complete or incomplete failure to undergo a normal pubertal development, with lack of or only partial virilization.
- The prevalence of early hypogonadism ranges around 1:500 male newborns (KS) to 1:10,000 for congenital hypogonadotropic hypogonadism (normosmic or with anosmia)



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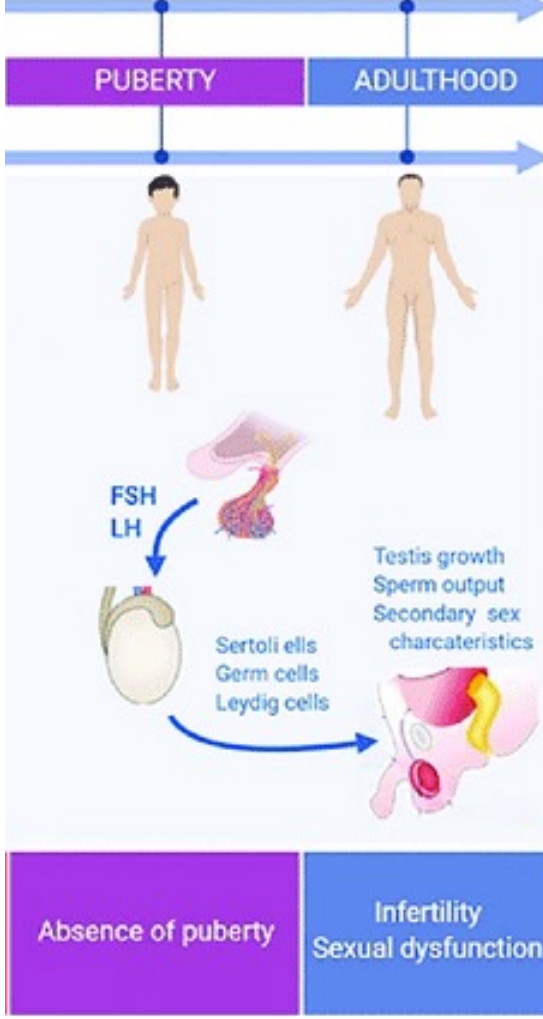
Adult hypogonadism

- In men with a previous history of normal virilization and/or fertility, symptoms of T deficiency are relatively mild even if T levels are very low (<170 ng/dl) due to, for instance, a pituitary macroadenoma.
- However, reduced libido, sexual dysfunction, asthenia, low energy, depressed humor, and more specific symptoms such as reduced volume of the ejaculate and poor growth of facial hair are often present in these patients.
- If hypogonadism has a duration of many months/years, a reduced volume of the testes as well as of the prostate can be objectively assessed.
- In men with sexual dysfunction a brief 12-item structured interview providing scores useful for detecting hypogonadism, defined as low total T (<300 ng/dL) with a sensitivity and specificity of 68% and 65%, respectively, (Androtest) has been recently developed



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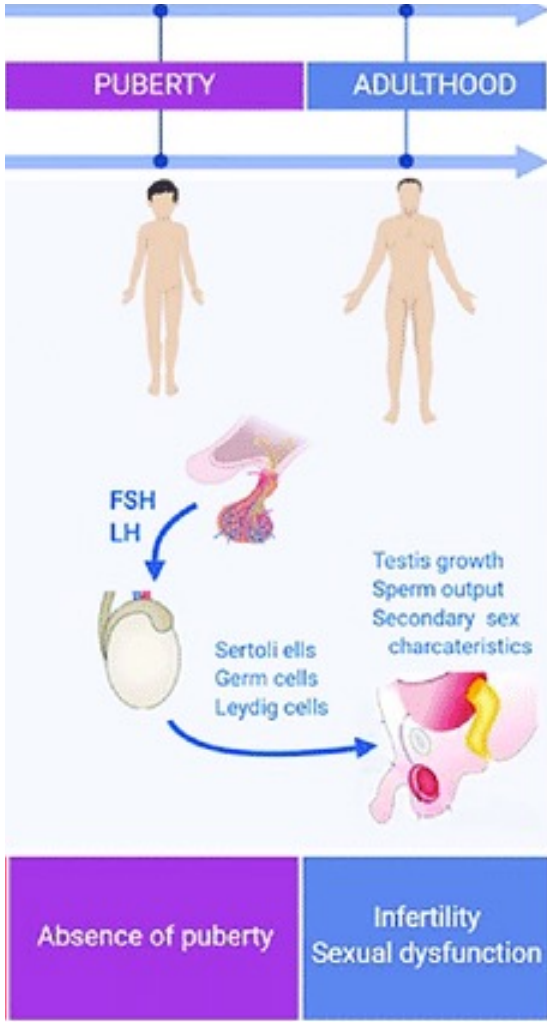
Late onset hypogonadism (LOH)

- In addition to severe late-onset hypogonadism due to specific causes, there is a more frequent form or milder hypogonadism, the hypogonadism occurring with age in a significant number of elderly men.



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CLINICAL INVESTIGATION IN MALE HYPOGONADISM

- The diagnosis of hypogonadism is based on:
  - Clinical symptoms and signs of androgen deficiency
  - Hormone measurements
  - Semen analysis

History taking is an important issue in the diagnosis of hypogonadism

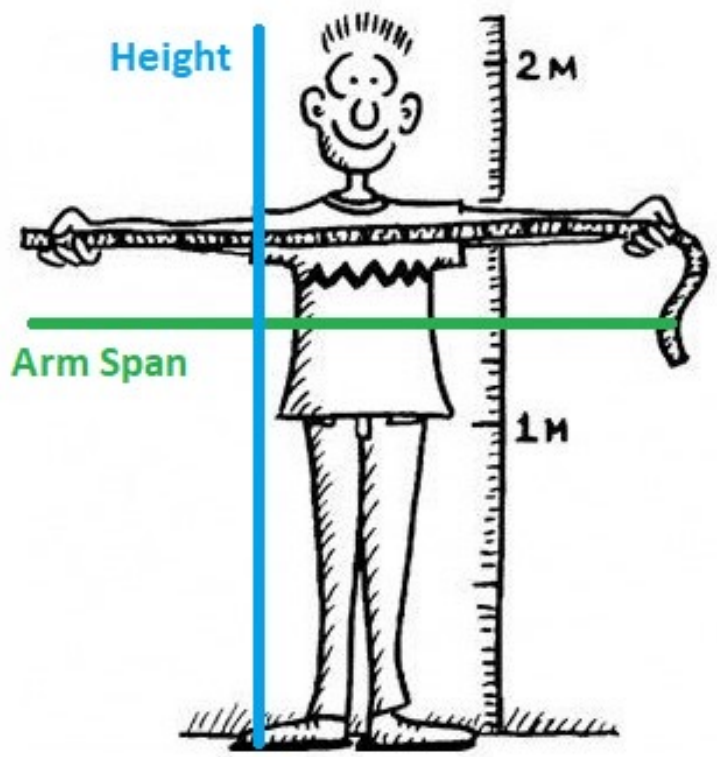
- Lack of or low libido
- Erectile dysfunction
- Poor beard growth
- All the previous symptoms from libido to ejaculate are closely related to low testosterone levels. An important symptom is hyposmia/anosmia, which may cause by congenital hypogonadotropic hypogonadism

Less specific symptoms of androgen deficiency are:

- Decreased muscle mass and strength
- Increased body fat
- Osteoporosis
- Low energy,
- Decreased vitality
- Depressed mood

Clinical examination: typical signs of testosterone deficiency

- Eunuchoid proportions (arm span > height)
- Underdeveloped genitalia
- Sparse low hair
- Gynecomastia
- Small prostate
- Low testicular volume



LABORATORY INVESTIGATION IN MALE HYPOGONADISM

- Endocrine Function
- Genetic Assessment
- Spermatogenetic Function
- Imaging

Endocrine Function

- **Testosterone and Sex Hormone–Binding Globulin (preferably before 10 AM)**
- **Luteinizing Hormone**
- **Prolactin**
- **The GnRH Stimulation Test**
- **Human Chorionic Gonadotropin Stimulation Test**

Spermatogenetic Function

- **Semen Analysis**
- **Follicle-Stimulating Hormone and Inhibin B**

Primary hypogonadism is more frequently characterized by a decreased/absent sperm production than by decreased T production. **Many infertile men have a low sperm count with normal/ high FSH, but normal T concentration.**

Men with secondary hypogonadism usually have a combined reduction of T concentration and sperm production.

Genetic Assessment

- Leukocyte blood karyotype (Klinefeter)

- Gene Mutations
  - CFTR (Azoospermia men)
  - Y Chromosome microdeletion (azoospermia and severely oligozoospermia males
  - A KAL1 and FGGR1 (anosmia/hyposmia coupled hypogonadotropic hypogonadism
  - Beta subunit of LH

Imaging in Male Hypogonadism

- **Ultrasound Examination of the Testis**
- **Magnetic Resonance Imaging/Computed Tomography**

SUMMARY: DIAGNOSIS OF MALE HYPOGONADISM

- At prepubertal age, the diagnosis of male hypogonadism is difficult because testes are physiologically quiescent.

No specific Symptom is present and hormone assays are in the normal range.

- In a postpubertal/adult male, impairment of testosterone secretion by the testes can be suspected on the basis of history taking and physical examination.

Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)

American Urological Association

The diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)

The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. (Moderate Recommendation; Evidence Level: Grade B)

American Urological Association

RECOMMENDATION

Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use even in the absence of symptoms or signs associated with testosterone deficiency. (Moderate Recommendation;
Evidence Level: Grade B

American Urological Association

The use of validated questionnaires is not currently recommended to either define which patients are candidates for testosterone therapy or monitor symptom response in patients on testosterone therapy. (Conditional Recommendation; Evidence Level: Grade C)

RECOMMENDATION

In patients with low testosterone, clinicians should measure serum luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)

Serum prolactin levels should be measured in patients with low testosterone levels combined with low or low/normal Luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)

RECOMMENDATION

Patients with persistently high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders. (Strong Recommendation; Evidence Level: Grade A)

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RECOMMENDATION

Serum estradiol should be measured in testosterone deficient patients who present with breast symptoms or gynecomastia prior to the commencement of testosterone therapy.(Expert Opinion)

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RECOMMENDATION

Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation performed prior to treatment. (Moderate Recommendation; Evidence Level: Grade B)

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Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. (Strong Recommendation; Evidence Level: Grade A)

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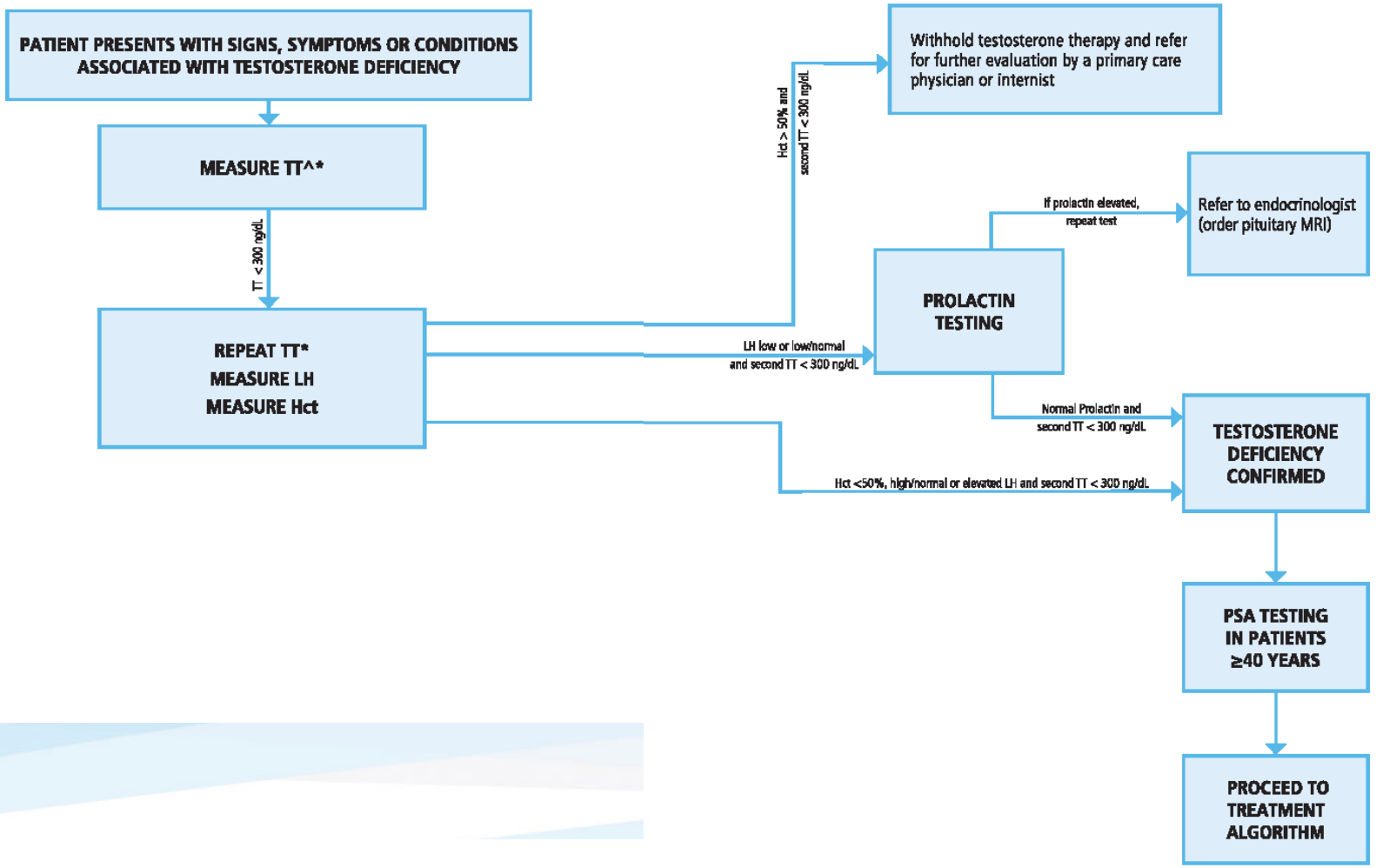
PSA should be measured in men over 40 years of age prior to commencement of testosterone therapy to exclude a prostate cancer diagnosis. (Clinical Principle)

Evaluation and Management of Testosterone Deficiency: Diagnosis Algorithm



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ADDITIONAL TESTS FOR SPECIAL CASES **		
Estradiol	**FSH**	**HbA1c**
Patients who present with gynecomastia or breast symptoms	Patients who are interested in preserving their fertility	Patients who may be at risk for diabetes
DEXA	**Karyotype**	**PSA**
Patients who have a history of low trauma bone fracture	Patients with unexplained hyper-gonadatropic hypogonadism	If first PSA is elevated, repeat test before initiating testosterone therapy

^Testosterone values are measured as ng/dL

*All TT measurements ≥ 300 ng/dL are considered normal

**After testosterone deficiency is confirmed additional tests may be considered for special cases

FSH = Follicle-Stimulating Hormone
Hct = Hematocrit
LH = Luteinizing Hormone
TD = Testosterone Deficiency
TT = Total Testosterone

PAST AND FUTURE SESSIONS

- Session One: Clinical investigation of the infertile male
- Session Two: Genetic causes of male infertility and their impact on future generations
- Session Three: Medical Treatments for Male Infertility
- Session Four: Surgical Treatments and Assisted Reproductive Technology (ART) for Male Infertility
- Session Five: Ejaculatory disorders, diagnosis, and management
- Session Six: Clinical investigation and laboratory analyses in male hypogonadism
- **Session Seven: Testosterone deficiency syndrome, , Androgen replacement—indications and principles**
- **Session Eight: Female-to-Male Transsexualism**

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