Hypogonadism, Male

Clinical Background

Hypogonadism is one of the most common endocrine disorders in men, and is characterized by low serum testosterone levels with clinical signs and symptoms of the disease and/or low sperm counts.

Epidemiology

- Prevalence
  - Estimated 4-5 million men in U.S. have hypogonadism
  - 20% of men ≥60 or older have hypogonadism
  - Frequency increases with obesity, type II diabetes mellitus and aging

Etiologies

- Primary (pathology in testes)
  - Autoimmune orchitis
  - Chemotherapy
  - Cryptorchidism
  - Dysgenetic testes
  - Klinefelter syndrome
  - Mumps orchitis
  - Myotonic dystrophy
  - Orchiectomy
  - Radiation
- Secondary (pathology in pituitary)
  - Alcohol abuse
  - Cushing syndrome
  - Drugs (corticosteroids, opiates)
  - Hyperprolactinemia
  - Iron overload
  - Pituitary lesions
  - Severe chronic illness (cancer, chronic liver disease, chronic renal disease, rheumatoid arthritis, diabetes mellitus and obesity)
  - Other genetic mutations
- Tertiary (pathology in hypothalamus)
  - Kallman syndrome
  - Prader-Willi syndrome
- Age-related hypogonadism (pathology in testes and hypothalamus)

Pathophysiology

- Gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus
- GnRH stimulates the release of leuteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary
- LH promotes secretion of testosterone from Leydig cells
- FSH stimulates spermatogenesis and inhibin B production from Sertoli cells inhibits FSH
- 2% of circulating testosterone is free; 98% is bound
  - 60% bound to albumin
  - 40% bound to sex hormone binding globulin

- Bioavailable testosterone = free testosterone plus albumin bound testosterone
- Substantial alterations in sex hormone binding globulin affect total testosterone level
  - Free testosterone and bioavailable testosterone levels more accurately reflect bioactive testosterone under these circumstances

Clinical Presentation

- Manifestations depend on the following:
  - Age of onset of hypogonadism
  - Duration of deficiency
  - Profoundness of deficiency
- Pre-pubertal/pubertal hypogonadism
  - Eunuchoidal body habitus
  - Gynecomastia
  - Small testes
  - Lack of secondary sexual characteristics
- Postpubertal hypogonadism
- Weakness
  - Decreased libido
  - Depressed mood
  - Impotence
  - Normal penile size
  - Low bone mineral density
  - Gynecomastia
  - Muscle loss
  - Abdominal adiposity

Treatment

- Androgen replacement

Diagnosis

- Indications for testing – signs and symptoms of hypogonadism
- Laboratory testing
  - Screen with serum testosterone concentration (preferably between 8-10 am)
    - For children, use mass spectrometry assay
    - For adult males, use radioimmunoassay (mass spectrometry not necessary) – <300 ng/dL suggests hypogonadism
  - If total testosterone is abnormal, may consider testing for free testosterone concentrations – helpful in determining bioavailable testosterone
  - FSH/LH to differentiate between primary and secondary etiologies
    - Primary – FSH and LH are elevated
    - Secondary – LH decreased or normal
- Imaging studies
  - Testosterone <150 ng/dL – consider MRI for pituitary imaging and if LH is normal to low prolactin may be increased
    - Expect to see low LH and normal prolactin in these patients

Differential Diagnosis

- Pituitary lesions
- Dementia
- Hypothyroidism adrenal tumor
- Depression
- Diabetes mellitus
- Hemochromatosis
- Cystic fibrosis

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Testosterone, Adult Male 0070130 Method: Electrochemiluminescent Immunoassay	Diagnose and monitor hypogonadism	This test is not recommended for females or children	
Luteinizing Hormone and Follicle Stimulating Hormone 0070193 Method: Electrochemiluminescent Immunoassay	Diagnose and monitor hypogonadism		
Testosterone, Bioavailable & Sex Hormone Binding Globulin (Includes Total Testosterone), Adult Male 0070102 Method: Electrochemiluminescent Immunoassay The concentrations of free and bioavailable testosterone are derived from mathematical expressions based on constants for the binding of testosterone to albumin and/or sex hormone binding globulin.	Diagnose and monitor hypogonadism Use for patients with suspected plasma protein abnormalities	This test is not recommended for females or children	

Testosterone Free, Adult Male 0070111 Method: Electrochemiluminescent Immunoassay The concentration of free testosterone is derived from a mathematical expression based on the constant for the binding of testosterone to sex hormone binding globulin.	Diagnose and monitor hypogonadism	Not recommended for testing females or children	

Additional Tests Available

Test Name and Number	Comments
Testosterone, Free & Total (Includes Sex Hormone Binding Globulin), Adult Male 0070109 Method: Electrochemiluminescent Immunoassay The concentration of free testosterone is derived from a mathematical expression based on the constant for the binding of testosterone to sex hormone binding globulin.	Not recommended for testing females or children
Testosterone, Bioavailable & Sex Hormone Binding Globulin (Includes Total Testosterone), Females or Children 0081057 Method: High Performance Liquid Chromatography/Tandem Mass Spectrometry/Electrochemiluminescent Immunoassay The concentrations of free and bioavailable testosterone are derived from mathematical expressions based on constants for the binding of testosterone to albumin and/or sex hormone binding globulin.	This test is suggested for children due to an improved sensitivity of testosterone by LC-MS/MS
Testosterone Free, Females or Children 0081059 Method: High Performance Liquid Chromatography/Tandem Mass Spectrometry/Electrochemiluminescent Immunoassay The concentration of free testosterone is derived from a mathematical expression based on the constant for the binding of testosterone to sex hormone binding globulin.	
Sex Hormone Binding Globulin 0099375 Method: Electrochemiluminescent Immunoassay	

Testosterone, Urine 0070716 Method: Chemiluminescent Immunoassay	
Androstenedione 2001638 Method: High Performance Liquid Chromatography/Tandem Mass Spectrometry	
5-a-Dihydrotestosterone by Tandem Mass Spectrometry, Serum 2002349 Method: High Performance Liquid Chromatography/Tandem Mass Spectrometry	

Guidelines

American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients--2002 update.Endocr Pract. 2002; 8 (6) :440-456.

General References

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Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Hypogonadism Testing Algorithm

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