MEDICAL AND NON-MEDICAL TESTOSTERONE AND STEROID HORMONE USAGE

AMANDA HO, MD
I have no relevant financial interests to disclose.
LEARNING OBJECTIVES

▪ Explain the different effects of testosterone on men and women.
▪ Compare different steroid hormone testing options.
▪ Describe ways in which testing of hormones differs from testing for other analytes.
▪ Explain the ways in which anabolic steroid usage for athletic performance differs from medical usage of testosterone therapy.
TESTOSTERONE
**DEFINITIONS**

- **Hormone:** a small molecule produced by an endocrine gland that acts on other cells
  - Growth and development
  - Homeostasis
  - Energy usage

- **Steroid hormone:** a fat-soluble hormone with four fused rings in its structure

- **Other types of hormones:** proteins and amino acid derivatives
STEROID HORMONES

- Fat-soluble
- Can pass through cell membranes
- Act on nuclear receptors
- Affect gene expression
- Act more slowly than protein or amino acid hormones
ANDROGENS

- Hormones that develop and maintain male secondary sexual characteristics

**Hormones**
- Steroids
  - Corticosteroids
    - Glucocorticoids
    - Mineralocorticoids
  - Sex steroids
    - Androgens
    - Estrogens
    - Progestogens
- Proteins
- Amino acids
- Made out of cholesterol
- Precursors: DHEA, androstenedione
- 95% is made in Leydig cells in the testes
- Remaining 5% is made peripherally
- Circulate through the blood bound to transport proteins
TESTOSTERONE IN CIRCULATION

- Total
- SHBG
- BIOAVAILABLE
- Albumin
- FREE
Three peaks in the male life cycle:
- 2nd trimester of fetal development
- 2-3 months of age
- Puberty (reaches a plateau) – 300-1080 ng/dL

Starting around age 40, testosterone levels decline by 0.5-2%/year
- Decrease in number of Leydig cells
- Decrease in the GnRH pulse amplitude
Diurnal pattern of testosterone secretion

Hourly serum testosterone levels in normal young (n = 17) and old (n = 12) men. The circadian rhythm is lost in old men. Blood samples were obtained using an indwelling peripheral venous cannula, which allowed free movement and normal sleep.

CONCENTRATIONS - FEMALE

- 9-55 ng/dL
- Made in the ovaries and the adrenal glands
- No fetal or neonatal peak
- Does increase at puberty
- Diurnal variation
- Total testosterone peaks slightly before ovulation
- Seems to decrease with menopause
Figure 2. Mean serum total and free testosterone and LH levels during the normal menstrual cycle in 34 healthy women. Data are the mean ± sd.
# CONCENTRATIONS

## Reference Interval

Effective August 19, 2013

<table>
<thead>
<tr>
<th>Age</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28 weeks)</td>
<td>5-16 ng/dL</td>
<td>59-125 ng/dL</td>
</tr>
<tr>
<td>Premature (31-35 weeks)</td>
<td>5-22 ng/dL</td>
<td>37-198 ng/dL</td>
</tr>
<tr>
<td>Newborn</td>
<td>20-64 ng/dL</td>
<td>75-400 ng/dL</td>
</tr>
<tr>
<td>1-5 months</td>
<td>Less than 20 ng/dL</td>
<td>14-363 ng/dL</td>
</tr>
<tr>
<td>6-24 months</td>
<td>Less than 9 ng/dL</td>
<td>Less than 37 ng/dL</td>
</tr>
<tr>
<td>2-3 years</td>
<td>Less than 20 ng/dL</td>
<td>Less than 15 ng/dL</td>
</tr>
<tr>
<td>4-5 years</td>
<td>Less than 30 ng/dL</td>
<td>Less than 19 ng/dL</td>
</tr>
<tr>
<td>6-7 years</td>
<td>Less than 7 ng/dL</td>
<td>Less than 13 ng/dL</td>
</tr>
<tr>
<td>8-9 years</td>
<td>1-11 ng/dL</td>
<td>2-8 ng/dL</td>
</tr>
<tr>
<td>10-11 years</td>
<td>3-32 ng/dL</td>
<td>2-165 ng/dL</td>
</tr>
<tr>
<td>12-13 years</td>
<td>6-50 ng/dL</td>
<td>3-619 ng/dL</td>
</tr>
<tr>
<td>14-15 years</td>
<td>6-52 ng/dL</td>
<td>31-733 ng/dL</td>
</tr>
<tr>
<td>16-17 years</td>
<td>9-58 ng/dL</td>
<td>158-826 ng/dL</td>
</tr>
<tr>
<td>18-39 years</td>
<td>9-55 ng/dL</td>
<td>300-1080 ng/dL</td>
</tr>
<tr>
<td>40-59 years</td>
<td>9-55 ng/dL</td>
<td>300-890 ng/dL</td>
</tr>
<tr>
<td>60 years and older</td>
<td>5-32 ng/dL</td>
<td>300-720 ng/dL</td>
</tr>
<tr>
<td>Premenopausal (Greater than 10 years)</td>
<td>9-55 ng/dL</td>
<td>Does Not Apply</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>5-32 ng/dL</td>
<td>Does Not Apply</td>
</tr>
<tr>
<td>Tanner Stage I</td>
<td>2-17 ng/dL</td>
<td>2-15 ng/dL</td>
</tr>
<tr>
<td>Tanner Stage II</td>
<td>5-40 ng/dL</td>
<td>3-363 ng/dL</td>
</tr>
<tr>
<td>Tanner Stage III</td>
<td>10-63 ng/dL</td>
<td>10-651 ng/dL</td>
</tr>
<tr>
<td>Tanner Stage IV-V</td>
<td>11-62 ng/dL</td>
<td>152-847 ng/dL</td>
</tr>
</tbody>
</table>
REGULATION: HYPOTHALAMIC-PITUITARY-GONADAL AXIS

Hypothalamus

Gonadotropin-releasing hormone (GnRH)

Anterior pituitary gland

Luteinizing hormone (LH), follicle-stimulating hormone (FSH)

Gonads

Testosterone, inhibin

Hypothalamus
EFFECTS ON THE BODY

- Affects cells that are sensitive to androgens
- Male sexual characteristics
- Acne
- Erythropoiesis
- Increased lean body mass
- Increased energy and libido
HOW WE TEST FOR TESTOSTERONE
My patient is receiving testosterone injections.

What test do I order to measure testosterone?
SOME OF THE QUESTIONS THAT NEED TO BE ANSWERED

- Man, woman, or child?
- Expected levels?
- Total, free, or bioavailable?
MEN VS WOMEN AND CHILDREN

- Men: 300-1080 ng/dL
- Women and children: as low as 1 ng/dL

Electrochemiluminescent immunoassay vs HPLC-MS/MS

- Analytical sensitivity:
  - Immunoassay: 3 ng/dL, but imprecise
  - HPLC-MS/MS: 1.0 ng/dL
TOTAL, FREE, OR BIOAVAILABLE?

- **Total**: measures all testosterone
  - Free
  - Bound to SHBG
  - Bound to albumin

- **Free**: unbound, dissolved in blood
  - Either calculated or measured directly with equilibrium dialysis

- **Bioavailable**: free + albumin-bound
  - Calculated
MEASURING SHBG

- Quantitative electrochemiluminescent immunoassay
- Helps to determine free vs bound testosterone
- Many conditions may affect SHBG and thus affect total testosterone
<table>
<thead>
<tr>
<th>FACTORS AFFECTING SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decrease</strong></td>
</tr>
<tr>
<td>- Obesity</td>
</tr>
<tr>
<td>- Hypothyroidism</td>
</tr>
<tr>
<td>- Diabetes</td>
</tr>
<tr>
<td>- Glucocorticoids and progestins</td>
</tr>
<tr>
<td>- Androgenic steroids</td>
</tr>
<tr>
<td><strong>Increase</strong></td>
</tr>
<tr>
<td>- Aging</td>
</tr>
<tr>
<td>- Liver disease</td>
</tr>
<tr>
<td>- Hyperthyroidism</td>
</tr>
<tr>
<td>- HIV</td>
</tr>
<tr>
<td>- Estrogens</td>
</tr>
<tr>
<td>- Anti-seizure medications</td>
</tr>
</tbody>
</table>
PITFALLS OF STEROID HORMONE TESTING

- Present in small amounts
- Bound to carrier molecules
- Diurnal variation
TESTING CONSIDERATIONS

- Gender and age
- Expected levels – in concordance with patient’s gender and age?
- Need more information than a total level?
MEDICAL TESTOSTERONE THERAPY
ACCORDING TO THE FDA...

- Testosterone replacement therapy should only be given to men with confirmed low levels of testosterone and symptoms of testosterone deficiency.
# Symptoms of Androgen Deficiency

**Nonspecific**
- Decreased energy
- Depression
- Anemia
- Reduced muscle bulk and strength
- Diminished performance

**Specific**
- Decreased libido
- Loss of body hair
- Low bone mineral density or low-trauma fracture
- Hot flushes
- Infertility
- Small testicular size
**HYPOGONADISM**

**Primary**
- Disease of the testes
- High GnRH, FSH, LH
- Acquired or congenital

**Secondary**
- Disease of the hypothalamus or pituitary
- Low GnRH, FSH, LH
- Acquired or congenital
Remember, testosterone decreases by 0.5-2%/year

Only problematic when symptomatic

Many names:
- Testosterone deficiency syndrome (TDS)
- Late-onset hypogonadism (LOH)
- (Partial) androgen deficiency of the aging male ((P)ADAM)

Goal: to improve signs and symptoms of deficiency

- Don’t screen everybody
- Measure morning testosterone levels twice
- If borderline low, consider testing free or SHBG
MALE CONTRACEPTION

- Testosterone inhibits production of LH and FSH.
- The testes need FSH in order to produce sperm.

Hypothalamus

Gonadotropin-releasing hormone (GnRH)

Luteinizing hormone (LH), follicle-stimulating hormone (FSH)

Testosterone, inhibin

Gonads

Anterior pituitary gland
FEMALE TO MALE TRANSITION

- Hormone therapy is one part of the overall gender transition in transgender patients.

- Two goals of hormone therapy in transitioning from female to male:
  - Suppress native (female) hormones
  - Induce and maintain male secondary sexual characteristics
FEMALE TO MALE TRANSITION: EFFECTS OF TESTOSTERONE ADMINISTRATION

What changes

- Facial hair growth
- Deepening of the voice
- Increase in lean body mass
- Acne
- Increased libido
- Breast changes
- Susceptibility to male pattern baldness
- Cessation of menstruation

What stays the same

- Female bone structure
  - Shorter height
  - Broader hips
- Breast fat mass
- Genitalia
FORMULATIONS

- Oral?
  - Almost completely metabolized in first pass

- Intramuscular injection
- Gel, cream, or patch
- Intradermal implant
- Nasal spray
- Buccal patch
Structure of the different testosterone preparations

**Testosterone**

**Alkylated testosterones**

- Methyltestosterone
- Fluoxymesterone
- Oxandrolone

**Testosterone esters**

- Enanthate
- Cypionate

Structure of the testosterone preparations available for the treatment of men with hypogonadism.
MONITORING RECOMMENDATIONS

  
  - Measure serum testosterone 3-6 months after starting supplementation and then annually
  
  - Goal is to achieve a total serum testosterone level in the middle of the normal range for a young, healthy adult male (300-1000 ng/dL)
ADVERSE EFFECTS

- May increase risk of cardiovascular disease
- May worsen symptoms of BPH
- May increase risk of prostate cancer
- Probably increases hematocrit
- Acne
- Gynecomastia
- Suppression of spermatogenesis
NON-MEDICAL TESTOSTERONE USAGE
ANABOLIC STEROIDS
Hormones that have the same biological effects as testosterone

We’ve discussed the androgenic (masculinizing) effects of testosterone

Also anabolic (muscle-building) effects

Synthetic hormones designed to have more anabolic than androgenic effects
DO THEY WORK?

- Hard to determine, because often used in supratherapeutic doses
- Lean body mass increase of 2-5kg
- Increase in circumference of shoulders, neck, upper arms
- Increase in muscle strength
ADVERSE EFFECTS

- Hard to determine, because often used in supratherapeutic doses

- Suppression of HPG axis
  - Decreased sperm production and testicular atrophy

- Increased aggression and hostility

- Acne

- Gynecomastia
Over 630 sports agencies follow the guidelines of the World Anti-Doping Agency (WADA)

- International Olympics Committee (IOC)

- Major US sports leagues have their own policies
WADA DOCUMENTS

- Prohibited Substances
- Int’l Standard for Therapeutic Use Exemptions
- Int’l Standard for Protection of Privacy
- Int’l Standard for Testing and Investigation
- Int’l Standard for Laboratories
WORLD ANTI-DOPING CODE
INTERNATIONAL STANDARD

PROHIBITED LIST
JANUARY 2016
BANNED AAS

- Exogenous AAS, and other substances with a similar chemical structure or similar biological effect(s).
- Endogenous AAS, when administered exogenously, and their metabolites and isomers.
Tests available to measure many different anabolic steroids in the urine

- Testosterone to epitestosterone ratio
- Testosterone to LH ratio
- Creatinine
- Masking agents
IN SUMMARY

- Testosterone is present in both men and women and exerts similar masculinizing effects on both.
- Choosing a lab test to measure testosterone depends on the demographics of the patient and expected levels.
- Steroid hormone levels change throughout the day and throughout the lifespan.
- FDA recommends administration to a small group.
- There are many possible side effects of exogenous administration.
- Positive and negative effects of anabolic steroids are difficult to measure.
THANK YOU!