



A Personalized Approach to Managing Male Hormones

What You Must Know About Male Hormones

Pamela W. Smith, M.D., MPH, MS





Lahnor Powell, ND, MPH

Medical Education Specialist for Genova Diagnostics



Pamela W. Smith, M.D., MPH, MS



Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.



DISCLAIMER: Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.

Need More Resources?

Explore
WWW.GDX.NET

for more information and
educational resources, including...

LIVEGDX – Previous webinar recordings

GI University – Focused learning modules

MYGDX – Order materials and get results

GENOVA
DIAGNOSTICS

International About Us Contact Us Search myGDX US

HOME CLINICIANS PATIENTS

Introducing PCR Parasitology for Enhanced Sensitivity

GI Effects Stool Profiles GI Effects Gut Pathogen Profile

NOW AVAILABLE — LEARN MORE >

Getting Started

Simple account setup. Licensed healthcare practitioners may begin the process of opening a free account here.

NEW USERS

Test Menu

A comprehensive menu of our diagnostic tests, including test descriptions, specimen requirements and kit instructions.

SEARCH TESTS

MYGDX Login

Clinicians: Log in to the MYGDX™ portal to order test kits and materials, download patient results, edit account information.

LOG IN

Online Education

Start Using These Free Resources Today!

Visit our Medical Education section for access to LIVEGDX Webinars, Educational Modules, Conferences, and LEARNGDX – short learning modules that demonstrate the clinical utility and diagnostic significance of key biomarkers. The modules are absolutely free to view!

LEARN NOW



Objectives for This Presentation

- Describe the signs and symptoms of hormone deficiency in a male
- Understand the functions of testosterone in a male
- Discuss how to effectively and consistently dose male hormones in men of all ages

OBJECTIVE

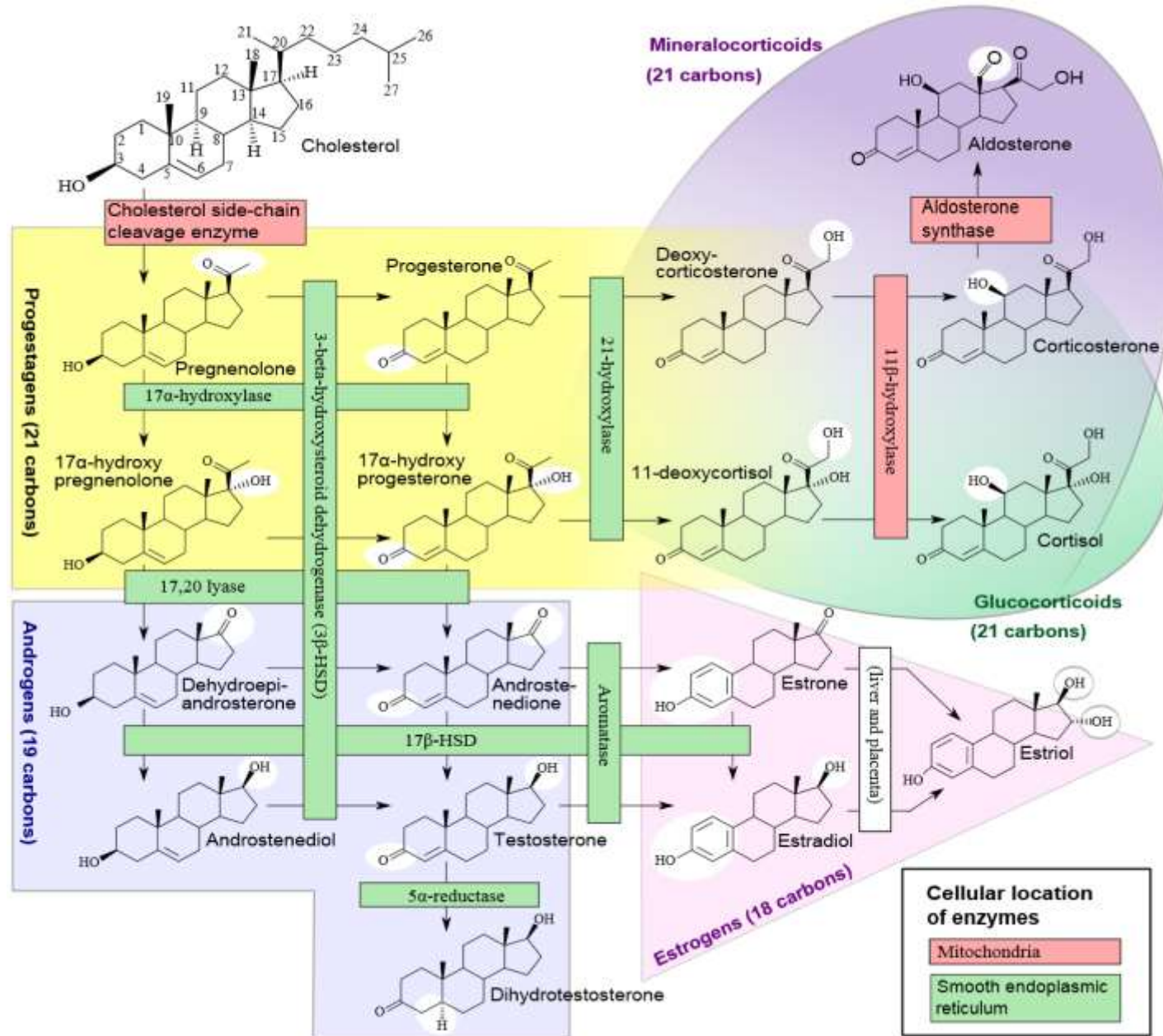




Reference

- Carruthers, M., Androgen Deficiency in the Adult Male. London: Taylor & Friends, 2004.
- Stanton, A., Hormone Replacement in Men, In Rakel, D., Integrative Medicine. 3rd Ed., Philadelphia: Elsevier/Saunders, 2012, p. 321-34.







Andropause

Definition

- An absolute or relative insufficiency of testosterone or its metabolites in relation to the needs of that individual at that time in his life
 - Carruthers, M., “The diagnosis of androgen deficiency,” *Aging Male* 2002; 4:254.





Levels of Testosterone

- 30% to 60% of men in their 70s are hypogonadal
 - Wang C, et al. ISA, ISSAM, EAU, EAA, and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male*. 2009;12(1):5-12.



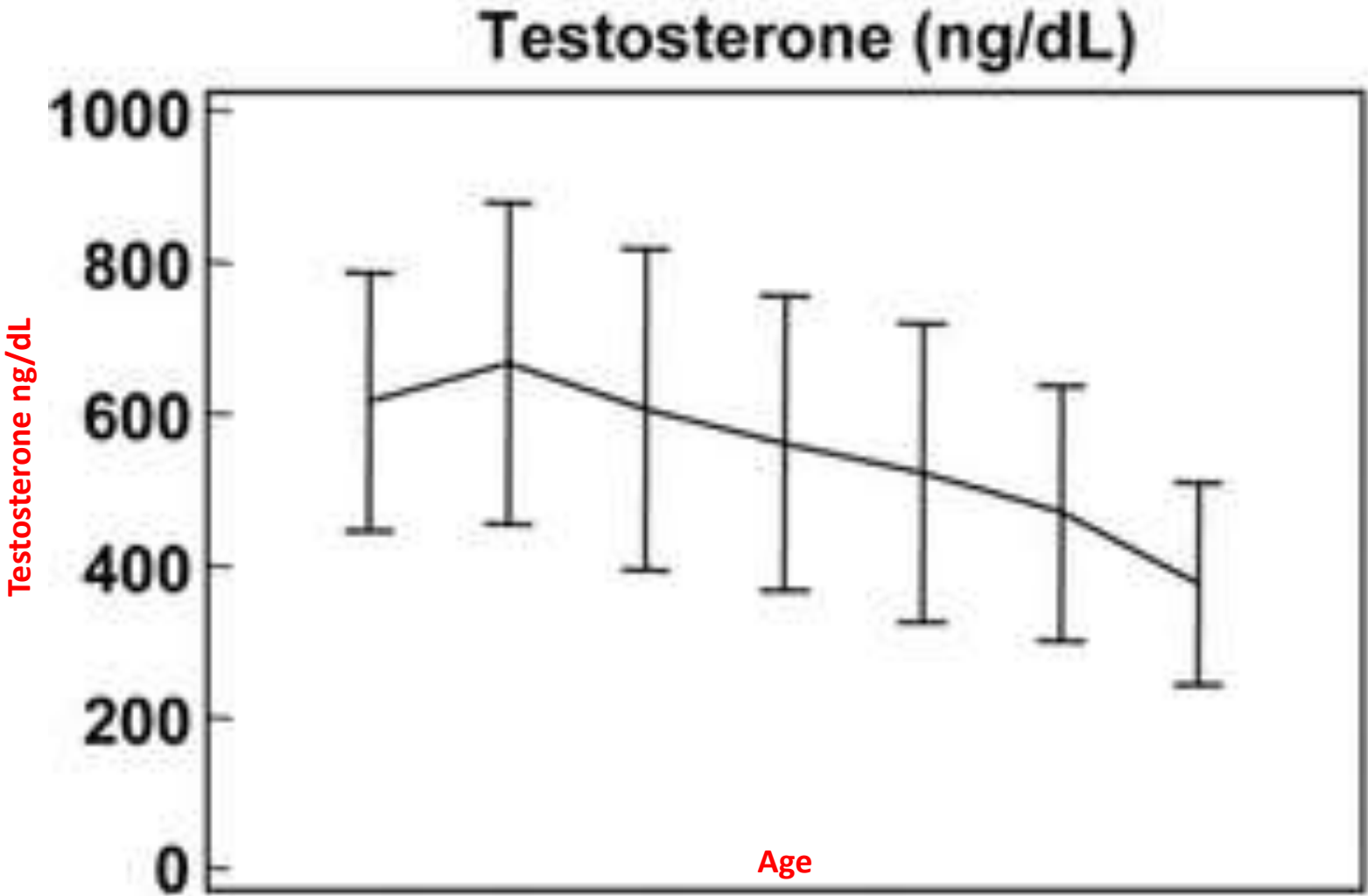


Levels of Testosterone (Cont.)

- Half of healthy men between the ages of 50-70 years will have a testosterone level below the lowest level seen in healthy men who are 20-40 years of age
 - Korenman SG, et al. Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocrinol Metab.* 1990;71(4):963-69.



Men - Testosterone Decline





Levels of Testosterone

- The Massachusetts Male Aging Study showed a 30-year fall in total testosterone in men averaging 48% and a decline in free testosterone of 85%
 - Feldman HA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab.* 2002;87(2):589-98.



Levels of Testosterone

- There are also seasonal variations in levels of testosterone with peak levels found in the summer and early fall and lower levels in the winter and early spring
 - Smals AG, et al. Circannual cycle in plasma testosterone levels in man." *J Clin Endocrinol Metab.* 1976;42(5):979-82.



Healthy Male Daily Hormone Production

- Cortisol
20-30 mgs/day
- Testosterone
5-6 mgs/day
- Androstenedione
3 mgs/day
- DHT
0.300 mgs/day
- Estrone
0.066 mgs/day
- Estradiol
0.045 mgs/day
- DHEAS
50 mgs/day
- DHEA
15 mgs/day



Testosterone

- Testosterone replacement therapy for men is safe and can provide significant benefits
- Uncontrolled and controlled trials date back over 70 years
- There is not a reported age at which hormone replacement in men over the age of 50 should not be considered



Functions of Testosterone





Functions of Testosterone

- Sex hormone
- Receptors all over a male's body
- Involved in the making of protein and muscle formation
- Helps manufacture bone
- Improves oxygen uptake throughout the body
- Helps control blood sugar
- Needed for normal sperm development
- Regulates acute HPA responses under dominance challenge



Functions of Testosterone

- Helps regulate cholesterol
- Helps maintain a powerful immune system
- Aids in mental concentration
- Improves mood
- Helps protect the brain against Alzheimer's disease
- Regulates the population of thromboxane A2 receptors on megakaryocytes and platelets and therefore platelet aggregation



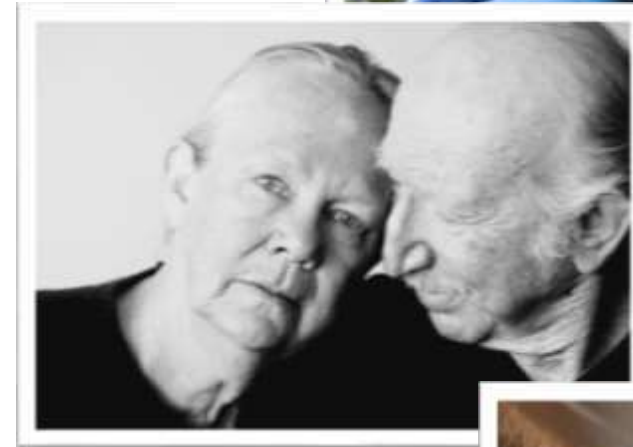
Signs and Symptoms of Andropause





Signs and Symptoms of Andropause

- Fatigue, tiredness, or loss of energy
- Depression, low or negative mood
- Irritability, anger, or bad temper
- Anxiety or nervousness
- Loss of memory or concentration
- Loss of sex drive or libido
- Loss of erections or problems during sex
- Decreased intensity of orgasms
- Weight gain





Signs and Symptoms of Andropause

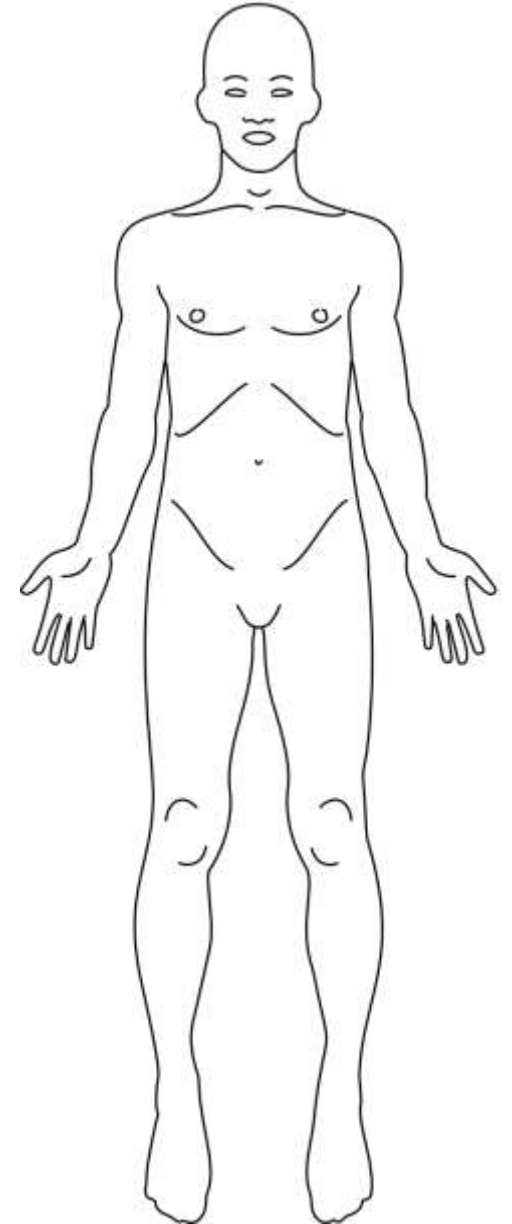
- Backache, joint pains, or stiffness
- Loss of fitness
- Feeling over-stressed
- Decrease in job performance
- Decline in physical abilities
- Bone loss
- Elevated cholesterol
- Increased risk of heart disease
- Increased risk of insulin resistance, diabetes, and metabolic syndrome





Impact of Testosterone

- **Muscle:** increased in strength and volume
- **Brain:** libido, mood, aggression, cognition
- **Kidney:** stimulation of erythropoietin
- **Bone Marrow:** stimulation of stem cells
- **Bone:** accelerated linear growth, closure of epiphyses, maintains BMD
- **Liver:** synthesis of serum protein
- **Fat:** decreased fat mass
- **Skin:** male pattern body and facial hair, balding, sebum production





Low Testosterone Levels/Related to Increased Risk of CHD

- Trial showed men with coronary heart disease had a significantly lower total testosterone, free testosterone, and bioavailable testosterone
 - English KM, et al. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J.* 2000;21(11):890-94.





Low Testosterone Levels/Related to Increased Risk of CHD

- Studies revealed low endogenous testosterone concentrations are related to mortality due to cardiovascular disease and other causes
 - Vermeulen A. Androgen replacement therapy in the aging male – a critical evaluation. *J Clin Endocrinol Metab.* 2001;86(6):2380-90.
 - Malkin CJ, et al. Low serum testosterone and increased mortality in men with coronary heart disease. *Heart.* 2010;96(22):1821-25.





Low Testosterone Levels/Related to Increased Risk of CHD

- Study showed a possible correlation between lower testosterone levels, erectile dysfunction and conditions associated with higher cardiovascular risk
 - Ma RC, et al. Erectile dysfunction predicts coronary heart disease in type 2 diabetes. *J Am Coll Cardiol.* 2008;51(21):2045-50.





Low Testosterone Levels/Related to Increased Risk of CHD

- Study revealed that men with coronary heart disease that were under the age of 45 had total and free testosterone levels significantly lower than controls
 - Turhan S, et al. The association between androgen levels and premature coronary artery disease in men. *Coron Artery Dis.* 2007;18(3):159-62.





Low Testosterone Levels/Related to Increased Risk of CHD

- Serum free testosterone levels were found to be inversely related to carotid intima-media thickness (IMT) and plaque score
 - Fukui MD, et al, Association Between Serum Testosterone Concentration and Carotid Atherosclerosis in Men With Type 2 Diabetes. *Diabetes Care*. 2003;26(6):1869-73.





Low Testosterone Levels/Related to Increased Risk of CHD

- Low testosterone levels were found to be associated with atherosclerosis in men
 - Svartberg J, et al. Low testosterone levels are associated with carotid atherosclerosis in men. *J Intern Med.* 2006;259(6):576-82.





Low Testosterone Levels/Related to Increased Risk of Diabetes and Metabolic Syndrome

- Low testosterone levels are associated with an increased risk for the development of type II diabetes and metabolic syndrome
 - Ding EL, et al. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2006;295(11):1288-99.
 - Laaksonen DE, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-age men. *Diabetes Care*. 2004;27(5):1036-41.





Low Testosterone Levels/Related to Increased Risk of Diabetes and Metabolic Syndrome

- Since testosterone has been shown to lower blood sugar levels, the Endocrine Society now recommends measurement of testosterone in all male patients with type II diabetes
 - Dandona P, et al. Update: hypogonadotropic hypogonadism in type 2 diabetes and obesity. *J Clin Endocrinol Metab.* 2011;96(9):2643-51.





Low Testosterone Levels Related to Increased Risk of Mortality

- Study showed that low testosterone predicts mortality from cardiovascular disease
 - Hyde Z, et al. Low free testosterone predicts mortality from CVD but not other causes: The Health in Men Study. *J of Clin Endocrinol Metab.* 2012;97(1):179-89.





Low Testosterone Levels Related to Increased Risk of Mortality

- Study showed that low testosterone levels were associated with an increased risk of all-cause mortality independent of numerous risk factors
- Serum testosterone levels were inversely related to mortality due to cardiovascular disease and cancer
 - Haring R, et al. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. *Eur Heart J.* 2010; 31(12):1494-501.





Low Testosterone Levels Related to Increased Risk of Mortality

- Low endogenous testosterone levels are associated with an increased risk of death from all causes and cardiovascular disease
 - Araujo AB, et al. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2011;96(10):3007-19.





Low Testosterone Levels and Hypertension

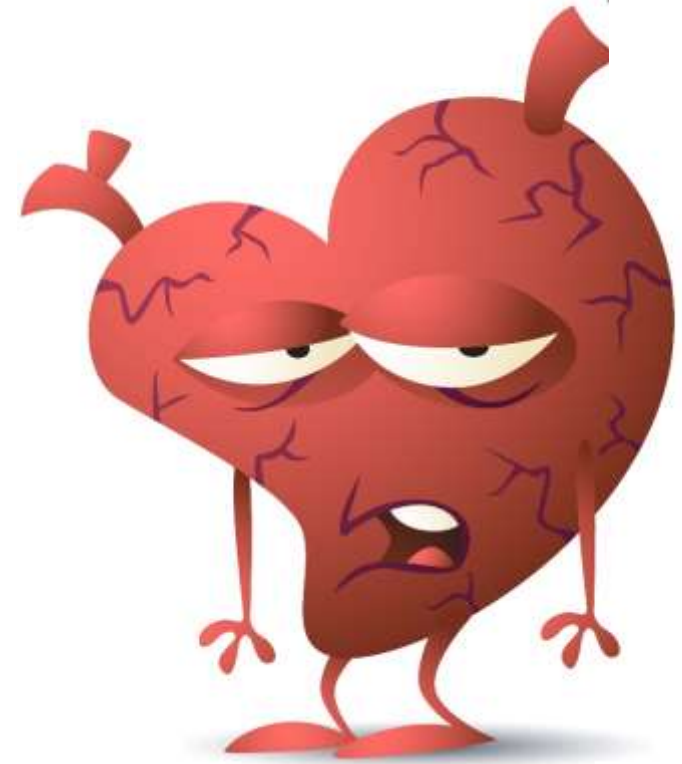
- Study showed that low total testosterone concentrations are predictive of hypertension, suggesting total testosterone as a potential biomarker for increased cardiovascular risk
 - Torkler S, et al. Inverse association between total testosterone concentrations, incident hypertension and blood pressure. *Aging Male*. 2011;14(3):176-82.





Low Testosterone and Congestive Heart Failure

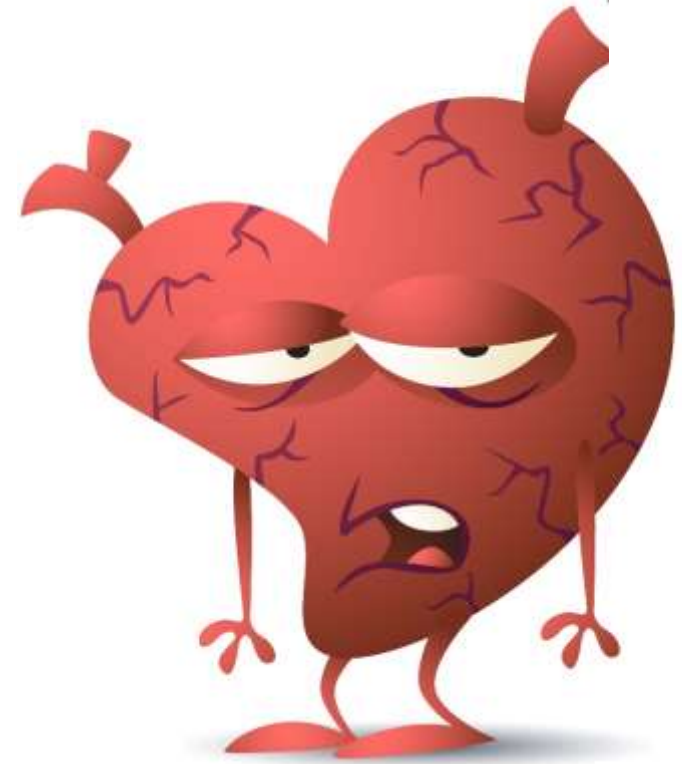
- In males with heart failure, low serum androgens were associated with an adverse prognosis
 - Guder G, et al. Low circulating androgens and mortality risk in heart failure. *Heart*. 2010;96(7):504-09.





Low Testosterone and Congestive Heart Failure

- In men with chronic heart failure, anabolic hormone depletion is common and deficiency of each anabolic hormone is an independent marker of poor prognosis
 - Jankowska EA, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation*. 2006; 114(17):1829-37.





Men: Testosterone and Memory

- In an animal trial, the authors suggested that the development of memory loss in males is related to the loss of testosterone that occurs with age in a male
 - Flood JF, et al. Age-related decrease of plasma testosterone in SAMPS mice: replacement improves age-related impairment of learning and memory. *Physiol Behav.* 1995;57(4):669-73.





Men: Testosterone and Memory

- In men, testosterone plays a major role in brain functioning
- Subclinical androgen deficiency has been suggested to increase the expression of amyloid-B-related peptides in vivo
 - Gillett MJ, et al. “Relationship between testosterone sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia,” *J Alzheimers Dis.* 2003;5(4):267-69.





Men: Testosterone and Memory

- In this study, age-related decline in free testosterone predicted age-related decline in visual and verbal memory
 - Morley JE, et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. *Proc Natl Acad Sci USA*. 1997;94(14):7537-42.





Men: Testosterone and Memory

- Low levels of bioavailable testosterone are a positive predictor of memory loss in men as they age
 - Morley, J., et al., “Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone,” Proc Natl Acad Sci USA 1997; 94:7537-42.





Men: Testosterone and Memory

- In a medical trial done in Hong Kong, in men with low bioavailable testosterone levels there was a strong correlation with memory loss/Alzheimer's disease
 - Chu LW, et al. Bioavailable testosterone is associated with a reduced risk of amnesic mild cognitive impairment in older men. *Clin Endocrinol (Oxf)*. 2008;68(4):589-98.





Men: Testosterone and Memory

- Males that have a higher ratio of total testosterone to SHBG have a lower rate of development of Alzheimer's disease
 - Moffat SD, et al. Free testosterone and risk for Alzheimer disease in older men. *Neurology*. 2004;62(2):188-93.





Men: Testosterone and Memory

- Patients with Alzheimer's disease have been shown to have a lower ratio of total testosterone to SHBG when compared with age-matched controls
 - Hogervorst E, et al. Low free testosterone is an independent risk factor for Alzheimer's disease. *Exp Gerontol.* 2004; 39(11-12):1633-39.





Men: Testosterone and Memory

- In another medical trial, which was a prospective longitudinal study, revealed that the risk of Alzheimer's disease was decreased by 26% for each 10-unit (nmol/nmol) increase in free testosterone at 2, 5, and 10 years before the diagnosis of Alzheimer's disease was made
- Low levels of testosterone may occur prior to the diagnosis of Alzheimer's disease
 - Moffat SD. Effects of testosterone on cognitive and brain aging in elderly men. *Ann NY Acad Sci.* 2005;1055:80-92.





Men: Testosterone and Memory

- Low testosterone levels have also been associated with mild memory loss that is not related to Alzheimer's disease
 - Chu LW, et al. Bioavailable testosterone is associated with a reduced risk of amnesic mild cognitive impairment in older men. *Clin Endocrinol (Oxf)*. 2008;68(4):589-98.





Men: Testosterone and Memory

- Studies have also shown a correlation between testosterone levels and cognitive abilities such as spatial performance and mathematical reasoning
 - McKeever WF, et al. Testosterone, dihydrotestosterone and spatial task performance of males. *Bull Psychon Soc.* 1990;28(4):305-08.





Men: Testosterone and Memory

- Studies done in animals have shown that depletion of androgens results in increased pathologic conditions that are associated with Alzheimer's disease
 - Increased antibody levels
 - Increased neuronal death
 - Hyperphosphorylation
 - Drummond ES, et al. Androgens and Alzheimer's disease. *Curr Opin Endocrinol Diabetes Obes.* 2009;16(3):254-59.





Men: Testosterone and Memory

- Studies in animals also have shown that both testosterone and dihydrotestosterone have an effect on the upregulation of the hippocampal neurogenesis in adult male rats
 - Galea LA, et al. Endocrine regulation of cognition and neuroplasticity: our pursuit to unveil the complex interaction between hormones, the brain, and behavior. *Can J Exp Psychol.* 2008;62(4):247-60.





Men: Testosterone and Memory

- Higher levels of free concentrations have been associated with better performance in specific aspects of memory and cognitive function
- Furthermore, optimal processing capacity was found in men between the ages of 35 and 90 even after adjustment for age, education, and CV morbidity
 - Yaffe K, et al. Sex hormones and cognitive function in older men. *J Am Geriatr Soc.* 2002;50(4):707-12.
 - Thilers PP, et al. The association between endogenous free testosterone and cognitive performance: a population based study in 35 to 90 year-old men and women. *Psychoneuroendocrinology.* 2006;31(5):565-76.





Men: Testosterone and Memory

- The same was not true of total testosterone levels
 - Yeap BB, et al. Higher serum free testosterone is associated with better cognitive function in older men, whilst total testosterone is not. The Health In Men Study. *Clin Endocrinol (Oxf)*. 2008;68(3):404-12.





Men: Testosterone and Memory

- In men that have undergone hormonal treatments for prostate cancer with suppression of endogenous testosterone synthesis and blockade of the androgen receptor, studies have shown that there is a beneficial effect on verbal memory but an adverse effect on spatial performance
 - Cherrier MM, et al. The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. *J Urol*. 2003;170(5):1808-11.





Men: Testosterone and Memory

- Likewise, in another study on males receiving treatment for prostate cancer, these patients also had visuomotor slowing and slowed reaction times in several attentional domains
- In the same patients plasma amyloid levels elevated as testosterone levels declined
 - Salminen EK, et al. Associations between serum testosterone fall and cognitive function in prostate cancer patients. *Clin Cancer Res.* 2004;10(22):7575-82.





Men: Testosterone and Memory

- In this study, when treatment for prostate cancer was discontinued, memory improved but visuospatial abilities did not
 - Almeida OP, et al. One year follow-up study of the association between chemical castration, sex hormones beta-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004;29(8):1071-81.





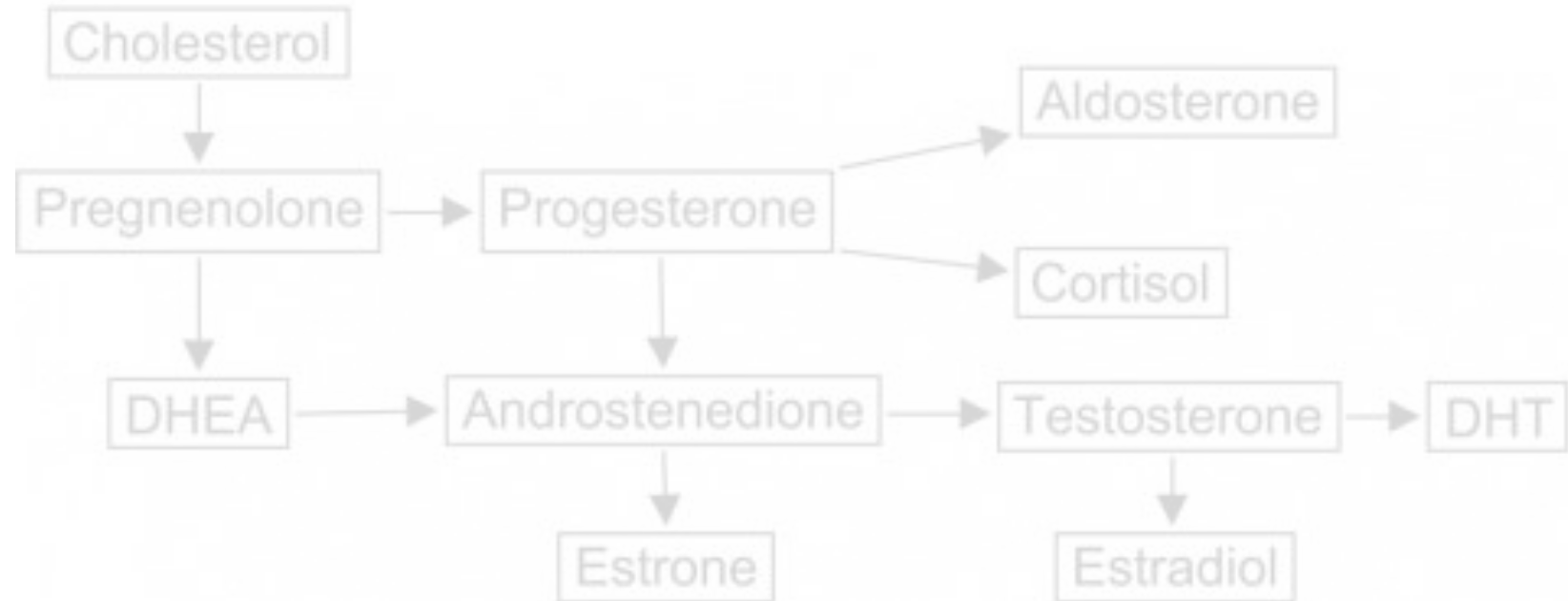
Replacement of Male Hormones





Male Hormones

- Pregnenolone
- DHEA
- Estrone/Estradiol
- Dihydrotestosterone
- Testosterone





Lab Work

- Total testosterone, free testosterone vs. salivary testing
- DHT
- Estradiol
- Estrone
- DHEA
- CBC
- Cortisol
- SHBG
- Progesterone
- PSA
- Albumin
- Traditional lab work: SMA





Digital Rectal Examination

- Digital rectal examination should be performed every six months if the patient is on testosterone replacement therapy





Lab Work

- A PSA of <4.0 but rising by 1.5 ng/ml in one year or 0.75 ng/ml per year over two years should have further evaluation
- $PSA > 4$ should have further evaluation





Estrogens





Estrogen Levels in Males

- Men make estrone, estradiol, and estriol
- It is important to measure both estrone and estradiol
- Estriol is still experimental
- Males need a small amount of estrogen to help maintain memory and maintain bone structure
- Androgens aromatizes into estrogens via the enzyme aromatase

Estrogen



Lowers Aromatase

- Chrysin
- Zinc
- Flaxseed
- EGCG
- Anastrozole





Increases Aromatase

- Inflammation
- Obesity
- High insulin levels
- Excessive alcohol intake
- Mold/biotoxin illness
- CIRS (Chronic Inflammatory Response Syndrome)





Estrogen: Men and Memory

- Estradiol has a protective effect on the brain structures in older males
 - Gibbs RB, et al. Estrogen and cognition: applying preclinical findings to clinical perspectives. *J Neurosci Res.* 2003;74(5):637-43.





Estrogen: Men and Memory

- Serum estradiol and testosterone levels have been shown to be lower in men with Alzheimer's disease compared with age-matched controls
 - Hogervorst, E., et al., "Serum total testosterone is lower in men with Alzheimer's disease," *Neuro Endocrinol Lett* 2001; 22(3):163-68.
 - Bowen, R., et al., "An association of elevated serum gonadotropin concentrations and Alzheimer disease?" *J Neuroendocrinol* 2000; 12(4):351-54.





Estrogen Levels in Males

- Medications may lower estrogen levels in men and cause estrogen levels to be too low
 - Phenobarbital
 - Chlordiazepoxide
 - Carbamazepine
 - Trazodone
 - Sucralfate

Estrogen



Estriol Replacement in Males

- It is experimental at this time but for autoimmune encephalitis and multiple sclerosis, estriol replacement is being used in males
 - Palaszynski MK, et al. Estriol treatment ameliorates disease in males with experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *J Neuroimmunol.* 2004;149(1-2):84-89.





Estrogen Levels in Males

- Estrogen levels may elevate as men age due to:
 - Increased aromatase activity
 - Alteration in liver function
 - Zinc deficiency
 - Obesity
 - Overuse of alcohol
 - Ingestion of estrogen-containing food or environmental estrogens
 - High doses of testosterone
 - Environmental estrogens, endocrine disruptors, plastics
 - Foods that may increase estrogen levels
 - Medications

Estrogen



Estrogen Levels in Males

- Elevated levels of estrogen in males are associated with:
 - Gynecomastia
 - Decreased sex drive/erectile dysfunction
 - Doubled risk of stroke
 - Higher rates of heart attack, peripheral artery disease, and coronary atherosclerosis
 - Insulin resistance
 - Rheumatoid arthritis
 - BPH
 - Prostate cancer
 - Farnsworth WE. Roles of estrogen and SHBG in prostate physiology. *Prostate*. 1996;28(1):17-23.

Estrogen



Elevated Estrogen Levels in Males

- Study showed that high estradiol in males was associated with an increased risk of stroke
 - Abbott RD, et al. Serum estradiol and risk of stroke in elderly men. *Neurology*. 2007;68(8):563-68.

Estrogen



Elevated Estrogen Levels in Males

- High estradiol levels in men were associated with acute myocardial infarctions
 - Mohamad MJ, et al. Serum levels of sex hormones in men with acute myocardial infarction. *Neuro Endocrinol Lett.* 2007;28(2):182-86.

Estrogen



Elevated Estrogen Levels in Males

- High estrone and low testosterone levels were associated with promoting the development of atherogenic lipid milieu in men with coronary heart disease
 - Dunajska K, et al. Evaluation of sex hormone levels and some metabolic factors in men with coronary atherosclerosis. *Aging Male* 2004;7(3):197-204.

Estrogen



Elevated Estrogen Levels in Males

- Low testosterone and elevated estradiol was associated in this study with lower extremity peripheral artery disease in older men
 - Tivesten A, et al. Low serum testosterone and high serum estradiol associated with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden. *J Am Coll Cardiol.* 2007;50(11):1070-76.

Estrogen



Elevated Estrogen Levels in Males

- Men with myocardial infarction had high estradiol and low testosterone levels
 - Tripathi Y, et al. Serum estradiol and testosterone levels following acute myocardial infarction in men. *Indian J Physiol Pharmacol.* 1998;42(2):291-94.

Estrogen



Elevated Estrogen Levels in Males

- Elevated levels of estradiol in men were associated with an increase incidence of strokes, peripheral vascular disease, and carotid artery stenosis compared to subjects with lower estradiol levels
 - Lerchbaum E, et al. High estradiol levels are associated with an increase in mortality in older men referred to coronary angiography. *Exp Clin Endocrinol Diabetes*. 2011;119(8):490-96.

Estrogen



Elevated Estrogen Levels in Males

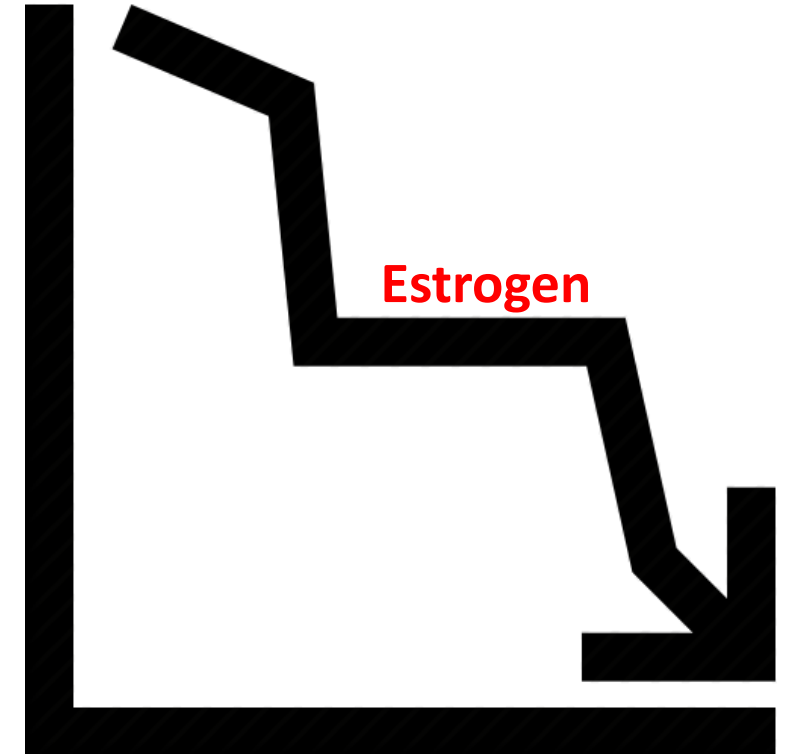
- Elevated levels of estrogen in men are associated with an increased risk of heart disease
 - Sudhir K, et al. Cardiovascular actions of estrogens in men. *J Clin Endocrinol Metab.* 1999;84(10):3411-15.

Estrogen



Ways to Lower High Estrogen Levels in Males

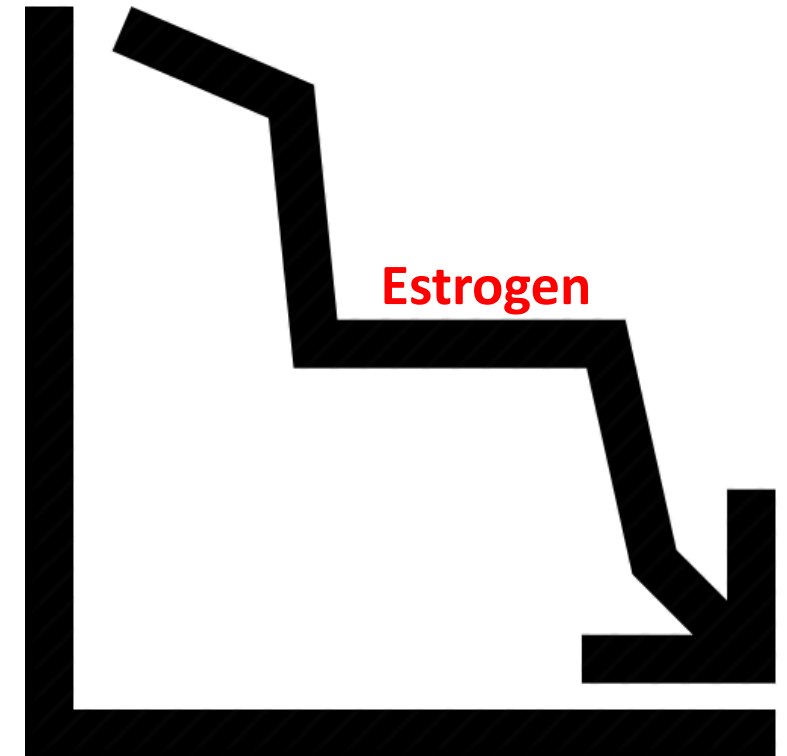
- Decrease dose of testosterone
- Zinc
- Chrysin
- Anastrozole and other aromatase inhibitors
- Grape seed extract
- Wild nettle root
- Decrease intake of estrogen containing foods
- Eat foods that decrease estrogen





Ways to Lower Estrogen Levels in Males

- Maca
- Decrease alcohol intake
- Lose weight
- Eat organic foods and avoid environmental estrogens
- High dose vitamin C (also increases testosterone production)
- Vitamin K
- Niacin





Dihydrotestosterone (DHT)





Dihydrotestosterone (DHT)

- Most potent naturally occurring androgen
 - 3 times more potent than testosterone
- Synthesized from the conversion of testosterone through 5-alpha reductase
- Responsible for formation of male sex-specific characteristics and development of male genitalia and prostate
 - Low levels can affect sexual function, libido, and muscle tone
 - Bartsch G, et al. Dihydrotestosterone and the concept of 5-alpha-reductase inhibition in human prostatic hyperplasia. *Eur Urol.* 2000;37(4):367-80.
 - Andriole G, et al. DHT and the prostate: the scientific rationale for 5 alpha-reductase inhibitors in the treatment of BPH. *J Urol.* 2004;172(4 Part 1): 1399-403.
- Elevated levels may cause
 - Hirsutism
 - Male pattern baldness
 - BPH



DHT

- DHT has growth promoting effect on prostate cells that is greater than that of testosterone – 2.4-10 times greater
 - Deslypere JP, et al. Testosterone and 5 alpha-dihydrotestosterone interact differently with the androgen receptor to enhance transcription of the MMTV-CAT reporter gene. *Mol Cell Endocrinol.* 1992;88(1-3):15-22.



DHT

- High DHT levels stimulate the androgen receptors to produce greater amounts of PSA
 - Lee C, et al. Regulation of proliferation and production of prostate-specific antigen in androgen-sensitive prostatic cancer cells, LNcaP by dihydrotestosterone,” *Endocrinology*. 1995;136(2):796-803.
- DHT interacts with extracellular tissues to elevate prostate cancer cell mobility
 - Murphy BC, et al. Effects of extracellular matrix components and dihydrotestosterone on the structure and function of human prostate cancer cells. *Prostate*. 1992;20(1):29-41.



DHT

- High DHT levels have been shown to enhance early atherosclerosis
 - Death AK, et al. Dihydrotestosterone promotes vascular cell adhesion molecule-1 expression in male human endothelial cells via a nuclear factor-kappaB-dependent pathway. *Endocrinology*. 2004;145(4):1889-97.



Progesterone

- Progesterone used transdermally is an effective method to lower DHT levels without side effects





Studies on Testosterone Replacement





Testosterone Cognitive Function

- Testosterone replacement improves cognitive function
 - Alexander GM, et al. Androgen-behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities. *Horm Behav.* 1998;33(2):85-94.



Testosterone and Alzheimer's

- Testosterone replacement prevents the production of beta amyloid precursor protein in men
 - Gouras GK, et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. *Proc Natl Acad Sci USA*. 2000;97(3):1202-05.



Testosterone and Memory

- Study showed that testosterone therapy in elderly men showed some reversal of cognitive dysfunction
 - Lyngdorf P, et al. Epidemiology of erectile dysfunction and its risk factors: a practice-based study in Denmark. *Int J Impot Res.* 2004;16(2):105-11.



Testosterone and Memory

- Testosterone therapy has been shown to help with mild cognitive impairment.
 - Morley JE. Testosterone and behavior. *Clin Geriatr Med.* 2003;19(3):605-16.



Testosterone and Memory

- Animal studies have shown that testosterone replacement can improve memory possibly by reducing amyloid-B peptide production
 - Flood JF, et al. Age-related decrease of plasma testosterone in SAMP8 mice: replacement improves age-related impairment of learning and memory. *Physiol Behav.* 1995;57(4):669-73.



Testosterone and Memory

- Testosterone therapy in older hypogonadal men improved spatial cognition and verbal fluency
 - Orwoll, E., et al., “Transdermal testosterone supplementation in normal older men. Proceedings of the 74th meeting of The Endocrine Society, San Antonio, TX, 1992; p. 319.
 - Alexander GM, et al. Androgen-behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities. *Horm Behav.* 1998;33(2):85-94.



Testosterone and Memory

- In older men without dementia testosterone replacement reduced working memory errors
 - Janowsky JS, et al. Sex steroids modify working memory. *J Cogn Neurosci*. 2000;12(3):407-14.



Testosterone and Memory

- In this trial testosterone improved verbal and spatial memory and constructional abilities in non hypogonadal men with mild memory loss and early Alzheimer's disease
 - Cherrier MM, et al. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology*. 2005;64(12):2063-68.



Testosterone and CAD

- “Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease. This effect may be related to a direct coronary-relaxing effect.”
 - Rosano GM, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*. 1999;99(13):1666-70.



Testosterone and CAD

- Study revealed that testosterone replacement was associated with a decrease in HDL-C and lipoprotein a
 - Baum NH, et al. Testosterone replacement in elderly men. *Geriatrics*. 2007;62(9):15-18.



Testosterone and CAD

- The mechanism of testosterone replacement decreasing lipids may be due to testosterone's positive effects on abdominal fat and insulin resistance
 - Marin P, et al. Androgen treatment of abdominally obese men. *Obes Res.* 1993;1(4):245-51.



Testosterone and CAD

- Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary heart disease. This effect may be related to a direct coronary-relaxing effect of testosterone
 - Rosano GM, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*. 1999; 99(13):166-70.



Testosterone and CAD

- Short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and an increase in coronary blood flow in men with established coronary heart disease
 - Webb CM, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 1999;100(16):1690-96.



Testosterone and CAD

- Low-dose supplementation with testosterone in men with chronic stable angina reduced exercise-induced myocardial ischemia
 - English KM, et al. Low dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation*. 2000;102(16):1906-11.



Testosterone and CAD

- Testosterone replacement has been shown to increase coronary blood flow in patients with coronary heart disease
 - Channer KS, et al. Cardiovascular effects of testosterone: implications of the “male menopause”?. *Heart*. 2003; 89(2):121-22.
 - Whitsel EA, et al. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. *Am J Med*. 2001;111(4):261-69.



Testosterone and CAD

- Transdermal testosterone replacement has been shown to improve chronic stable angina by increasing the angina-free exercise tolerance vs. controls that were getting placebos
 - English KM, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation*. 2000;102(16):1906-11.



Testosterone and CAD

- Another study showed that testosterone replacement reduced exercise induced myocardial ischemia
 - English KM, et al. Testosterone acts as a coronary vasodilator by a calcium antagonistic action. *J Endocrinol Invest.* 2002;25(5):455-58.



Testosterone and CAD

- Testosterone is a coronary vasodilator by functioning as a calcium antagonistic agent
 - Corona G, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol.* 2011;165(5):687-701.



Testosterone and CAD

- Testosterone replacement therapy in hypogonadism moderates metabolic components associated with cardiovascular risk
 - Malkin CJ, et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab.* 2004;89(7):3313-18.



Testosterone and CAD

- Testosterone replacement has been shown to decrease inflammation and lower total cholesterol
 - Caminiti G, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol.* 2009;54(10):919-27.



Testosterone and CAD

- Testosterone replacement in patients with congestive heart failure has been shown to improve exercise capacity, improve insulin resistance, and improve muscle performance
 - Malkin CJ, et al. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Hear J.* 2006;27(1):57-64.



Testosterone and Prostate Cancer

- “There is no clinical evidence that the risk of either prostate cancer or BPH increases with transdermal testosterone replacement.”
 - Morley JE, et al. Testosterone replacement and the physiologic aspects of aging men. *Mayo Clin Proc.* 2000;75(Suppl):S83-7.



Testosterone and Prostate Cancer

- Interestingly, men that are older with the highest risk of prostate cancer have the lowest levels of testosterone
 - Roddam AW, et al. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst.* 2008;100(3):170-83.
 - Hoffman MA, et al. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol.* 2000;163(3):824-27.



Testosterone and Insulin Resistance

- Testosterone replacement decreases insulin resistance
 - Rizza RA. Androgen effect on insulin action and glucose metabolism. *Mayo Clin Proc.* 2000;75(Suppl):S61-4.
- Supraphysiologic doses of testosterone increase insulin resistance
 - Stellato RK, et al. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care.* 2000;23(4):490-94.
- Hyperinsulinemia decreases testosterone and replacement decreases hyperinsulinemia
 - Pasquali R, et al. Effects of acute hyperinsulinemia on testosterone serum concentrations in adult obese and normal-weight men. *Metabolism.* 1997;46(5):526-9.



Testosterone Replacement Therapy





Treatment

- Transdermal
- Use compounding pharmacy
 - Less expensive than commercial available forms
 - Can titrate to the individual needs of the patient





Testosterone and Erectile Function

- Transdermal 81% effective
- Oral 51% effective
- IM 53% effective
 - Jain P, et al. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol.* 2000;164(2):371-75.



TRT: Transdermal Patches

- Testosterone Transdermal System
 - Available in 2.5-mg and 5-mg preparations
 - Typical starting dose is 5-mg/day; can increase to 7.5-mg or decrease to 2.5-mg as needed
 - Applied at night to a clean, dry area of skin on the back, stomach, upper arms, or thighs.
 - Sites should be rotated daily, allowing 7 days before re-applying to the same site
 - Side effects:
 - Skin irritation, vesicle formation, contact dermatitis, headache, and depression



TRT: Gel Formulations

- Testosterone Gel
 - Applied in the morning to the shoulders, abdomen, or upper arm; preferably at the same location every day
 - Use gloves or wash hands after application
 - Allow gel to dry (10-15 min) before covering with clothing
 - Wait 4 hours prior to showering or swimming
 - Wash with soap and water if skin-to-skin contact with another person anticipated
 - Dosing: 5 grams (50 mg testosterone) daily, can be increased to 7.5 – 10 grams as needed
 - Side effects: acne, headaches, emotional lability, nervousness, gynecomastia, mastodynia, insomnia, hypertension, hot flashes, polycythemia, and increased PSA
 - Local skin irritation occurs much less frequently than with patches



TRT: Transbuccal Tablet

- Testosterone Buccal System
 - Sustained release formulation of 30 mg unmodified testosterone given every 12 hours
 - Absorption unaffected by food and beverage intake
 - Avoids first-pass metabolism by absorption into buccal mucosa
 - Side effects: gingivitis, edema, or blistering at application site, bitter taste, xerostomia, toothache, stomatitis, anxiety, and stinging of the lips
 - Generally well tolerated
 - Cannot use saliva testing to evaluate
 - Korobonits M, et al. A comparison of a novel testosterone bioadhesive buccal system, striant, with a testosterone adhesive patch in hypogonadal males. *J Clin Endocrin Metab.* 2004;89(5):2039-43.



TRT: Testosterone Esters

- Testosterone enanthate:
 - 200 – 400 mg IM every 2 – 4 weeks
- Testosterone cypionate:
 - 50 – 400 mg IM every 2 – 4 weeks
- Testosterone propionate:
 - 10 – 25 mg IM 2 – 3 x/week (not for long-term use)
- Esterification of testosterone
 - More hydrophobic, longer duration of action
- Supraphysiologic concentrations reached 24 hours after a 200-mg injection (of enanthate or cypionate), followed by gradual decline to hypogonadal levels
- Adverse effects:
 - Mood swings and variability in libido, sexual function, and energy levels due to varying PK; injection site reactions, polycythemia, acne, nonproductive cough, and gynecomastia



TRT: Testosterone Esters

- Testosterone undecanoate
 - 1,000 mg every 12 weeks following a 6-week loading dose
- Longer half life and duration of action than that of other testosterone esters
 - Due to longer hydrophobic side chain & castor oil carrier
 - Maintains testosterone levels consistently within normal physiologic range
 - Minimizes side effects due to varying PK of shorter acting esters



Testosterone Undecanoate

- Possible adverse effects
 - Injection site reactions
 - Increase in hemoglobin and erythrocyte count
 - Gynecomastia and breast tenderness
 - Increased PSA and prostate size in the elderly



Compounded Sterile Testosterone Injections

- May compound testosterone cypionate IM and propionate IM in one syringe with sesame seed oil
- May compound testosterone, anastrozole, and HCG into one syringe IM
- May compound testosterone IM with zinc IM
- May compound testosterone IM with anastrozole IM.
 - Dose of anastrozole is usually 0.05 mg/ml to 1mg/ml
 - Dose of testosterone is according to lab results



Testosterone Injections

- DO **NOT** HAVE PATIENT USE TESTOSTERONE SQ. IT IS FOR IM USE ONLY.
- OTHERWISE THE PATIENT MAY DEVELOP AN ABSCESS AT THE SITE OF INJECTION!





Testosterone Options	Doses	Advantages	Disadvantages
Testosterone transdermal patch	5-mg and 2.5-mg patches, replaced nightly	Recreation of normal circadian rhythm	Skin irritation
Testosterone topical gel	5-10 g/day	Skin irritation less common than with patch	Concern of transfer to others
Testosterone Transbuccal tablet	30 mg tablet twice daily (every 12 hours)	Avoids first pass metabolism	Unpleasant taste, tolerability
IM Testosterone: -cypionate -enanthate -propionate	200 mg q 2-4 wks 200 mg q 2-4 wks 10-25 mg 2-3x/wk	Inexpensive	Invasive, painful, injection site reactions
IM Testosterone undecanoate	1,000 mg every 12 wks following a 6-wk loading dose	Consistent levels, 4 injections/yr	Concern for effects on prostate



Testosterone Topical Solution

- 30mg/pump = 1.5mL
- Recommend 30 mg under each arm pit
- Has application cup
 - Cover under arms with clothes after the solution dries~ 3 minutes
 - Flammable until dry. Let dry before smoking or going near an open flame



Dosing of Compounded Testosterone Cream or Gel

- Dose of testosterone is 5-50 mg cream or gel according to lab results
- May compound chrysin in the same syringe with testosterone
 - Chrysin is a natural aromatase inhibitor to lower estrogen levels
 - Male skin has a higher concentration of aromatase enzyme on the surface
 - Chrysin has natural yellow color, it does not stain skin. Dose of chrysin depends on the level of estone or estradiol: usually 5-50 mg cream
 - Cannot put chrysin in a gel base
- May compound progesterone in the same syringe as testosterone and chrysin



Contraindications to Testosterone Use

- Prostate cancer
- Breast cancer
- Prolactinoma
- Prostate nodules or indurations
- Unexplained PSA increase
- Severe BPH
- Severe untreated sleep apnea



Younger Males

- In younger males with low testosterone, clomiphene citrate and HCG are used to help maintain fertility as opposed to using testosterone





Stimulating Endogenous Production of Testosterone





Natural Therapies to Increase Testosterone and Suppress Estrogen

Zinc	May play a role in testosterone synthesis.
Chrysin	Natural aromatase inhibitor; extracted from various plants, found in high concentrations in honey.
Carnitine	Amino acid derivative; may be more active than testosterone in aging men with sexual dysfunction and depression caused by androgen deficiency.
Muira puama	Derived from <i>Ptychopetalum olacoides</i> shrub in Brazil. Considered an aphrodisiac and effective treatment of impotence.
Cruciferous vegetables	Contain isothiocyanates and glucosinolates, which act as antioxidants and inducers of proteins that may suppress prostate cancer.
Quercetin	Found in wine, inhibits synthesis of estrogen by inhibiting aromatase.
Saw palmetto and nettle extracts	Reduce symptoms of BPH. Saw palmetto reduces nocturnal urinary urgency, increased urinary flow rate, decreased residual urine volume in the bladder, and reduced discomfort from urination symptoms. Nettle root may increase free testosterone levels by binding to SHBG.
Antioxidants	Support testosterone production by decreasing oxidative damage to tissues synthesizing testosterone.



Erythrocytosis

- Having erythrocytosis is associated with an increased risk in the development of heart disease and thrombosis
 - Merchant S, et al. Erythrocytosis. In: His E. *Hematopathology*. 2nd ed. Philadelphia, PA: Elsevier/Saunders, 2012.
- A major study on the risk and benefits of testosterone replacement suggested that a baseline hematocrit should be checked at three and six months and then every six to twelve months
- If the hematocrit is more than fifty-four percent then testosterone therapy should be stopped until the hematocrit is at a safe level
 - Bassil N, et al. The benefits and risk of testosterone replacement: a review. *Ther Clin Risk Manag*. 2009;5:427-48.



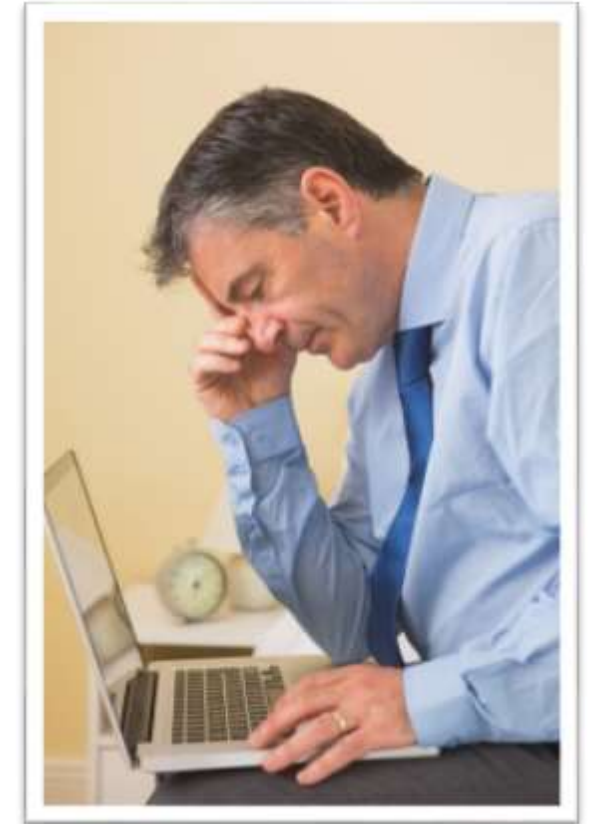
Clinical Case Study #1





Case Study #1

- 52-year-old male with the chief complaint of fatigue
 - He saw his primary care physician and lab work and physical were totally normal
 - Wants to know why he is so tired
- PH: unremarkable
- FH: father has Parkinson's disease, mother died in a car accident at the age of 30
- SH: works as a lawyer in a solo practice and works 80 hours a week
- ROS: unremarkable
- Medications: none
- P/E: per PCP, patient appears older than stated age



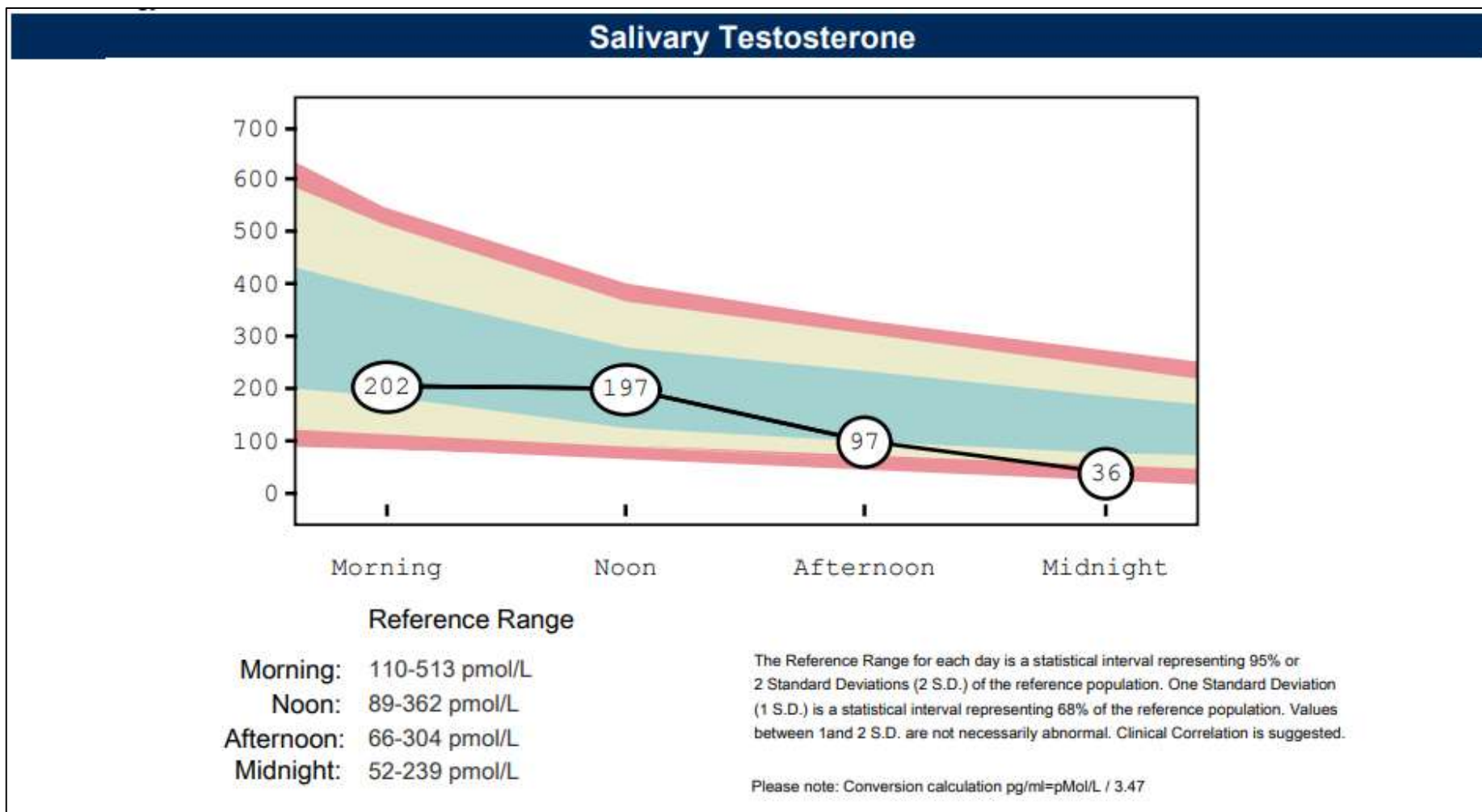


What Do You Want To Do With This Patient?



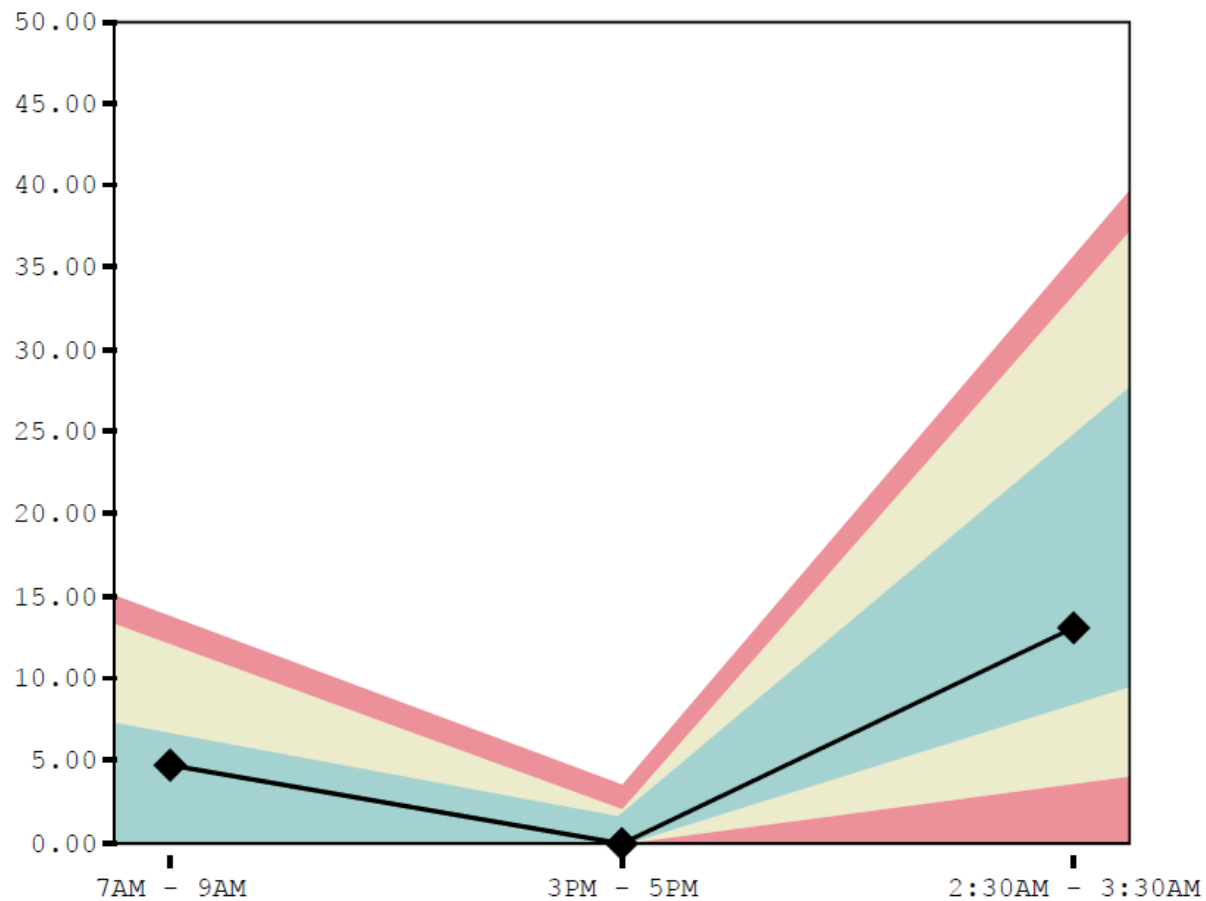


Case Study #1





Salivary Melatonin



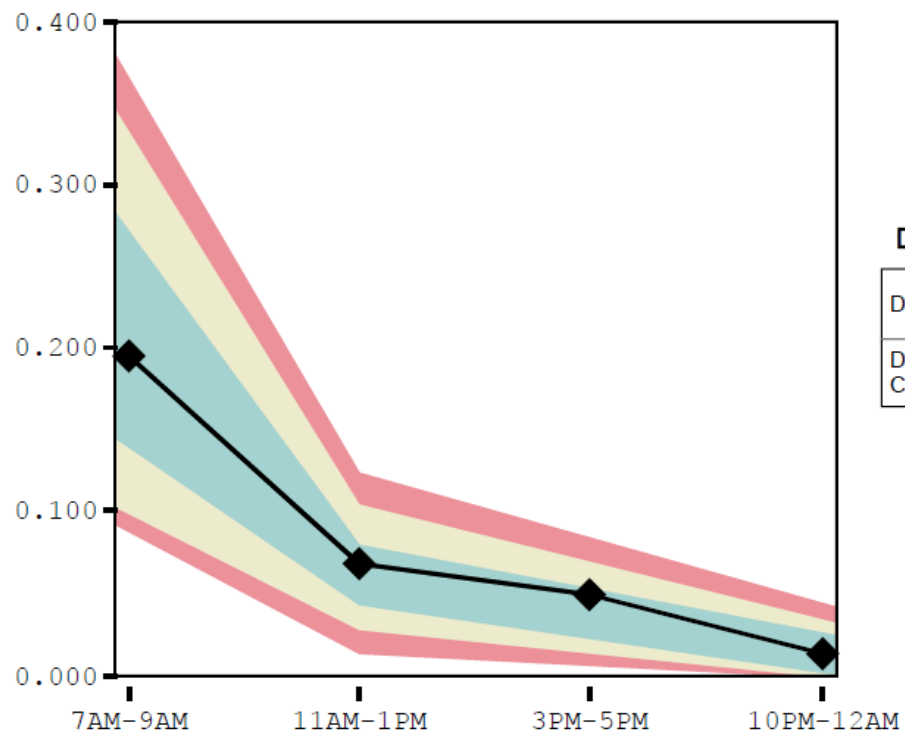
Results

	7AM-9AM*	3PM-5PM*	2:30AM - 3:30AM*
Patient Results (pg/mL) >>	4.73	<1.56	13.11
Reference Range (pg/mL)	<=12.12	<=1.97	3.71-33.38
*Based on Collection Times			



Salivary Cortisol and DHEA

Salivary Cortisol



DHEA

Reference Range

DHEA 7AM - 9AM♦	49		71-640 pg/mL
DHEA: Cortisol Ratio/10,000♦	251		358-2,538

Results

	7AM-9AM*	11AM-1PM*	3PM-5PM*	10PM-12AM*
Patient Result (mcg/dL) >>	0.195	0.067	0.049	0.013
Reference Range (mcg/dL)	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
<small>*Based on Collection Times</small>				
Actual Collection Time	7:00AM	11:35AM	3:30PM	9:45PM



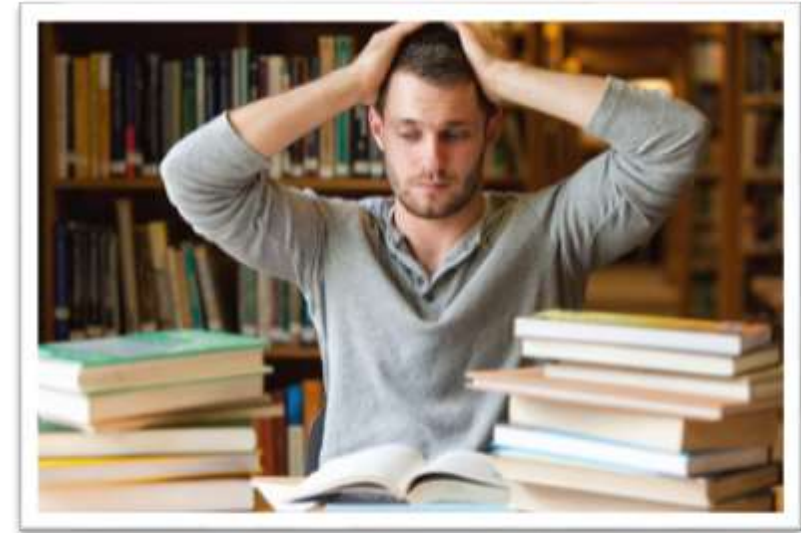
Clinical Case Study #2





Case Study #2

- This is a 21-year-old male with the chief complaint of fatigue
 - He has seen another personalized medicine doctor who tested him for Lyme disease, CMV, and E-B: All the tests were negative
 - He also had complete thyroid studies done and his thyroid function was optimal
 - FBS is 74
- PH:+ stress- His father died in car accident recently
- SH: is a college student at a major university
- FH: + diabetes
- Meds: takes a multivitamin
- ROS: + works out seven days a week for 90 minutes
- P/E: Patient appears very tired



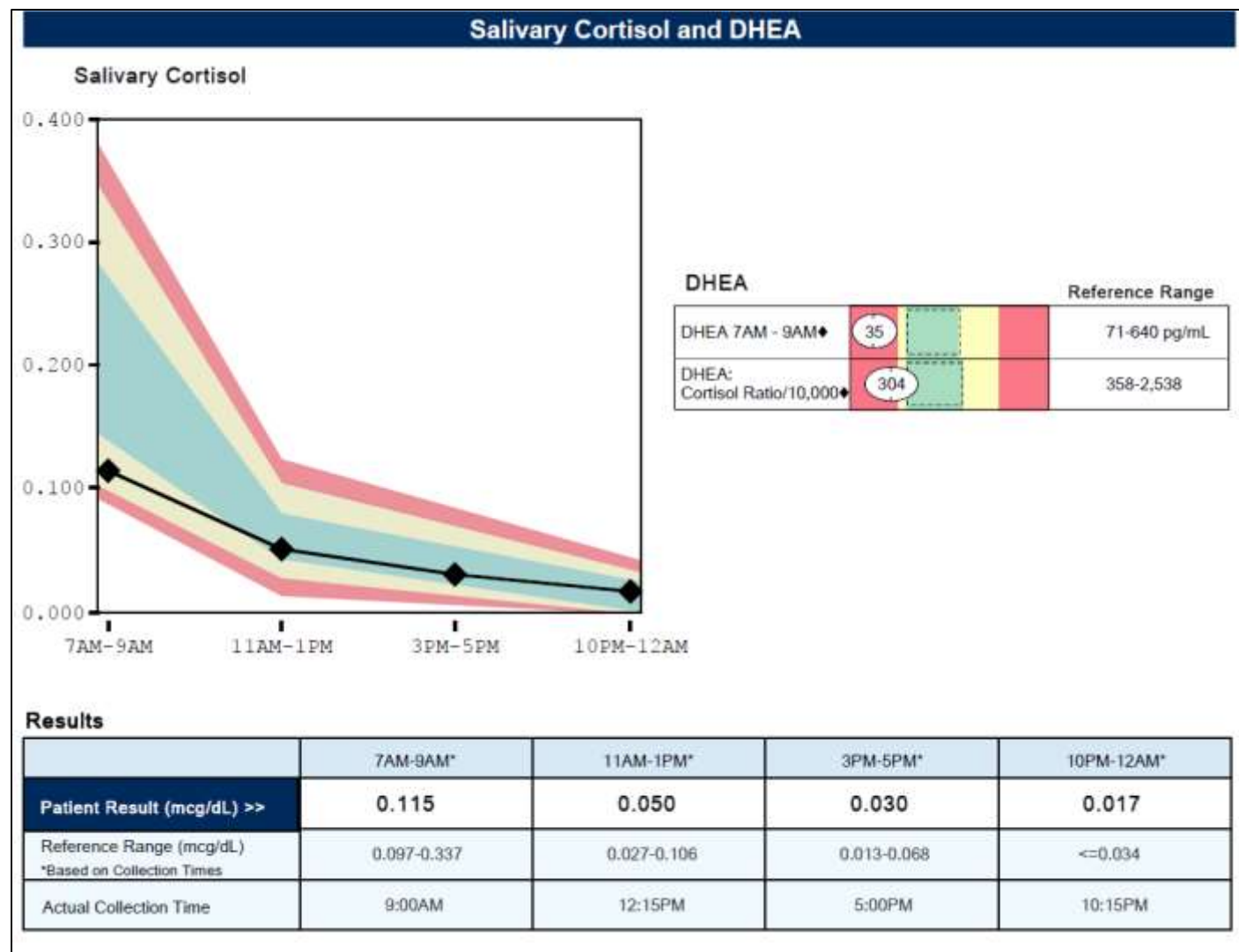


What Do You Want To Do With This Patient?





Case Study #2





Clinical Case Study #3





Case Study #3

- This is a 56-year-old male with the chief complaint that he just had an acute MI and his cardiologist wanted him to see me
 - He was unsure exactly why
- PH: acute MI one month ago
- FH: + father died of MI age 44. Paternal grandfather died of CVA age 67
- SH: works as an autoworker and is divorced
- Meds: statin drug, testosterone pellet
- ROS: + fatigue and memory not as sharp since the acute MI
- P/E: per cardiology



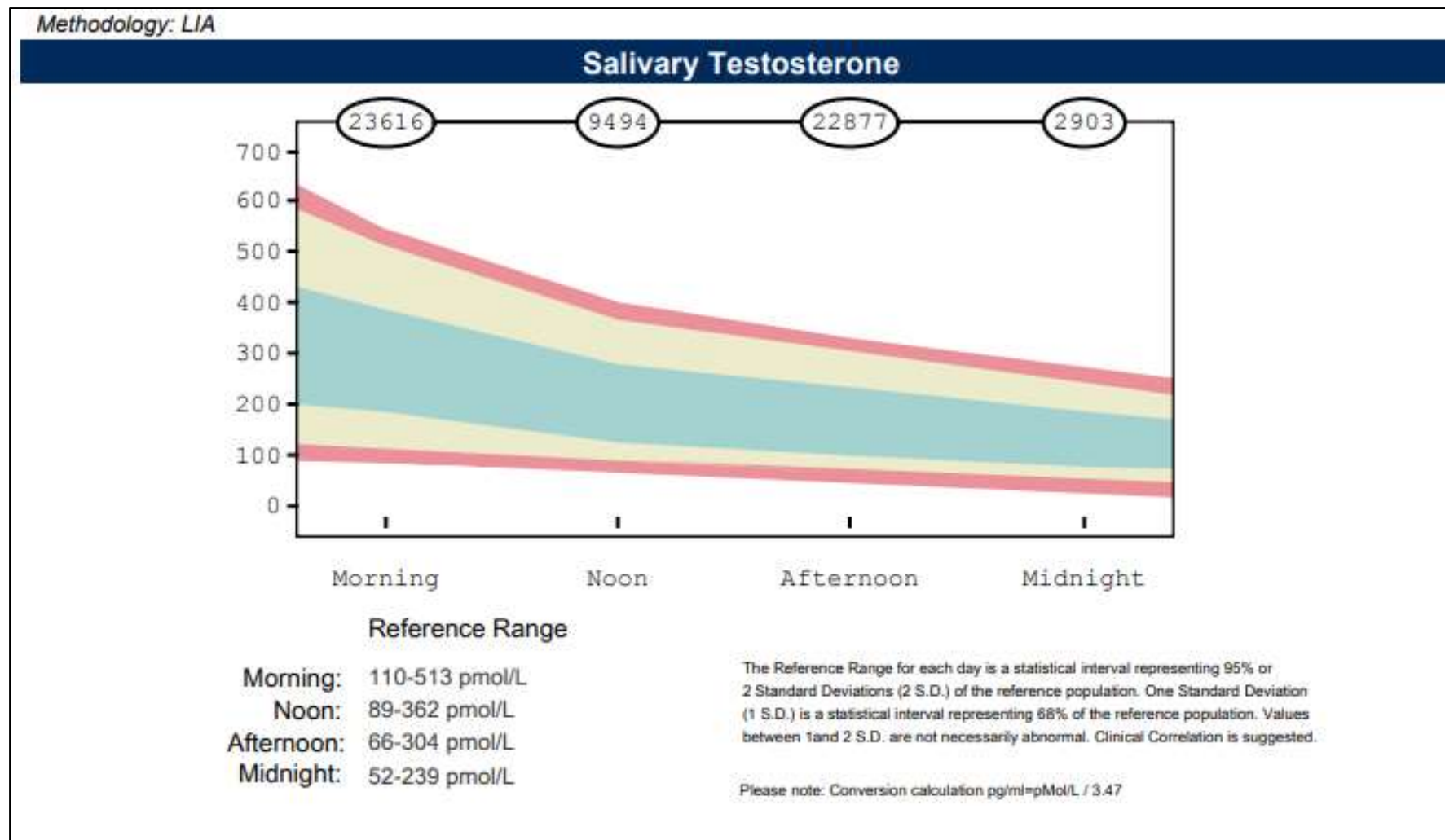


What Do You Want To Do With This Patient?



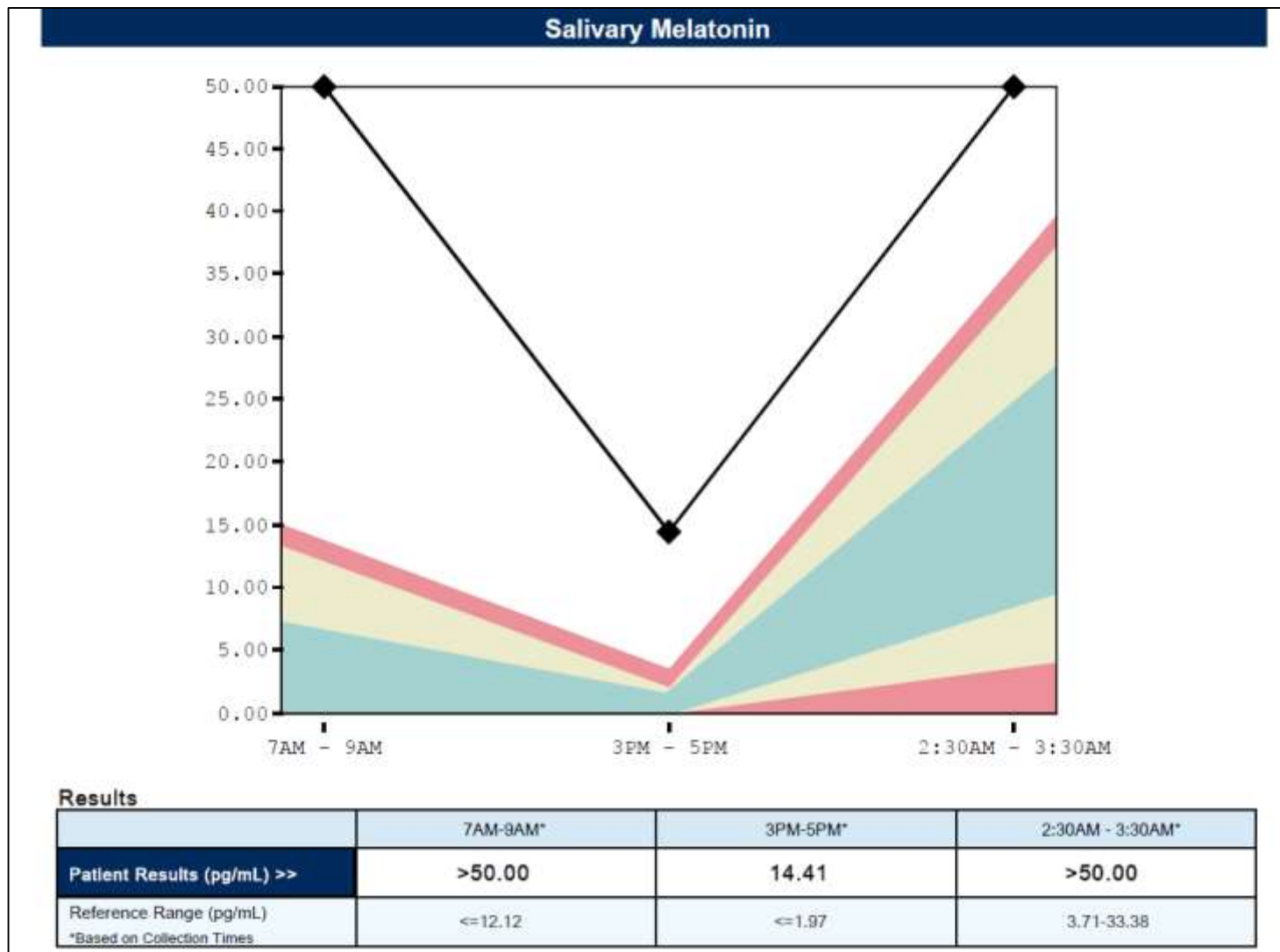


Case Study #3



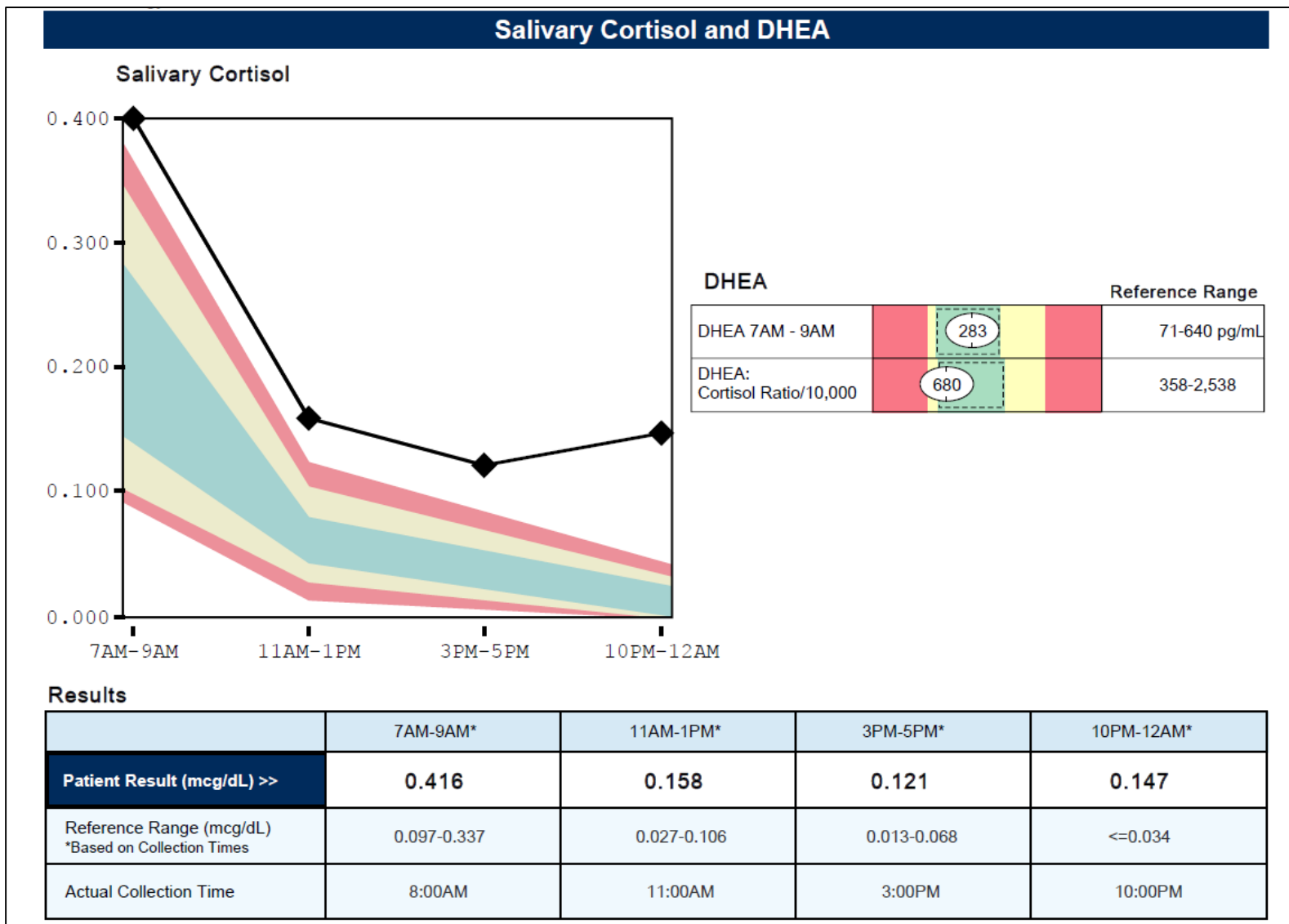


Case Study #3





Case Study #3





Conclusion

- Estrogen, progesterone, testosterone, DHEA, and cortisol are all important hormones for males.
- Normal DHT levels are also key for a male to maintain optimal health throughout his life.





Additional References:

Functions of Testosterone

- Annewieke, W, et al., “Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men,” *The J Clin Endocrinol Metab.* 2000; 85(9):3276-3282.
- Harman, S., et al., “Male menopause, myth or menace,” *Endocrinologist* 1994; 4(3):212-217.
- Swerdloff, R., et al., “Androgen deficiency and aging in men,” *West J Med.* 1993; 159(5):579-585
- Vermuelen, A., et al., “Androgens in the aging male,” *J Clin Endocrinol Metab.* 1991; 73(2):221-224.
- Menta, P., et al., “The social endocrinology of dominance: basal testosterone predicts cortisol changes and behavior following victory and defeat,” *J Pers Soc Psychol* 2008; 94(6):1078-93.
- Ajayi, A., et al., “Testosterone increases human platelet thromboxane A-2 receptor density and aggregation responses,” *Circulation* 1995; 91(11):2742-47.

Low Testosterone Levels

- Pasquali, R., et al., “Effects of acute hyperinsulinemia on testosterone serum concentrations in adult obese and normal-weight men,” *Metabolism* 1997; 46(5):526-29.
- Rizza, R., et al., “Androgen effect on insulin action and glucose metabolism,” *Mayo Clin Proc* 2000; 75(Suppl):S61-S64.
- Stellato, R., et al., “Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study,” *Diabetes Care* 2000; 23(4):490-94.
- Rizza, R., et al., “Androgen effect on insulin action and glucose metabolism,” *Mayo Clin Proc* 2000; 75(Suppl):S61-S64.



Presenter:
Pamela W. Smith, M.D., MPH, MS

US Client Services: 800-522-4762

UK Client Services: 020.8336.7750

*We look forward to
hearing from you!*

Questions?