Testosterone: Physiology, Deficiency, and Screening in the Military

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- Dr. Ted Crisostomo-Wynne is a urologist and fellowship trained andrologist. He is an Assistant Professor of Surgery at the Uniformed Services University. Dr. Crisostomo-Wynne specializes in Men's Health including sexual medicine, male infertility, and testosterone management.
- He earned his undergraduate degree from the United States Military Academy at West Point and medical degree from the Uniformed Service University. Dr. Crisostomo-Wynne completed general surgery internship and urology residency at Madigan Army Medical Center. He completed fellowship in Andrology - male sexual and reproductive medicine and microsurgery – at the University of Washington.
- Dr. Crisostomo-Wynne focuses on seeing patients for sexual medicine and fertility care including conditions like erectile dysfunction, Peyronie's disease, male infertility, pre-mature ejaculation, and low testosterone. He also specializes in the treatment of chronic genital pain syndromes and male urinary incontinence. He is a surgical expert in urologic microsurgery and prosthetic urology. He also is active in research and academics with ongoing research in the areas of erectile dysfunction, testicular pain, and male hormone management.

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Learning Objectives

At the conclusion of this activity, participants will be able to:

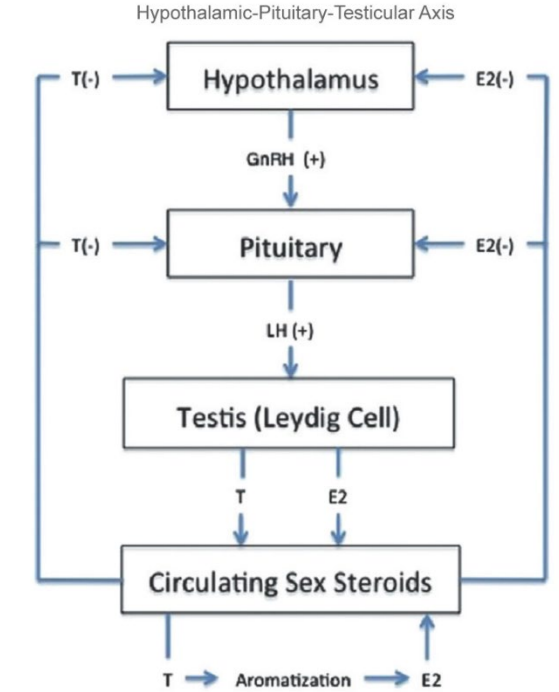
1. Describe the physiology of testosterone, its role in male health, and the clinical manifestations of testosterone deficiency.
2. Evaluate the benefits, risks, and clinical considerations of testosterone deficiency screening in military populations.
3. Compare available treatment options for testosterone deficiency, including their effectiveness, potential adverse effects, and considerations for military deployability.

Agenda

- Testosterone Physiology
- Defining Testosterone Deficiency
- Operator Syndrome
- Other Comorbidities Affecting Testosterone
- Benefits and Risks of Screening
- Treatment Options

Testosterone (T) Physiology

- Steroid hormone that acts on the androgen receptor causing it to translocate to the nucleus to regulate gene expression
  - Acts indirectly through conversion to Dihydrotestosterone (DHT) and Estradiol (E2)
    - ✓ DHT 5x more potent binding to androgen receptor (AR)
    - ✓ E2 critical for bone density; probably contributes to libido
- Primarily produced by Leydig cells in the testis
- 98% of T is bound to proteins in serum – Sex hormone-binding globulin (SHBG) and albumin



Testosterone Physiology: Effects of Testosterone

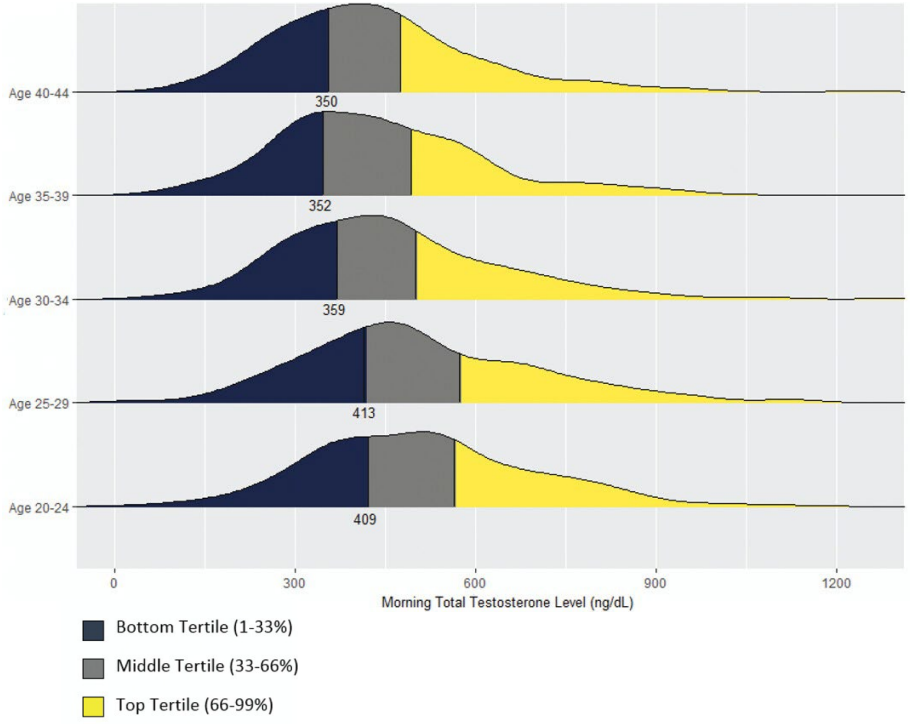
- Male secondary sexual characteristics:
  - Facial hair, body hair, voice change, increased skin thickness, bone growth
- Muscle Development
- Increased basal metabolic rate
- Erythropoiesis
- Central Nervous System (CNS) changes

Testosterone Deficiency

- Labs + Signs/Symptoms
- Labs:
  - American Urological Association: Early morning total testosterone value < 300ng/dL on two separate occasions
- Signs/Symptoms:
  - Low libido, erectile dysfunction (ED), reduced lean muscle mass, obesity, reduced energy, loss of body hair, depressive symptoms, irritability, cognitive dysfunction, reduced motivation, poor memory.

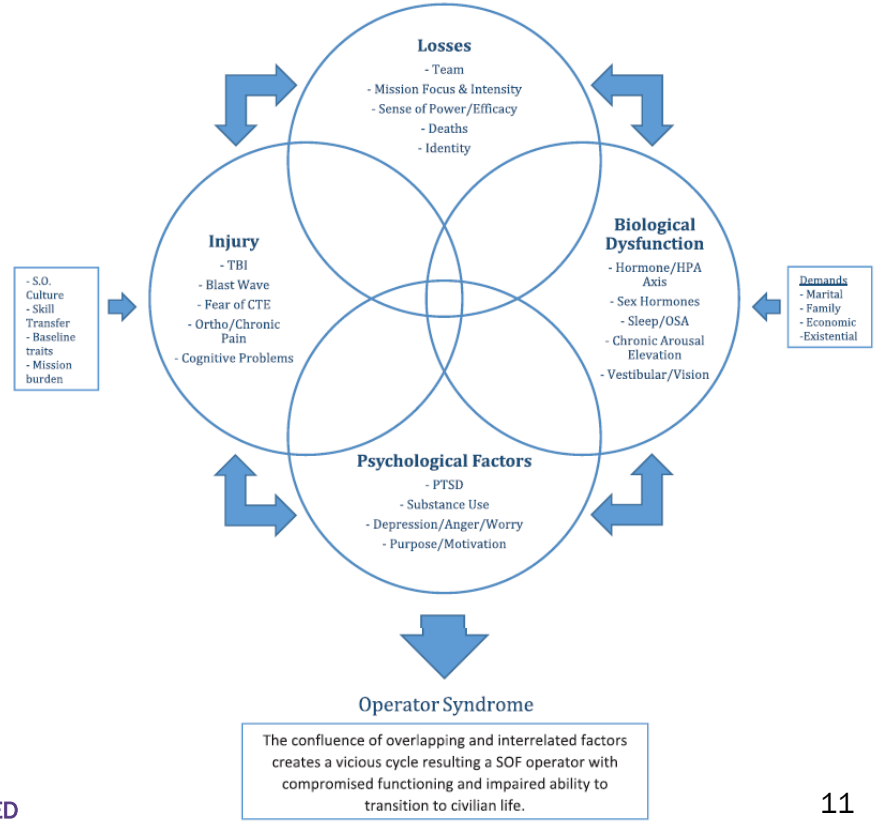
Testosterone Level by Age

- Testosterone Levels decline with age
- Middle tertile by age:
  - 409-558 ng/dL for men 20-24 years old
  - 413-575 ng/dL for 25-29 years old
  - 359-498 ng/dL for 30-34 years old
  - 352-478 ng/dL for 35-39 years old
  - 350-473 ng/dL for 40-44 years old



Operator Syndrome

- Cumulative and interrelated medical and psychological sequelae of serving in special operations forces (SOF)
  - Chronic stress, blast exposure/traumatic brain injury (TBI), sleep disruption leading to hormonal dysregulation, mood and cognitive changes



Operator Syndrome

- Distinct Entity separate from post-traumatic stress disorder (PTSD), TBI
- Highly prevalent in SOF seeking behavioral health care
- Prevalence in general population unknown

Original Operator Syndrome Framework	Revised Operator Syndrome Framework
	Criterion A – *exposure prerequisites*
Traumatic Brain Injury	Exposure to Trauma and/or Traumatic Brain Injury (TBI)
	Chronic exposure to high-tempo operations
	Criterion B – *need at least 5 out of 9*
Chronic Pain, Orthopedic Problems, Headache	Chronic Localized and Non-Specific Pain
	Headaches
	Cardiometabolic Disruption
Cognitive Impairments	Cognitive Disruption
Endocrine Dysfunction	Endocrine Disruption
	Gastrointestinal Disruption
Depression Anxiety Anger Hypervigilance PTSD	Mental Health Disruption (e.g., Dysphoric Arousal: fatigue, lack of interest/motivation, numb/blunted positive emotions, social withdrawal, hyperarousal/restless, irritability/anger, sleep disruption)
Perceptual System Impairments	Sensory Disruption
Sleep Disturbance	Sleep Disruption
Substance Abuse	-
Marital and Family Concerns	-
Intimacy Concerns	-
	Criterion C - *associated features and specifiers*
Toxic Exposures and Related Illness	*With Elevated Heavy Metals/Toxins*
Military-Civilian Transition	*With Moral Injury, Existential Disruption, and/or Military Transition*
Existential Concerns	

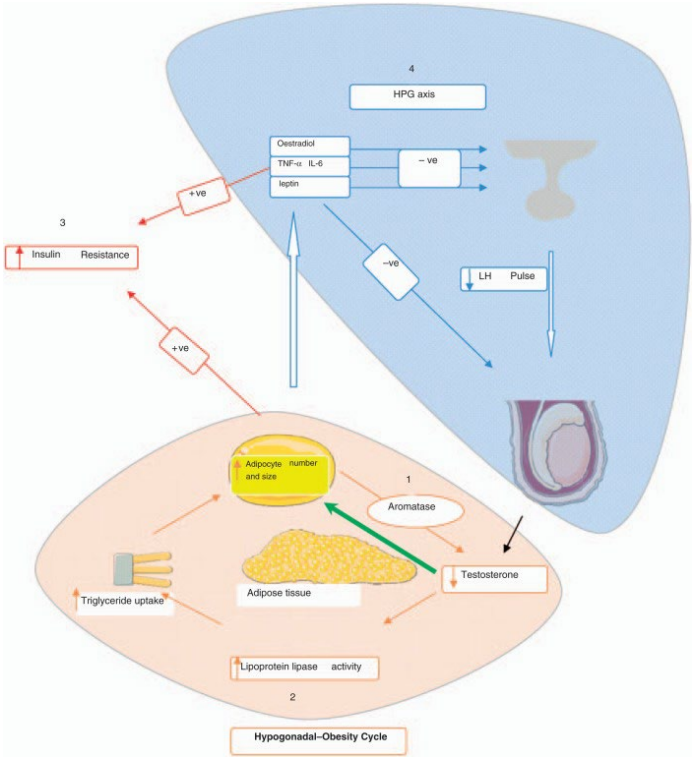
Validation and Refinement of Operator Syndrome in Active-Duty Special Operations Forces

Shane W. Adams, B. Christopher Frueh, Jerome Sabangan, Carey Pawlowski, Robert Oh, Cameron Pugach, Odette Harris

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Obesity and Metabolic Syndrome

- Testosterone and the Metabolic Syndrome have a bidirectional relationship
  - Low T is associated with obesity insulin resistance and adverse lipid profile
- Sex hormone-binding globulin (SHBG) is a glycoprotein produced in the liver – SHBG levels are correlated with multiple markers of metabolic health
  - Serum monosaccharides induce de novo lipogenesis
  - Lipogenesis downregulates Hepatocyte Nuclear Factor 4 (HNF-4α)
  - Decreased HNF-4α decreases SHBG synthesis



(Fernandez et al., 2019)

Other Comorbidities

- Obstructive Sleep Apnea (OSA)
- Chronic opioid use
- Previous anabolic steroid use/abuse
- Diabetes
- Pituitary Dysfunction
- Acute illness
- Acute stress

Screening for Testosterone Deficiency

- The American Urological Association (AUA) and Endocrine Society do not currently recommend screening all asymptomatic men
- AUA recommends testosterone testing in the absence of symptoms for:
  - Unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, human immunodeficiency virus (HIV), chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use

Benefits of Screening in the Military

- Testosterone is a marker of overall health
- Testosterone is a motivator for improved health in young men
- Screening will:
  - Identify the truly hypogonadal men who benefit from treatment
  - Identify and lead to treatment of diseases that cause low T
    - ✓ Operator Syndrome
    - ✓ Metabolic Syndrome
  - Motivate young men to improve their overall health

Risks of Screening in the Military

- Cost
- Manpower and systems for screening and treatment
- Potential for overtreatment
- Increase in side effects of Testosterone Replacement Therapy (TRT)
- Deployability issues with current T formulations
- Deployability issues with monitoring regimens

Treating Testosterone Deficiency

- Identify and treat comorbidities
  - Operator syndrome – multidisciplinary treatment
  - OSA – sleep study, continuous positive airway pressure (CPAP)
  - Metabolic Syndrome – Glucagon-like Peptide-1 (GLP1a), lifestyle interventions
- Identify fertility concerns and counsel, test if needed
- All men should be counseled on lifestyle modifications as a treatment strategy
- Where appropriate start therapy

Treating Testosterone Deficiency

- Non-Androgen Treatments:
  - Clomiphene Citrate– Selective Estrogen Receptor Modulator
    - ✓ Easy regimen, oral pill every other day
    - ✓ Well tolerated
    - ✓ Preserves fertility by boosting the body's own testosterone production
    - ✓ Will ground pilots due to rare vision side effects
  - Human chorionic gonadotropin (hCG)
    - ✓ Subcutaneous injection twice weekly
    - ✓ Well tolerated
    - ✓ Expensive
    - ✓ Preserves fertility

Treating Testosterone Deficiency

- Intramuscular – T cypionate, T enanthate
  - Weekly injection
  - Pro: cheap, reliable serum levels; Con: Polycythemia
- Topical – Androgel
  - Daily
  - Pro: Mimics natural rhythm, less side effects; Con: absorption issues, transference risk
- T undecanoate (Aveed)
  - Deep IM injection every 10 weeks
  - Expensive, painful injection
- Oral T – Kyzatrex, Jatenzo
  - Twice a day
  - Reliable levels but expensive
- Intranasal – Natesto
  - Supposedly maintains fertility
  - Expensive, TID (three times daily)
- Testopel – long-acting implantable testosterone pellets
  - Every 3-6 months
  - Minor procedure for placement

Treating Testosterone Deficiency

- Goal range on TRT is middle tertile of normal: 450 – 600
- Success is good levels + improvement in symptoms
- If normal levels and no change in symptoms after 3-6 months, stop therapy
- Symptom Improvement
  - More likely to improve: Libido, anemia, bone density, lean body mass
  - Hard to say: Depressive symptoms, cognitive function, energy, fatigue, quality of life measures

Risks of TRT

- Infertility
- Polycythemia
- Elevated estrogen/gynecomastia
- Worsening OSA if untreated
- Slight increase in atrial fibrillation and pulmonary embolism
- NO increased risk of myocardial infarction (MI), stroke
- NO increased of prostate cancer

Key Takeaways

- Testosterone is a window into Men's Health.
- Screening will identify hypogonadal men and men with comorbid disease that may benefit from treatment.
- Screening and increased TRT will introduce organizational and readiness challenges that require proactive planning and preparation to address.

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Questions?

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