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The Role of Estrogen and Testosterone Therapy in Heart Health

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Sex Hormones & Heart Health

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Dr. Tim Hyatt received his doctorate in naturopathic medicine in 2006. He brings a broad range of skills and perspectives from years of clinical practice and is currently serves as a clinical educator for Precision Analytical in McMinnville, Oregon. His medical interests include endocrine function, neurochemistry and physical medicine. Dr. Hyatt is also the president of Biogenic Nutrition LLC, a nutraceutical company specializing in unique, condition-specific formulas.

Overview

Cardiovascular disease was the number one killer of men and women in the United States in 2020 and the process of aging is a major factor in declining cardiovascular health. Here at DUTCH, we focus directly on hormone testing but in the functional medicine space, we're trained to incorporate all aspects of function including cardiovascular health. Today we want to look at how hormone health plays a role in cardiovascular function especially in aging individuals and give you some things to think about when it comes to hormone replacement therapy and testing.

Remember

The information in this presentation is provided for informational and educational purposes only and is not medical or treatment advice.

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The use of any information provided in this presentation is solely at your own risk.

Overview

1. High level look at cardiovascular disease (CVD) and the connection to hormones
2. Cardiovascular health and estrogen in women
3. Cardiovascular health and testosterone in men
4. Putting it all together

Cardiovascular Disease Statistics

Cardiovascular disease (CVD), accounted for

931,578 deaths

in the United States in 2020.

Risks of death from CVD has

increased about 1% per decade

since 1990.

Major risk factors include family history, age, smoking, diabetes, overweight/obesity, hypertension, poor sleep, inactivity, poor nutrition/diet, lipid status, genetic factors, and inflammation.

Four Categories of Cardiovascular Disease

Cerebrovascular disease

reduced blood flow to the brain caused by thromboembolism, aneurysm or ischemia.

Coronary heart disease (CHD)

reduced blood flow to the heart due to build up of plaques

Aortic atherosclerosis

caused by buildup of plaque, resulting in reduced blood flow in, or rupture of the aorta.

Peripheral artery disease

from thrombus, embolism or atherosclerosis resulting in reduced blood flow.

Up to date 2024 Statistics at a Glance, World Population by Year – Worldometer, World-Heart-Report-2023.pdf

Sex Hormones and Cardiovascular Health

Estrogen and testosterone have both been extensively studied to support the following in the cardiovascular system.

- Endothelial function and inflammatory response
- The microbiome
- Blood pressure
- Insulin production and sensitization
- Body composition

What Do We Know About Aging and Inflammation?

- We know that the processes of aging and inflammation dramatically increase the number of CV events.
- Hormone levels decline with age which coincides with a decline in health
- Hormone replacement therapy in aging men and women have beneficial effects on cardiovascular health.

Cardiovascular Health and Estrogen in Women

Estradiol in Serum

Cycling Females	Daily production is variable. Concentration in circulation - 30 to 400 pg/ml
Post Menopausal Females	Daily production: 18ug/day Concentration in circulation – 0-10pg/ml

Kuiper et al, Russel et al

Comparison of Quest Diagnostics vs DUTCH Test Levels

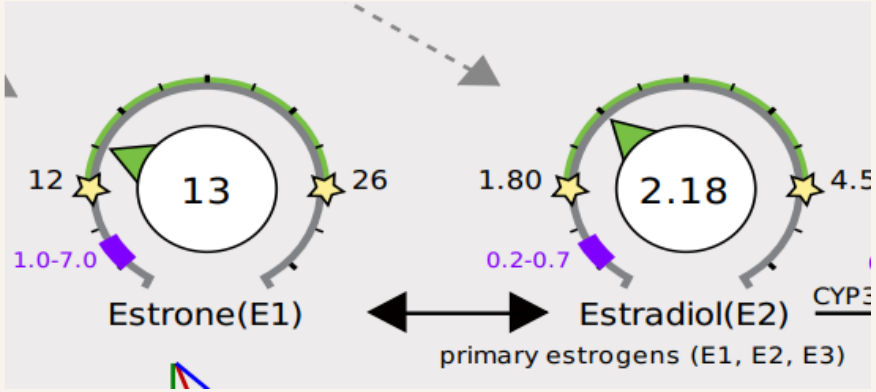
Quest Diagnostics Ranges for Estradiol*

Premenopausal Range: 48-440 pg/ml
Postmenopausal Range: < 10pg/ml

*Ranges are lab and method dependent

Dutchtest Ranges for estradiol (in ng/mg creatinine)

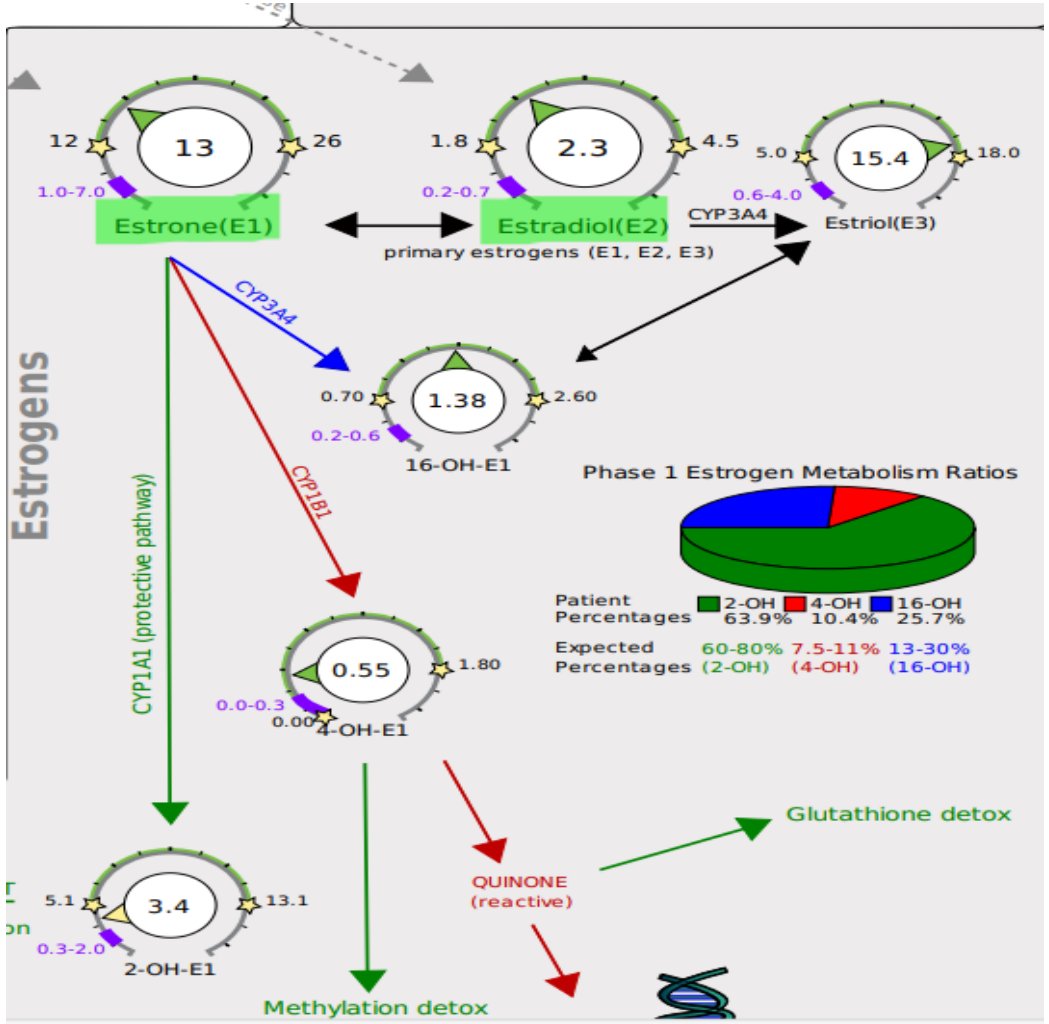
Follicular Range: 1.0-2.0
Luteal Range: 4.0-12.0
Postmenopausal Range: 0.2-0.7



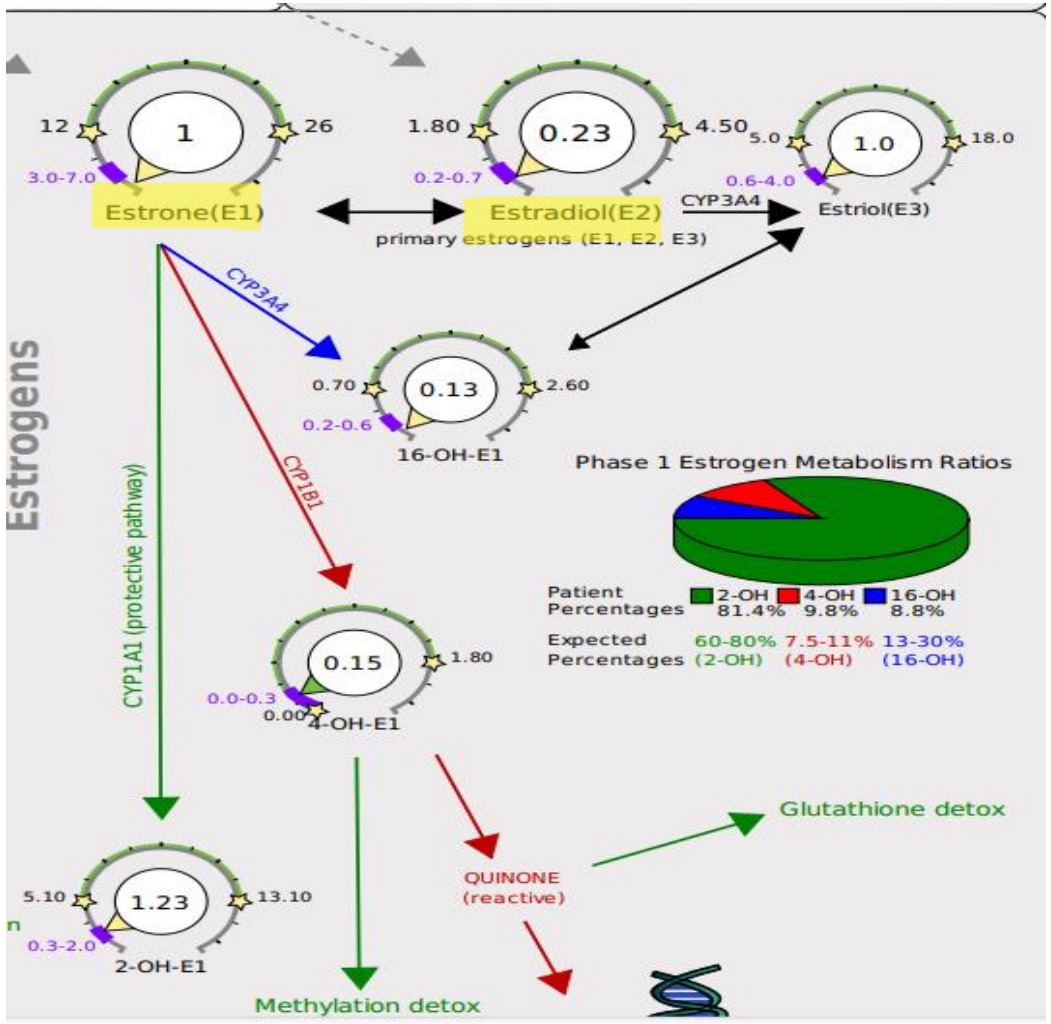
https://testdirectory.questdiagnostics.com/test/test-detail/30289/estradiol-ultrasensitive-lcms?cc=MASTER
https://testdirectory.questdiagnostics.com/test/test-detail/17183/progesterone-lc-ms?cc=MASTER

Estradiol on the DUTCHTEST

Cycling Female Levels – Luteal Phase



Postmenopausal Female Levels



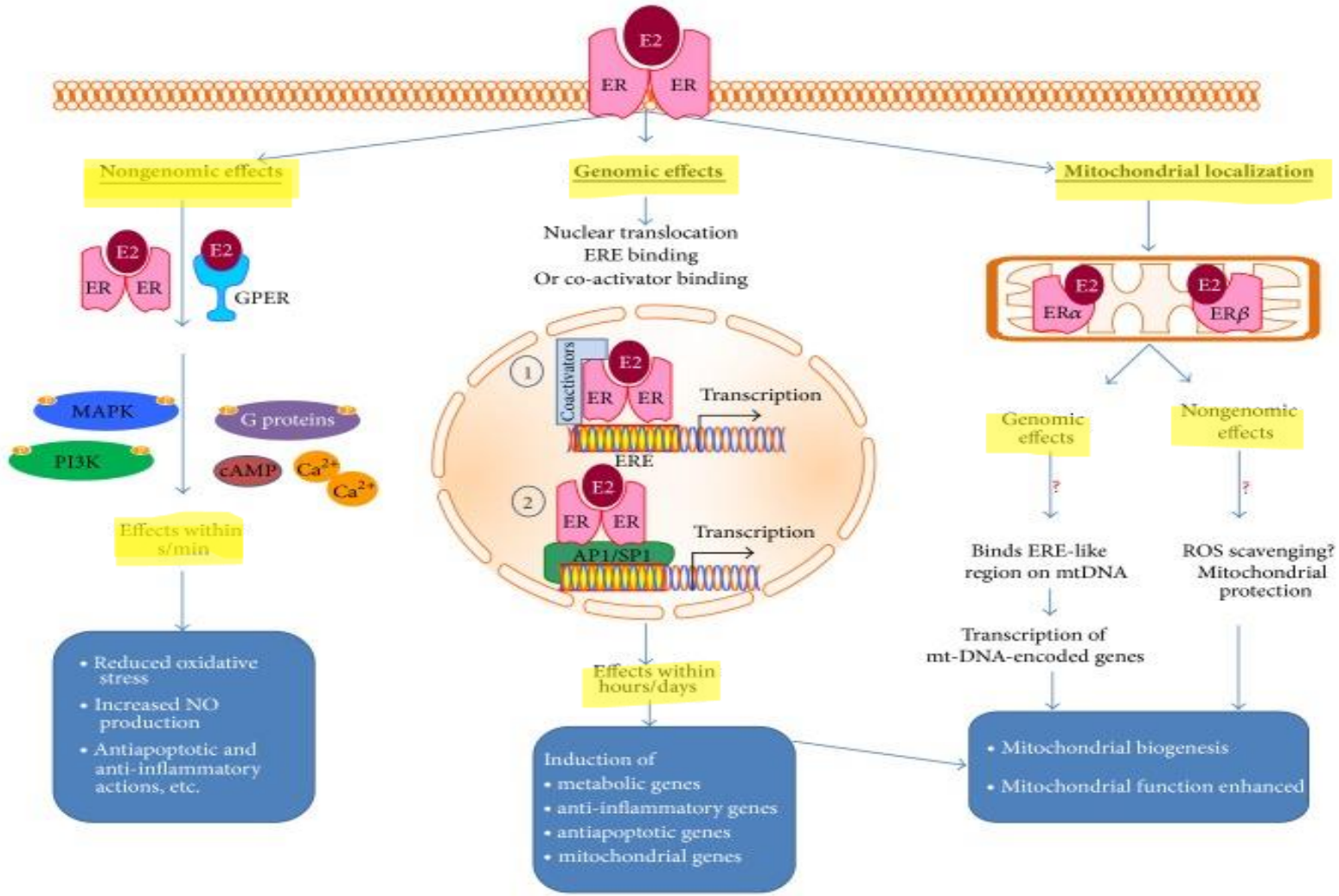
Biochemical Effects of Estrogen

Estradiol mediates its effects via 3 receptors:

- E2 receptor alpha
- E2 receptor beta
- G protein-coupled E2 receptor 1 (GPER).

. 2015 Mar 26;2015;916585. doi: 10.1155/2015/916585

Biochemical Effects of Estrogen



Gupte AA, Pownall HJ, Hamilton DJ. Estrogen: an emerging regulator of insulin action and mitochondrial function. J Diabetes Res. 2015;2015:916585. doi: 10.1155/2015/916585. Epub 2015 Mar 26. PMID: 25883987; PMCID: PMC4391691.

The Role of Estradiol in the Cardiovascular System

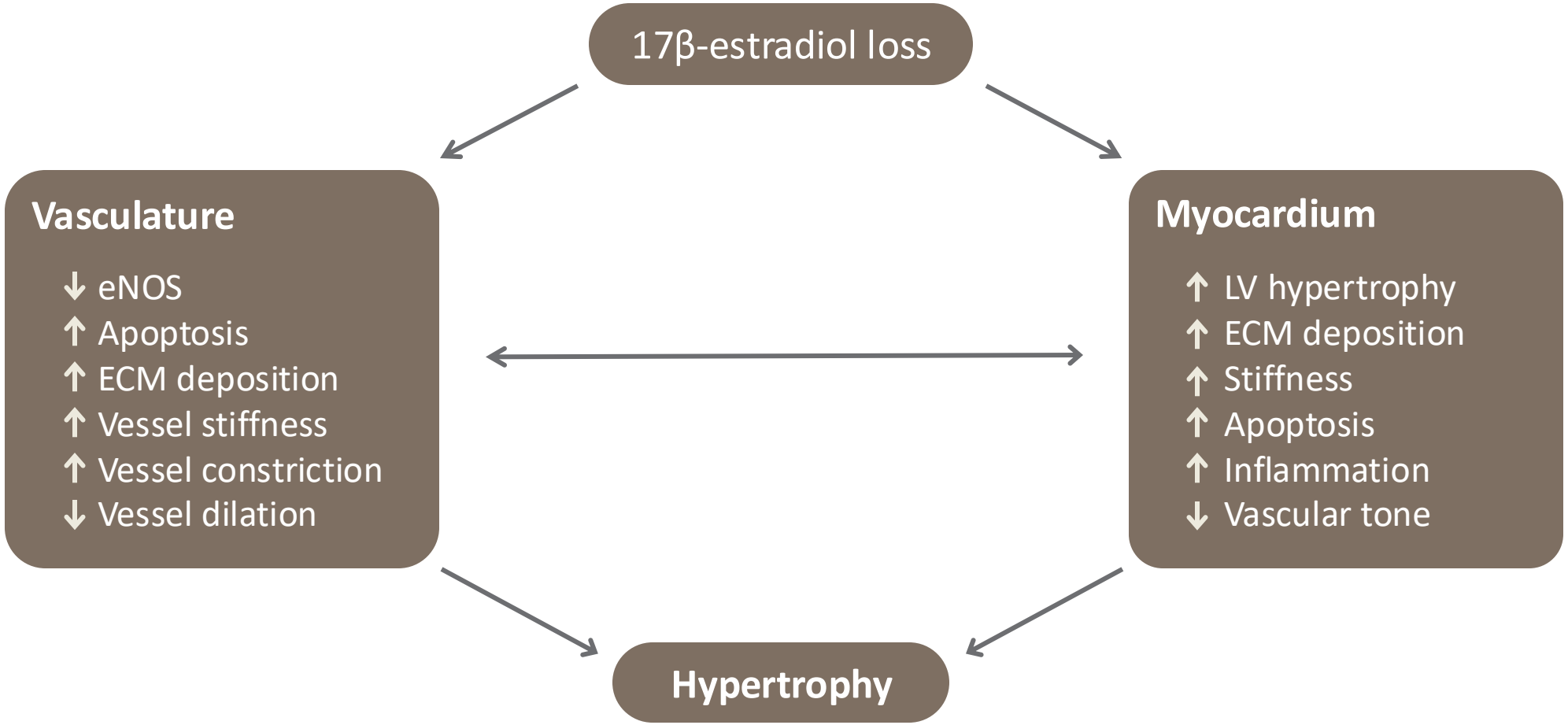
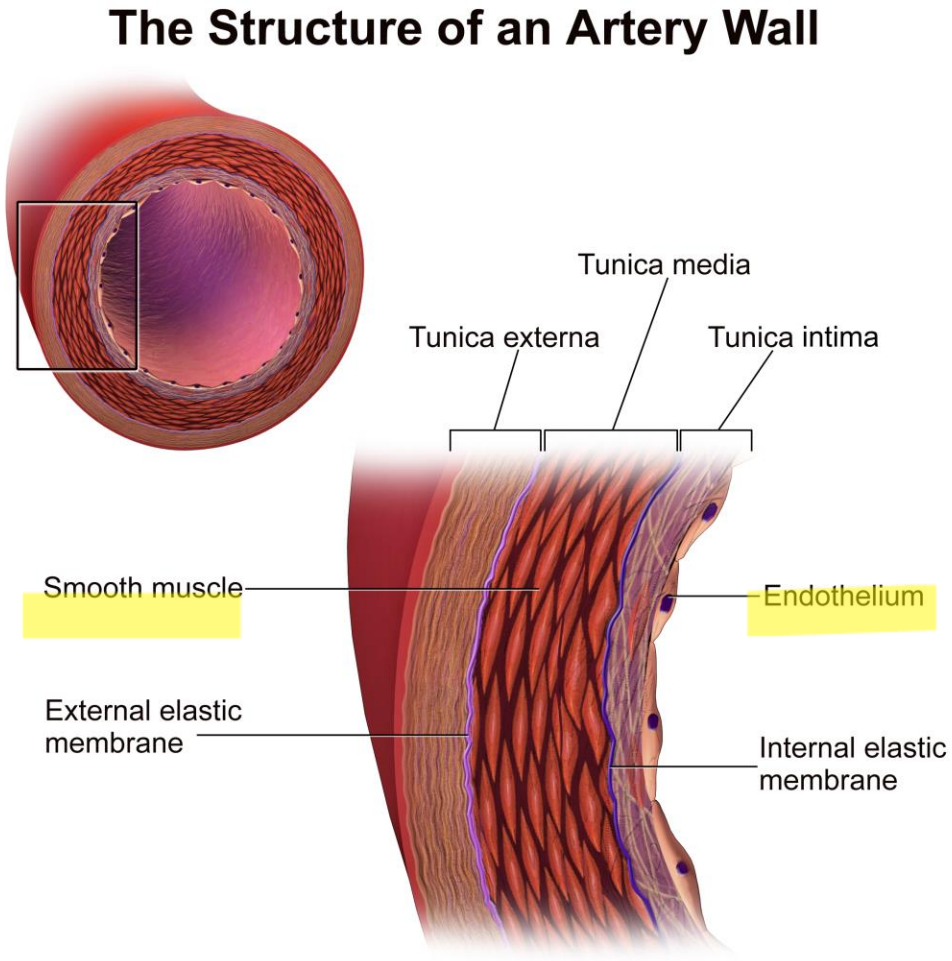


Figure 1: Estrogen, aging and the cardiovascular system - PMC

Stice JP, Lee JS, Pechenino AS, Knowlton AA. Estrogen, aging and the cardiovascular system. Future Cardiol. 2009 Jan;5(1):93-103. doi: 10.2217/14796678.5.1.93. PMID: 19371207; PMCID: PMC3972065

The Endothelium



Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014"

Endothelial Breakdown

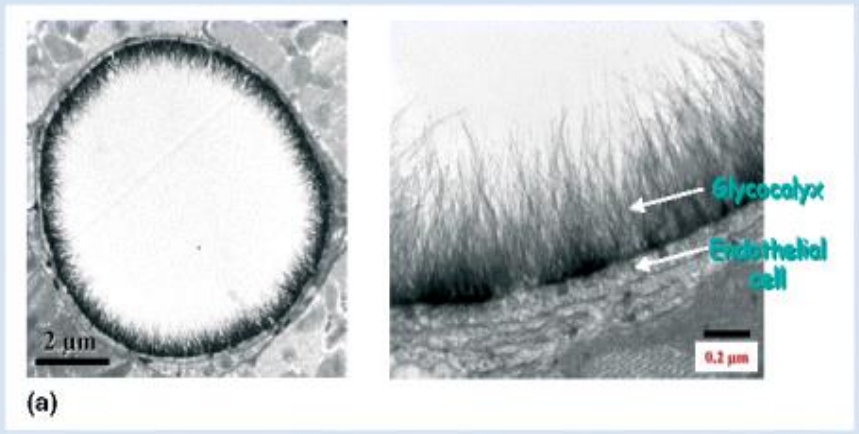
Inflammation caused by these factors,
leads to endothelial breakdown.

- Dyslipidemia
- Hypertension
- Insulin resistance
- T2 DM
- Obesity
- Perceived stress resulting in high cortisol

Glycocalyx Degradation

The process of inflammation leads to destruction of the glycocalyx which leads to Endothelial Dysfunction, causing:

1. Leaky blood vessels
2. LPS translocation
3. LPS induced oxidation
4. Oxidative stress
5. Immune activation
6. Foam cell formation
7. End organ damage



Saltiel, D, Women's cholesterol levels vary with phase of menstrual cycle | National Institutes of Health (NIH)

Hans Vink PhD, Department of Medical Physics, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands.

Estradiol and the Endothelium

- Sex hormone receptors are found in immune, endothelial, and vascular smooth muscle cells.
- Increases nitric oxide production.
- Decreases endothelin-1, a potent vasoconstrictor and pro-inflammatory peptide secreted by the endothelium.
- Has direct antioxidant effects where it scavenges and inhibits ROS.
- Increases mitochondrial antioxidant defense.
- Estrogen receptor A is a key factor in maintaining endothelial vascular function where it increases eNOS and SOD.
- Modulates endothelial cell ER expression, which impacts ER signaling, sensitivity and function.
- In premenopausal females E2 increases HDL cholesterol and reduces LDL cholesterol.
- Estrogen modulates inflammatory cytokines IL-1b, IL-6, and TNF-a and reduces inflammation through stimulation of anti-inflammatory cytokines IL4 and IL10.

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test

Women's cholesterol levels vary with phase of menstrual cycle | National Institutes of Health (NIH)

Inflammation and CVD

Inflammation is the key driver during all stages of the atherosclerotic process, from initiation through progression and ultimately leading to thrombotic complications such as MI, CVA, ischemic limb, DVT, and PE.

Estrogen and the Endothelium

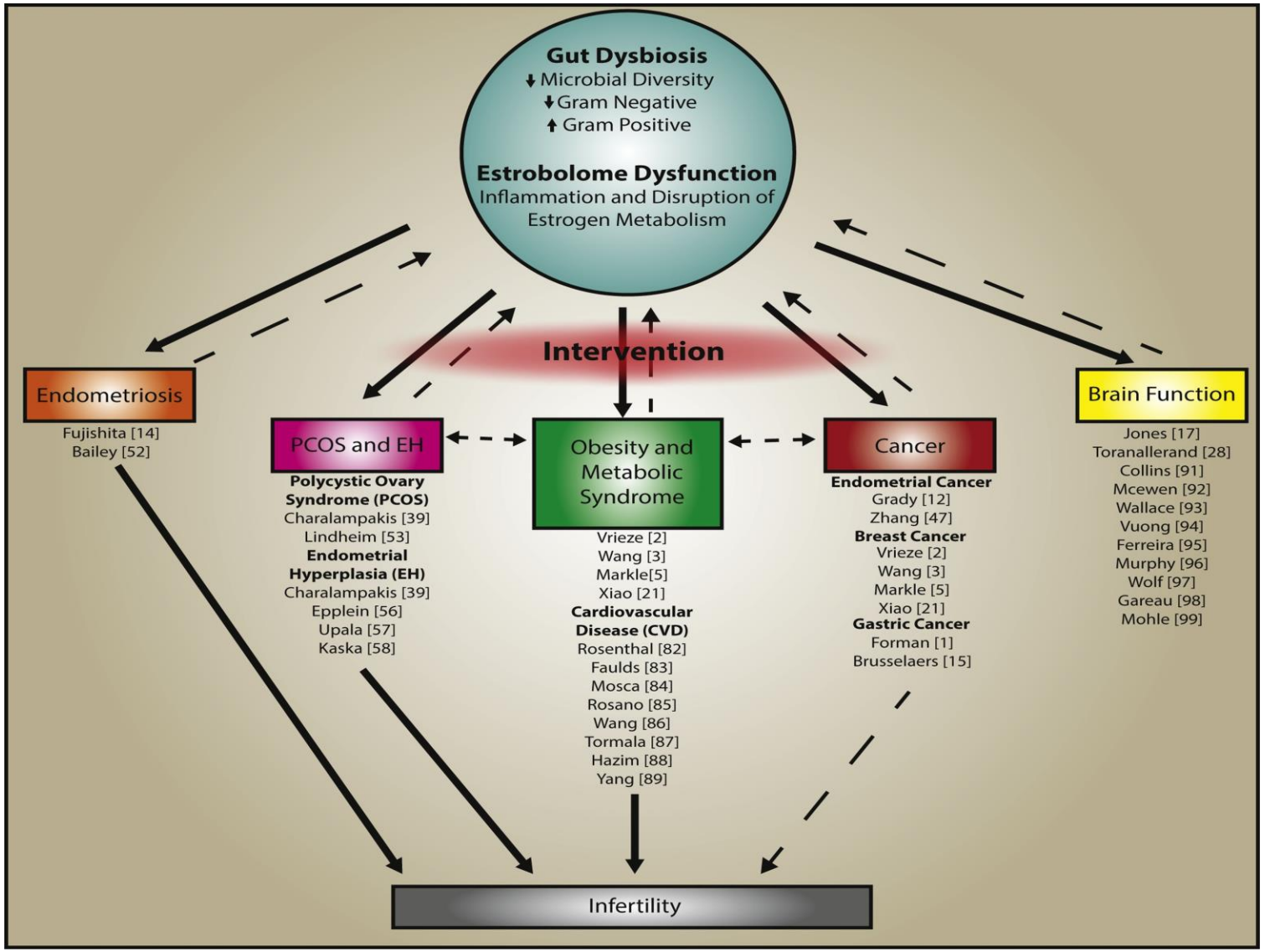
By reducing inflammation, estradiol reduces endothelial damage.

Estrogen and the Microbiome

The gut microbiome regulates circulating estrogens via the beta glucuronidase mechanism:

1. Beta glucuronidase deconjugates estrogens to their active forms.
2. Dysbiosis results in **less** beta glucuronidase secretion and **lower** levels of available estrogen in post-menopausal years.
3. This may contribute to the development of conditions discussed herein: **obesity, metabolic syndrome**, cancer, endometrial hyperplasia, endometriosis, **polycystic ovary syndrome**, fertility, **cardiovascular disease (CVD)** and cognitive function.

Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas. 2017 Sep;103:45-53. doi: 10.1016/j.maturitas.2017.06.025. Epub 2017 Jun 23. PMID: 28778332. er et al



Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas. 2017 Sep;103:45-53. doi: 10.1016/j.maturitas.2017.06.025. Epub 2017 Jun 23. PMID: 28778332

How Does Estradiol Affect Blood Pressure?

1. Increases prostacyclin receptors and nitric oxide production to improve vasodilation.
2. Decreases angiotensin II resulting in lower BP.
3. Inhibits vascular smooth muscle cell proliferation.
4. In vitro estrogen exerts a direct inhibitory effect on smooth muscle by activating potassium efflux and by inhibiting calcium influx.

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test

Ashraf MS, Vongpatanasin W. Estrogen and hypertension. Curr Hypertens Rep. 2006, Oct;8(5):368-76. doi: 10.1007/s11906-006-0080-1. PMID.
Tostes R.C., D. Nigro, Z.B. Fortes and M.H.C. Carvalho, Grupo de Pesquisa sobre Hipertensão Arterial, Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP, Brasil, **Effects of estrogen on the vascular system, Braz J Med Biol Res, September 2003, Volume 36(9) 1143-1158 (Review)**
Turner EC, Kinsella BT. Estrogen increases expression of the human prostacyclin receptor within the vasculature through an ERalpha-dependent mechanism. J Mol Biol. 2010 Feb 26;396(3):473-86. doi: 10.1016/j.jmb.2010.01.010. Epub 2010 Jan 11. PMID: 20070947.

Estrogen and Blood Sugar Regulation

The effects of estrogens on glucose and energy handling are mediated through four coordinated actions:

1. Protection and facilitation of insulin secretion and function in the control of glucose availability to tissues;
2. Modulation of energy partition, favoring the use of lipids as the main energy substrate when their availability is higher than that of carbohydrates;
3. Functional protection through antioxidant mechanisms;
4. There are central effects on whole body energy metabolism and homeostasis maintenance.

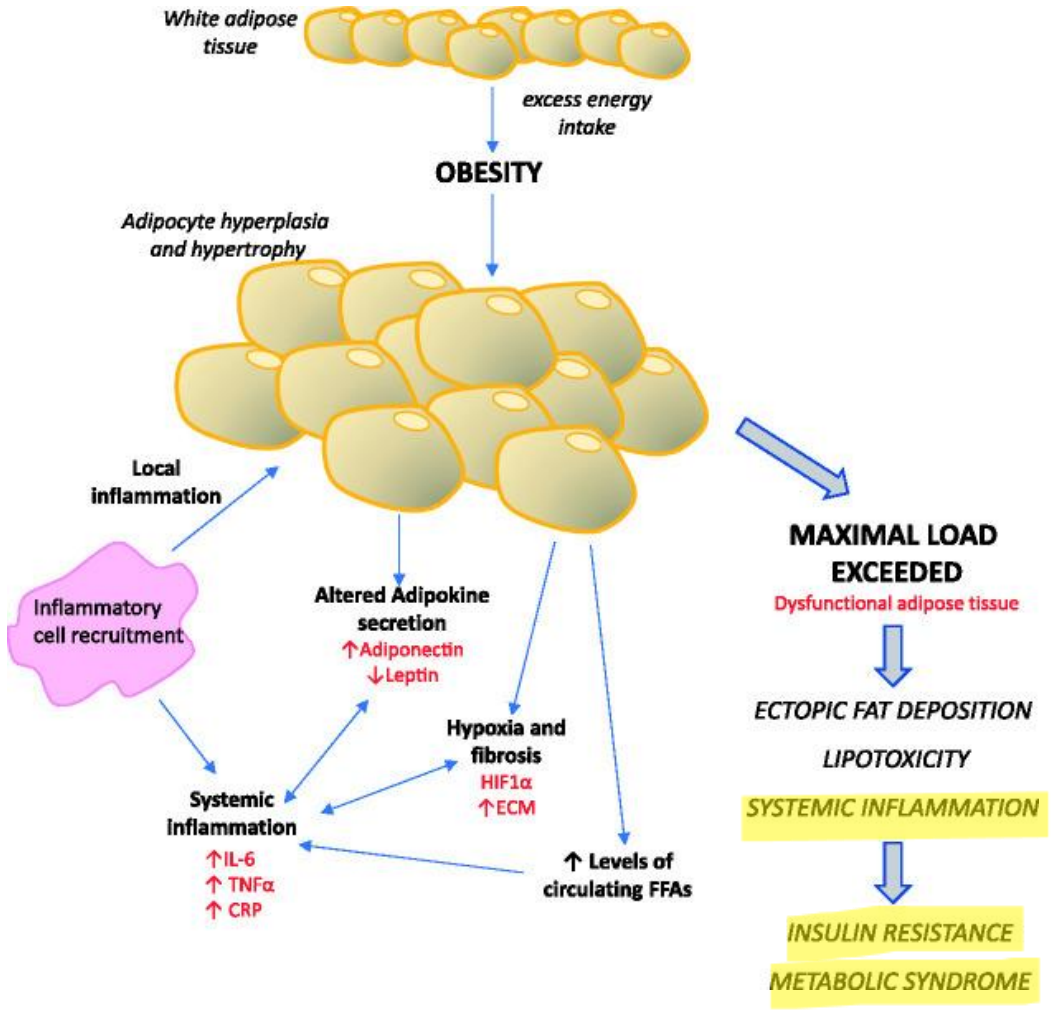
De Paoli, Monica et al. The Role of Estrogen in Insulin Resistance. The American Journal of Pathology, Volume 191, Issue 9, 1490 – 1498
Alemany M. Estrogens and the regulation of glucose metabolism. World J Diabetes. 2021 Oct 15;12(10):1622-1654. doi: 10.4239/wjd.v12.i10.1622. PMID: 34754368; PMCID: PMC8554369.

Key Point - Estrogen and Blood Sugar Regulation

Estrogen provides sustained control of core energy metabolism

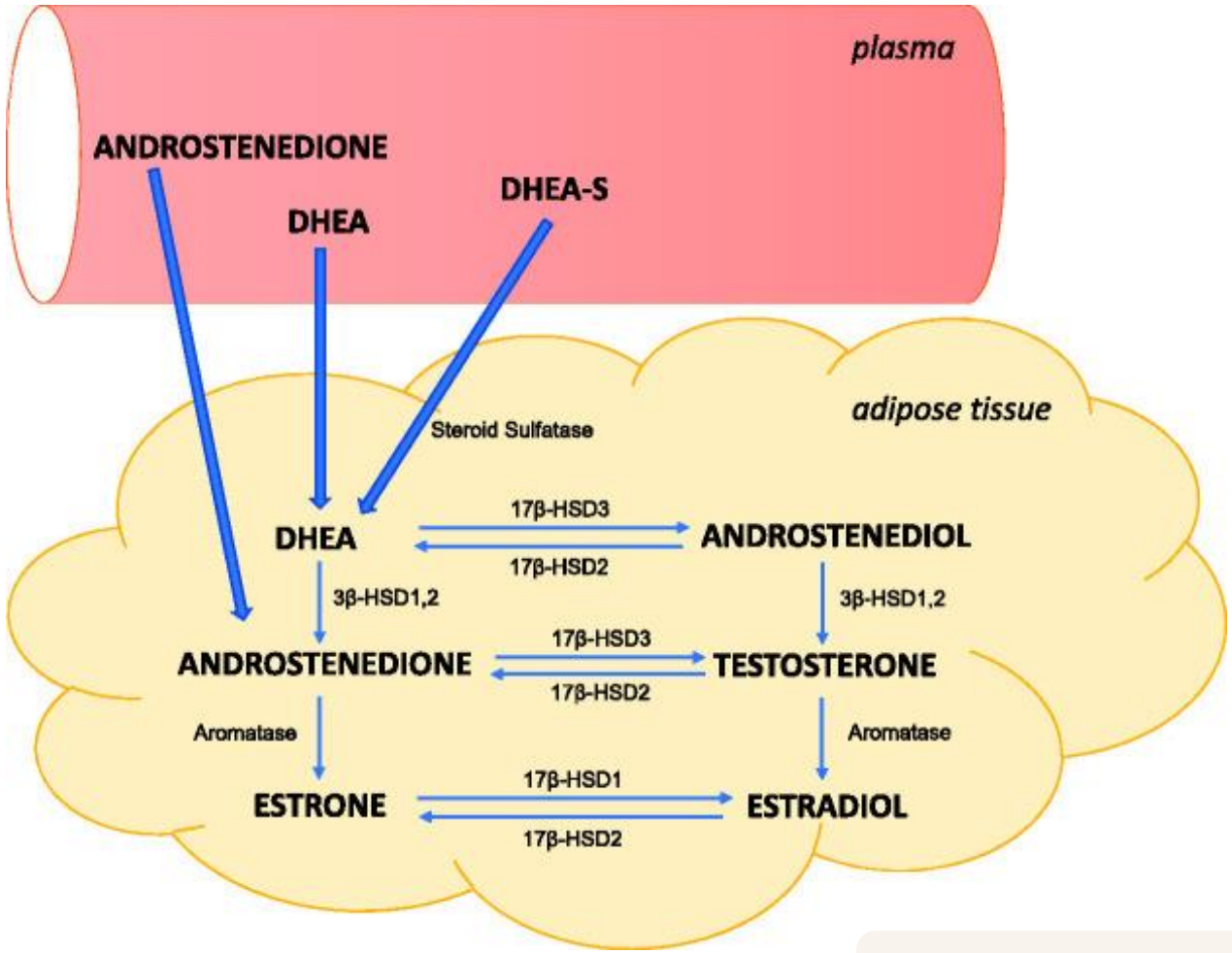
Alemany M. Estrogens and the regulation of glucose metabolism. World J Diabetes. 2021 Oct 15;12(10):1622-1654. doi: 10.4239/wjd.v12.i10.1622. PMID: 34754368; PMCID: PMC8554369.

Adipose Accumulation and the Consequences



Mair KM, Gaw R, MacLean MR. Obesity, estrogens and adipose tissue dysfunction - implications for pulmonary arterial hypertension. Pulm Circ. 2020 Sep 18;10(3):2045894020952019. doi: 10.1177/2045894020952023. PMID: 32999709; PMCID: PMC7506791.

The Process of Aromatization in Adipose Tissue



Mair KM, Gaw R, MacLean MR. Obesity, estrogens and adipose tissue dysfunction - implications for pulmonary arterial hypertension. Pulm Circ. 2020 Sep 18;10(3):2045894020952019. doi: 10.1177/2045894020952023. PMID: 32999709; PMCID: PMC7506791.

Estrogen and Body Composition

- E1 is the predominant estrogen in menopause but can be converted to E2 in the adipose tissue.
- Adipose tissue is the main peripheral site of estrogen production, and this is accomplished through aromatization.
- Due to much higher E2 secreted from the ovaries in premenopausal females, peripheral aromatization is not a significant source of E2 until after menopause. Also, 90% of postmenopausal E2 comes from adrenal DHEA.
- Adipose tissue deposition mainly in gluteal/femoral regions in perimenopausal years moves to visceral deposition after menopause.
- The exact mechanism for this is not known, but it is thought to involve many mechanisms around aging of the ovaries resulting in lower levels of estrogen, progesterone and testosterone and metabolic changes that favor fat deposition to help maintain postmenopausal levels of sex hormones.

Hetemäki Natalia, Tomi S. Mikkola, Matti J. Tikkanen, Feng Wang, Esa Hämäläinen, Ursula Turpeinen, Mikko Haanpää, Veera Vihma, Hanna Savolainen-Peltonen, Adipose tissue estrogen production and metabolism in premenopausal women,, The Journal of Steroid Biochemistry and Molecular Biology, Volume 209, 2021,105849, ISSN 09600760,

Estrogen and Body Composition in Summary

The process of aging, increasing chronic inflammation, and the decline of sex hormone production are thought to be the major players in the deposition of adipose tissue, resulting in significant changes in body composition leading to challenges in the normal function of the cardiovascular system.

Pre vs Postmenopausal Risk for CVD

Premenopausal

- CVD risk for cycling females with normal cycles is relatively low.
- CVD risk for patients with polycystic ovarian syndrome (PCOS) and primary ovarian insufficiency (POI) is increased when compared to patients with normal cycles.

Postmenopausal

- Estrogen, progesterone and testosterone levels decline significantly.
- Metabolic risk factors such as hypertension, weight gain, insulin resistance, diabetes increase and therefore, CVD risk is increased.

In Menopause...

- Both age and biological sex each play a role in the development of cardiometabolic disturbances.
- The frequency of cardiovascular disease before the age of 55, shortly after the onset of menopause, is lower in women.
- Lower estrogen levels in menopause are associated with a higher risk of cardiovascular disease.

Osadnik T, Pawlas N, Osadnik K, Bujak K, Góral M, Lejawa M, Fronczek M, Reguła R, Czarnecka H, Gawlita M, Strzelczyk JK, Gonera M, Gierlotka M, Poloński L, Gąsior M. High progesterone levels are associated with family history of premature coronary artery disease in young healthy adult men. PLoS One. 2019 Apr 15;14(4):e0215302. doi: 10.1371/journal.pone.0215302. PMID: 30986240; PMCID: PMC6464341.

Travison TG, O'Donnell CJ, Bhasin S, Massaro JM, Hoffmann U, Vasan RS, et al. Circulating Sex Steroids and Vascular Calcification in Community-Dwelling Men: The Framingham Heart Study. J Clin Endocrinol Metab. The Endocrine Society; 2016; 101: 2160–7. https://doi.org/10.1210/jc.2015-4299 PMID: 26930184

CVD for Age and Sex

- Gathered demographics and health data from UK Biobank, >226,000 participants for 12 years:
- Mean age 55 years, males (47%) and females (52%),
- Multiple CV outcomes measured against modifiable and socioeconomic risk factors, and age.

Tian, Fei et al., Ranking age-specific modifiable risk factors for cardiovascular disease and mortality: evidence from a population-based longitudinal study, eClinicalMedicine, Volume 64, 102230

Fei et al Study Results

Risk for CVD outcomes was higher for men at all age groups.

- Metabolic health was by far the most influential modifiable risk factor in this study for both sexes.
- Hypertension was the largest contributor, accounting for 14.04% of the population attributable risk percentage (PAR%), followed by abdominal obesity (9.58%),
- There was a significantly higher CVD incidence in males compared with females (11.72 versus 5.88/1000 person-years).

Sex	Age Range	% outcomes CVD
Females	40-50	2.21
	50-60	5.4
	>60	12.7
Males	40-50	5.63
	50-60	12.01
	>60	21.78

CVD Risks in Both Sexes

- Females are more protected than males because of estrogen.
- Premenopausal women have a decreased risk of cardiovascular disease (CVD) compared to their age-matched male counterparts
- At the age of 55, the lifetime risk of cardiovascular disease for males and females is similar.
- Males are more likely to suffer from coronary artery disease as an initial event.
- Females are more likely to suffer from cerebrovascular disease or develop heart failure,
- The lower frequency of premature coronary artery disease (P-CAD) in premenopausal women compared to men is primarily due to the protective effect of female sex hormones.

Osadnik T, Pawlas N, Osadnik K, Bujak K, Góral M, Lejawa M, Fronczek M, Reguła R, Czarnecka H, Gawlita M, Strzelczyk JK, Gonera M, Gierlotka M, Poloński L, Gąsior M. High progesterone levels are associated with family history of premature coronary artery disease in young healthy adult men. PLoS One. 2019 Apr 15;14(4):e0215302. doi: 10.1371/journal.pone.0215302. PMID: 30986240; PMCID: PMC6464341.

Travison TG, O'Donnell CJ, Bhasin S, Massaro JM, Hoffmann U, Vasan RS, et al. Circulating Sex Steroids and Vascular Calcification in Community-Dwelling Men: The Framingham Heart Study. J Clin Endocrinol Metab. The Endocrine Society; 2016; 101: 2160–7. https://doi.org/10.1210/jc.2015-4299 PMID: 26930184

What is MHRT?

- Menopausal hormone replacement therapy is replacement of estrogen, progesterone and testosterone during post-menopausal years.
- If using MHRT, providers must consider risk factors for breast cancer, cardiovascular health, bone loss, and risk for dementia prior to onset of therapy.
- Using bio-identical forms of hormones and staying within physiologic levels may reduce risk for adverse events related to initiation of therapy.
- Time of initiation of therapy matters.
- Consideration of lifestyle changes to minimize risk of mortality.
- Taking a functional/holistic medical approach improves the likelihood of success.

Women’s Health Initiative Study (WHI)

- In the 1990's the Women’s Health Initiative (WHI), followed over 68,000 women ages 50-79.
- Women with a uterus were given oral conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) or placebo, and women without a uterus were given oral CEE alone or placebo.
- Bio-identical estradiol estrogen was not used.
- The goals of the study were to determine outcomes for these study groups.
- The goal was to investigate whether oral CEE with or without MPA was an effective preventive intervention for common health concerns such as coronary heart disease (CHD) and osteoporosis-related fractures in postmenopausal women.

NAMS. Menopause. 2022;29(7):767-794.

Conclusions from the WHI

- MHRT has been found to be safe, with rare CVD risks, especially when started in women < 60 years old or < 10 years from onset of menopause.
- The formulation of estrogen and progestogen therapy also affect CVD risk. Oral E2 or TD E2 and oral micronized progesterone (OMP) show even less venous thromboembolism (VTE) risk compared to oral CEEs + MPA.
- The health of the patient at the time of initiation of HRT is important
- In a sub analysis of women who were 50-59 years old and less than 10 years since menopause, risks were rare, and benefits were more significant.
- Increased VTE and stroke risk reported in the study is thought to be due to first-pass metabolism with oral delivery of hormones.

NAMS. Menopause. 2022; 29: 767-794.
Renoux C, et al. BMJ. 2010;340(jun03 4):c2519-c2519.

Effects of Oral Estrogen

Oral estrogen increases liver production of the following proteins:

- Blood Clotting Factors
- Sex hormone-binding globulin (SHBG)
- Thyroxine binding globulin (TBG)
- Corticosteroid binding globulin (CBG)

Estrogen May also influence:

- Higher production of high-density lipoproteins (HDL cholesterol);
- Lower production of LDL cholesterol through bile excretion.

Van Erpecum KJ, et al. Gastroenterology. 1991;100(2):482-488.
Goldštajn MŠ, et al. Arch Gynecol Obstetrics. 2022;307(6):1727-1745.
Walsh BW, et al. N Engl J Med. 1991;325(17):1196-1204.

Oral Estrogen Replacement Therapy

Oral estrogen contraindications: In addition to the general contraindications to estrogen therapy, oral estrogen **should not be considered** in women with a moderate to high calculated 10-year CVD risk (5 to 10%).

Evaluating CVD Risk In Females Contemplating MHT

10 YEAR CVD RISK	YEARS SINCE MENOPAUSE ONSET <10 YEARS
Low (<5%)	Menopausal Hormone Therapy is ok
Moderate (5%-10%)	Menopausal Hormone Therapy is ok (choose transdermal)
High (>10%)*	Avoid Menopausal Hormone Therapy

CVD risk is calculated by American College of Cardiology / American Heart Association Cardiovascular Risk Calculator. Methods to calculate risk and risk stratification vary among countries.

CVD Risk Calculator Link

High risk includes known myocardial infarction (MI), stroke, peripheral artery disease, etc.

Martin KA et. al. UpToDate, Waltham, MA.

Transdermal Estrogen and Oral Micronized Progesterone

Further considerations:

- Transdermal (TD) estrogen therapy has not demonstrated increased VTE and stroke risk, which is likely due to bypassing liver metabolism, but it has not been as well-studied as oral estrogens.
- Switching to transdermal estrogens and oral bioidentical progesterone reduces both the benefit on the cholesterol profile AND the thrombogenic risk.
- TD E2 and OMP combo show CVS benefits.

Goldstajn, et al, Renoux C, et al. BMJ. 2010;340(jun03 4):c2519-c2519.
Goldštajn MŠ, Mikuš M, Ferrari FA, Bosco M, Uccella S, Noventa M, Török P, Terzic S, Laganà AS, Garzon S. Effects of transdermal versus oral hormone replacement therapy in postmenopause: a systematic review. Arch Gynecol Obstet. 2023 Jun;307(6):1727-1745. doi: 10.1007/s00404-022-06647-5. Epub 2022 Jun 17. PMID: 35713694; PMCID: PMC10147786.

HRT Estradiol

Oral

The most studied form, used in the WHI study. First pass effect can be problematic for some patients. Most oral forms are synthetically derived.

Transdermal

Well-studied for effectiveness for some conditions very few published studies. This includes the estradiol patch.

Transmucosal

Could include oral, vaginal and rectal applications. Used less frequently. Variable local and systemic delivery.

Percutaneous

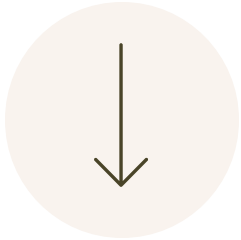
Pellet delivery system. Used in patients who want consistent delivery without having to pay daily attention to administration. Not much data on pellet therapy at this point.

Intramuscular

Less frequently used

https://www.pdr.net/drug-summary/?drugLabelId=2463

Considerations When Using Estrogen Therapy in PMP



Estradiol decreases CV morbidity and mortality.

Caution is advised with patients at high stroke or VTE risk for all estrogen therapy.

The health of the patient at the time of starting MHRT and their individual risk factors should be reviewed, and health status is very important.

E2 therapy has been found to support a healthy cardiovascular system, through maintaining vascular elasticity and endothelial function.

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test

Considerations When Using Estrogen Therapy in PMP cont:

Recently PM women, depending on CVD risk (those with subclinical ASCVD) may require higher serum E2 levels closer to the low luteal range (40-60pg/ml) or validated transdermal dried urine levels of roughly 1.8-2.0ng/mg of creatinine.

Older PMP women or women further from menopause onset probably do best with serum E2 levels just outside the PMP range (20 to <40pg/ml) or validated dried urine levels of 0.7 to 1.3 to 1.5ng/mg regardless of CVD risk.

Time since menopause and age >60 – we should consider risk stratification but not preclude MHRT initiation or continuation.

Ongoing risk stratification and follow up testing is a must for all women.

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test

Key Point About HRT

Remember to remind patients that estradiol is not indicated to prevent adverse cardiovascular outcomes. However, the data suggests that it will improve CVD outcomes and the earlier you initiate therapy, the greater the benefits.

Testosterone Production and Levels

Males produce about 3.7 (+/-) 2.2mg/day.

Published Labcorp serum ranges for total testosterone

- Age 40-49: 252-916 ng/dL
- Age 50-59: 215-878 ng/dL
- Age 60-69: 196-859 ng/dL
- Age 70-79: 156-819 ng/dL

- Ideal functional range for total testosterone in males is 500-1000 ng/dL
- In circulation, testosterone is loosely bound to albumin (~30–45%) and more strongly bound to SHBG (~65%) with a small fraction (1–3%) circulating as “free testosterone.”

Testing for testosterone by age

Testosterone Functions

- In males, most of the testosterone is produced in the gonads;
- Binds to androgen receptors (AR) throughout the body;
- Interacts with progesterone, estrogen and androgen receptor function;
- Regulates early brain development, cognitive function, social interactions, and sexual development and function;
- Stimulates connective tissue growth, maintenance and repair;
- As we'll see, it has important effects on the cardiovascular system.

Testosterone and the Effects on Cardiovascular Health

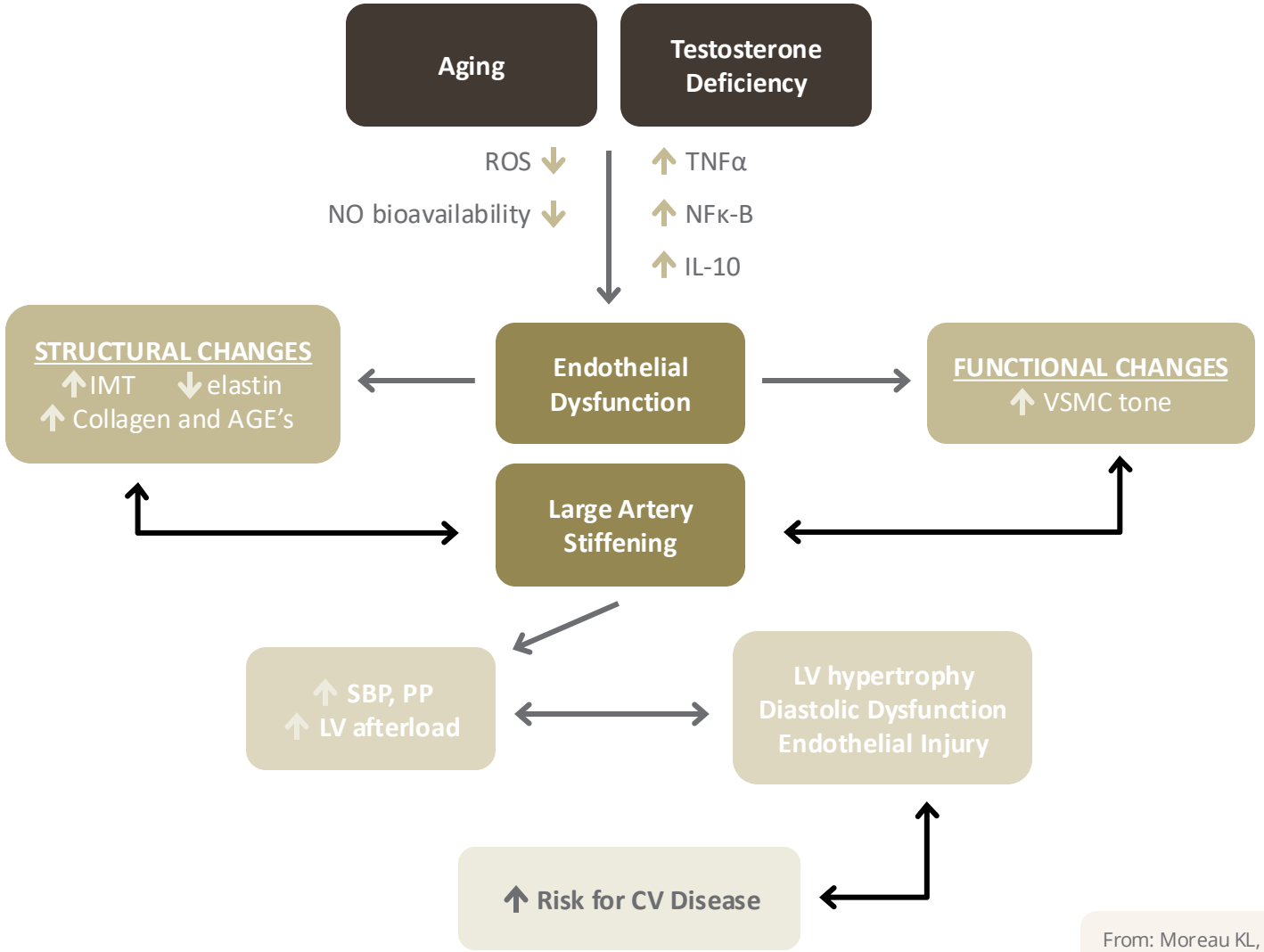
Endothelial function and inflammatory response

Blood Pressure

Insulin Resistance

Body Composition

Testosterone Deficiency – Vascular Mechanisms



Hypothesized mechanisms by which testosterone deficiency may contribute to vascular aging in women and men. AGEs, advanced glycation end products; CV, cardiovascular; IL-10, interleukin-10; IMT, intima-media thickness; LV, left ventricle; NFκ-B, nuclear factor κ-B; NO, nitric oxide; PP, pulse pressure; SBP, systolic blood pressure; ROS, reactive oxygen species; TNFα, tumor necrosis factor-α, VSMC, vascular smooth muscle cell

From: Moreau KL, Babcock MC, Hildreth KL. Sex differences in vascular aging in response to testosterone. Biol Sex Differ. 2020 Apr 15;11(1):18. doi: 10.1186/s13293-020-00294-8. PMID: 32295637; PMCID: PMC7161199.au KL et al

Endothelial Function and Inflammation

- Inflammation is the key driver during all stages of the atherosclerotic process,
- This is due to aging and other factors such as dyslipidemia, hypertension (angiotensin 2 release) cause generation of ROS and pro-inflammatory cytokines.

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test
Babcock MC, DuBose LE, Witten TL, Stauffer BL, Hildreth KL, Schwartz RS, Kohrt WM, Moreau KL. Oxidative Stress and Inflammation Are Associated With Age-Related Endothelial Dysfunction in Men With Low Testosterone. J Clin Endocrinol Metab. 2022 Jan 18;107(2):e500-e514. doi: 10.1210/clinem/dgab715. PMID: 34597384; PMCID: PMC8764347.

Testosterone and Endothelial Dysfunction

- Healthy middle-aged/older men with low testosterone appear to have greater age-associated endothelial dysfunction, related in part to greater oxidative stress and inflammation.

- Many studies have confirmed that low testosterone concentrations may contribute to accelerated vascular aging in men.
- Low testosterone leads to endothelial dysfunction.
- Testosterone modulates inflammatory cytokines IL1b, IL6, and TNF-a and reduces inflammation through stimulation of anti-inflammatory cytokines IL4 and IL10.
- Testosterone is an independent determinant of endothelial dysfunction (ED).

Babcock MC, DuBose LE, Witten TL, Stauffer BL, Hildreth KL, Schwartz RS, Kohrt WM, Moreau KL. Oxidative Stress and Inflammation Are Associated With Age-Related Endothelial Dysfunction in Men With Low Testosterone. J Clin Endocrinol Metab. 2022 Jan 18;107(2):e500-e514. doi: 10.1210/clinem/dgab715. PMID: 34597384; PMCID: PMC8764347.

CV and Renal Effects **Mediated** by Androgens

Androgen	Cell/tissue	Effect	Reference
Testosterone	Heart	↑ β1-Adrenoceptor, ↑ androgen receptor, ↑ Na^+/Ca^{2+} exchanger, ↑ L-type calcium channel	Golden et al. (2002)
Testosterone	**Cultured VSMCs**	↑ ROS	Chignalia et al. (2012)
Testosterone/dihydrotestosterone	**Human endothelial cells, blood vessels**	↑ ERK ½, ↑ PI3K, ↑ **eNOS, ↑ NO**	Goglia et al. (2010), Miller and Mulvagh (2007)
Testosterone	Brachial artery	↑ FMD	Sader et al. (2001)
Testosterone	Human internal mammary artery	↑ BK_{Ca} activation	Yildiz et al. (2005)
Testosterone	Rat epididymis, thoracic aortae, and mesenteric arteries	↑ COX-1 and COX-2	Cheuk et al. (2000), Song et al. (2004)
Testosterone	Rat thoracic aorta	↑ Kv channels	Zhou et al. (2008)
Testosterone	**Endothelial cells**	↑ EPCs	Foresta et al. (2008)
Dihydrotestosterone	Kidney	↑ **Sodium and water reabsorption**	Quan et al. (2004)
Dihydrotestosterone	Mesangial cells	↑ ROS	Reckelhoff et al. (2005)

Cardiovascular and renal effects mediated by androgens.
FMD, brachial artery flow-mediated dilatation; COX, cyclooxygenase; eNOS, endothelial nitric oxide synthases; EPC, endothelial progenitor cells; ERK 1/2, extracellular-signal-regulated kinase (ERK) 1/2; PI3K, phosphatidylinositol 3-OH kinase; ROS, reactive oxygen species; NO, nitric oxide; VSMC, vascular smooth muscle cell.

Testosterone and Blood Pressure

- Small studies show that higher testosterone levels are correlated to higher blood pressure.
- Androgens have various effects on both the vascular and renal tissue which result in hyper, hypo and normotensive effects.
- Hypogonadism is associated with lower nitric oxide output leading to less vasodilation and higher blood pressure.
- Androgens regulate sodium and water balance via the renin-angiotensin system.

Leening M.J., Ferket, B.S., Steyerberg, E.W. et al. (2014) Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population-based cohort study *BMJ* 349, g5992

Testosterone and Blood Pressure

Article published in the Journal of American Heart Association:

Association of Serum Testosterone and Luteinizing Hormone With Blood Pressure and Risk of Cardiovascular Disease in Middle-Aged and Elderly Men

- This was a multicenter, population-based, cross-sectional study of 6296 men conducted between 2013 and 2016.
- **Blood pressure** and plasma levels of **total testosterone**, **sex hormone–binding globulin**, **luteinizing hormone**, and **free testosterone** were determined in men in a multistage random, cluster sampling in 6 provinces of China.
- There were 5786 Chinese men (mean [SD] age 55.0 [10.1] years) included after exclusion criteria were applied; 37.2% (2150) of them were diagnosed with hypertension.

Results:

- **Free and total testosterone, and sex hormone–binding globulin were inversely associated with the prevalence of hypertension**.
- For men ages 65 and older, or for those with a BMI ≥24 they saw a negative impact on the inverse correlation between testosterone levels and hypertension. In addition, smoking and family history of hypertension strengthened the correlation.
- In participants with grade 2 hypertension, total testosterone was positively associated with the presence of stroke, and lute inizing hormone was also positively correlated with cardiovascular and cerebrovascular diseases

Qu, Mengyuan PhD, Feng, Chenzhao MD, Wang, Xiaotong PhD, Gu, Yiqun MD, Shang, Xuejun MD, PhD, Zhou, Yuanzhong PhD, Xiong, Chengliang MD, and Li, Honggang PhD *Association of Serum Testosterone and Luteinizing Hormone With Blood Pressure and Risk of Cardiovascular Disease in Middle-Aged and Elderly Men* https://orcid.org/0000-0002-6666-8527 Journal of the American Heart Association Volume 10, Number 7 https://doi.org/10.1161/JAHA.120.019559.

Testosterone and Blood Pressure Conclusion

1. Lower total testosterone could be a promising risk marker for prevalent hypertension.
2. Both low and high levels of testosterone are associated with greater cardiovascular risk.
3. Primary hypogonadism may be a risk marker for major cardiovascular diseases in men with severe hypertension.

Testosterone and Blood Pressure

If you are a male, it is important to know
if your testosterone levels are normal for age,
especially if you're hypertensive.

Testosterone and Insulin

What do we know?

- Testosterone acts on the androgen receptor (AR) in β cells to enhance glucose-stimulated insulin secretion (GSIS) by potentiating the action of glucagon-like peptide-1 (GLP1).
- Low serum testosterone levels are associated with an adverse metabolic profile and can independently predict the increase in insulin resistance.
- However, testosterone administration in men with low or low-normal testosterone levels does not improve insulin sensitivity.
- The molecular basis of functional deficiency in androgen receptor signaling and the pathophysiology of developing obesity and insulin resistance remain unclear.

Huang Grace, Karol M Pencina, Zhuoying Li, Shehzad Basaria, Shalender Bhasin, Thomas G Travison, Thomas W Storer, S Mitchell Harman, Panayiotis Tsitouras, Long-Term Testosterone Administration on Insulin Sensitivity in Older Men With Low or Low-Normal Testosterone Levels, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 4, April 2018, Pages 1678–1685, https://doi.org/10.1210/jc.2017-02545

Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care. 2005 Jul;28(7):1636-42. doi: 10.2337/diacare.28.7.1636. PMID: 15983313.

Ottarsdottir K, Nilsson AG, Hellgren M, Lindblad U, Daka B. The association between serum testosterone and insulin resistance: a longitudinal study.Endocr Connect. 2018 Dec 1;7(12):1491-1500. doi: 10.1530/EC-18-0480. PMID: 30592706; PMCID: PMC6311464.

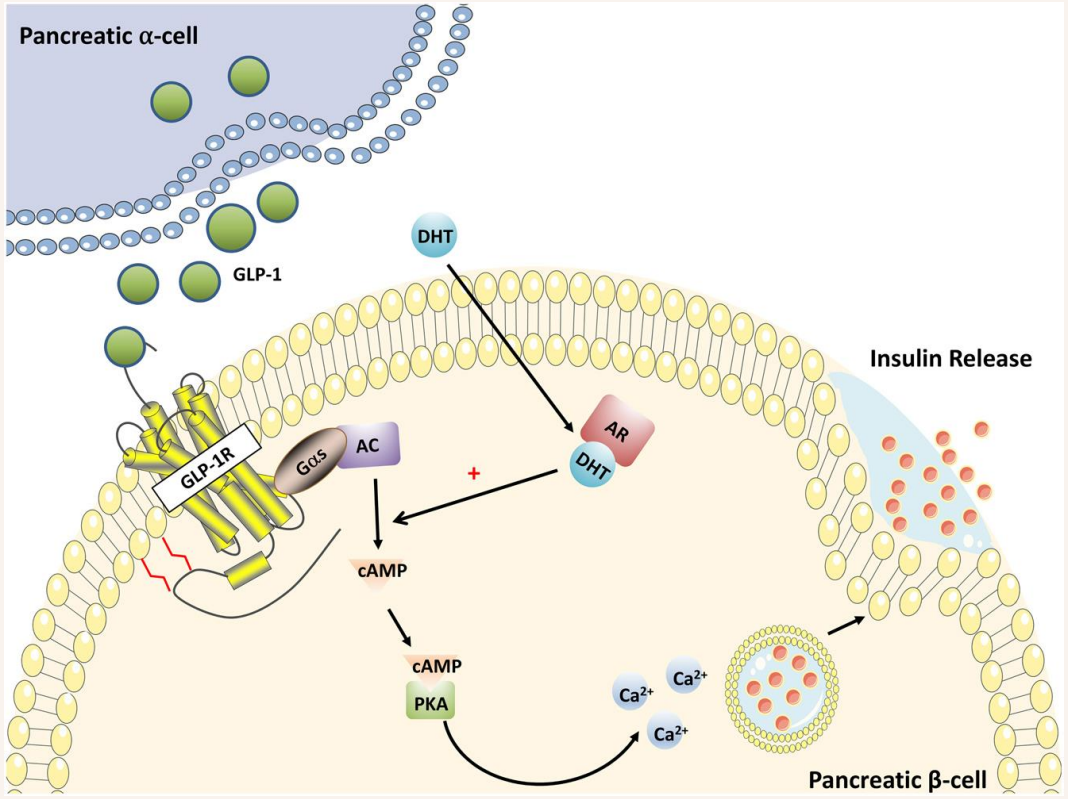


Figure 1: Mechanism of testosterone insulinotropic action in β cell. Testosterone action on an extranuclear AR in β cell amplifies the insulinotropic action of islet-derived GLP-1 by increasing cAMP production and PKA activation.

Xu W, Morford J, Mauvais-Jarvis F. Emerging role of testosterone in pancreatic β cell function and insulin secretion. *Journal of Endocrinology. 2019;240(3):R97-R105. doi:10.1530/JOE-18-0573*

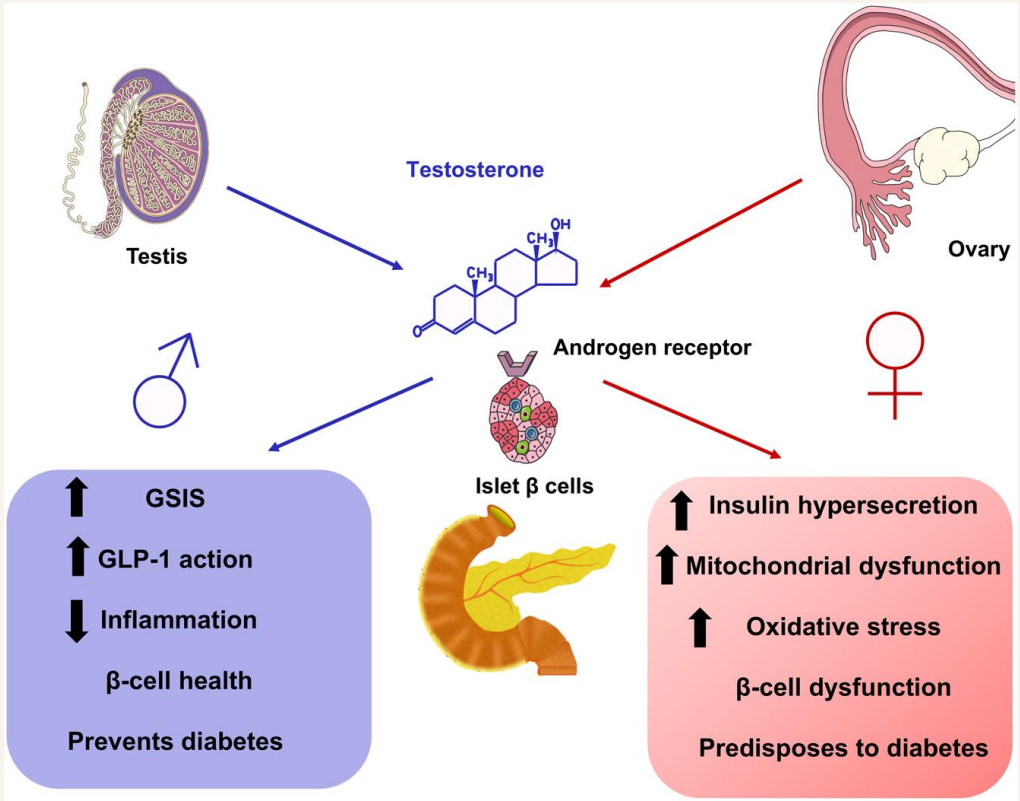


Figure 3: Summary of the bidirectional modulation of β cell function in males and females. In males, testosterone action in β cells increases GSIS by enhancing GLP-1 insulinotropic action, prevents inflammation and promotes β cell health. In females, testosterone excess in β cells promotes insulin hypersecretion, mitochondrial dysfunction, oxidative stress and predisposes to β cell dysfunction and failure.

Xu W, Morford J, Mauvais-Jarvis F. Emerging role of testosterone in pancreatic β cell function and insulin secretion. *Journal of Endocrinology. 2019;240(3):R97-R105. doi:10.1530/JOE-18-0573*

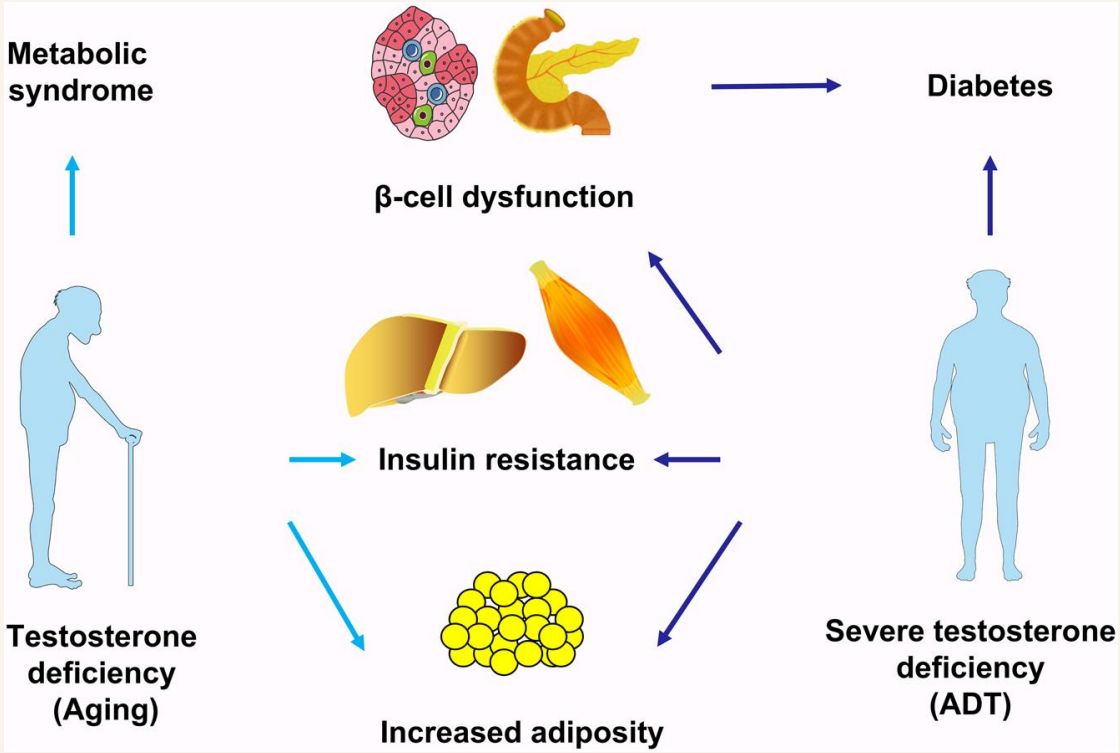


Figure 2: Mechanism of diabetes in men with androgen deficiency. Moderate androgen deficiency during aging predisposes men to increased adiposity and insulin resistance leading to metabolic syndrome. During severe androgen deficiency such as androgen depletion therapy (ADT), the additional β cell dysfunction predisposes to diabetes.

Xu W, Morford J, Mauvais-Jarvis F. Emerging role of testosterone in pancreatic β cell function and insulin secretion. *Journal of Endocrinology. 2019;240(3):R97-R105. doi:10.1530/JOE-18-0573*

Testosterone and Body Composition Study

In this study, Vermeulen looked at 372 males ages >20-85 and measured body fat by impedance, total and free testosterone levels in plasma, and insulin. Using multiple regression analyses found that:

Total testosterone decreased from **598**+/-188 (SD) ng/dl in the young controls to **453**+/-161 ng/dl in the elderly group, free testosterone decreased from **15.35**+/-4.10 to **8.38**+/-2.51 ng/dl. **Fat-free mass decreased by 18.9%.** In a subgroup of 57 men aged 70-80 years, testosterone levels correlated negatively with percentage body fat (r=-0.57), abdominal fat (r=-0.56) and plasma insulin levels (r=-0.40).

Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest. 1999;22(5 Suppl):110-6. PMID: 10442580.

Vermeulen Conclusions:

- BMI and age were independent determinants of testosterone levels.
- In elderly men with low T prior to treatment there was an **increase in lean body mass and in mid-arm circumference** and a **decrease in waist-to-hip ratio;**
- Aging is accompanied by an important **increase in fat mass** and a decrease in **lean body mass**.
- Age-associated **testosterone is a determinant of the changes in body composition**

Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest. 1999;22(5 Suppl):110-6. PMID: 10442580.

Goodale et al (TRT)

In a summary of research through 2017 Goodale et al concluded:

- After age 40, decline in testosterone is associated with an increased risk in all-cause mortality.
- Low T in men may increase their risk of developing coronary artery disease (CAD), metabolic syndrome, and type 2 diabetes.
- There are no large long-term, placebo-controlled, randomized clinical trials to provide definitive conclusions about TRT and CVD risk.

Goodale T, Sadhu A, Petak S, Robbins R. Testosterone and the Heart. Methodist Debakey Cardiovasc J. 2017 Apr-Jun;13(2):68-72. doi: 10.14797/mdcj-13-2-68. PMID: 28740585; PMCID: PMC5512682.

Goodale et al cont:

Testosterone replacement therapy (TRT) improves:

Myocardial ischemia in men with CAD

Exercise capacity in patients with CHF

Serum glucose levels, HbA1c, and insulin resistance in men with diabetes and prediabetes

Goodale T, Sadhu A, Petak S, Robbins R. Testosterone and the Heart. Methodist Debakey Cardiovasc J. 2017 Apr-Jun;13(2):68-72. doi: 10.14797/mdcj-13-2-68. PMID: 28740585; PMCID: PMC5512682.

Testosterone Replacement Therapy (TRT)

Forms of Delivery:

Oral

FDA approved for men but not for women

IM Injectable

Most frequently used form for males, short and long-acting preparations depending on what patient needs.

Sub Q Injectable

Once weekly injection

Transdermal gels, creams and pellets

Most frequently used form for females. Daily dosing closely mimics physiology.

Pellets

Increasing in popularity with steady delivery system

Intranasal

Daily use reliably raises levels within physiologic norms.

https://www.pdr.net/drug-summary/?drugLabelId=Depo-Testosterone-testosterone-cypionate-1870

TRT Benefits

TRT may produce a wide **range of benefits** for men with hypogonadism:

- Libido and Sexual Function
- Bone Density
- Muscle mass
- Body Composition
- Mood
- Erythropoiesis
- Cognition
- Overall Quality of Life

l-Zoubi RM, Yassin AA, Alwani M, Al-Qudimat A, Aboumarzouk OM, Zarour A, Al Ansari A. A systematic review on the latest developments in testosterone therapy: Innovations, advances, and paradigm shifts. Arab J Urol. 2021 Aug 8;19(3):370-375. doi: 10.1080/2090598X.2021.1959260. PMID: 34552788; PMCID: PMC8451690. et al

Systematic Review of 393 studies

- Several studies showed that in hypogonadal men with Type II DM significantly improved on TRT.
- Their observation indicated that testosterone administration improves body weight and metabolic factors in men with hypogonadism, but withdrawal of testosterone reverses these beneficial effects, which appear again when TRT is resumed.
- Most of these studies found that increased testosterone even over the long term does not affect PSA or its effect to be negligible.
- Among the available treatments, only transdermal gel delivery and long-acting injectable testosterone undecanoate provide pharmacokinetic behavior that gives a steady state level within a physiological range.

Al-Zoubi RM, Yassin AA, Alwani M, Al-Qudimat A, Aboumarzouk OM, Zarour A, Al Ansari A. A systematic review on the latest developments in testosterone therapy: Innovations, advances, and paradigm shifts. Arab J Urol. 2021 Aug 8;19(3):370-375. doi: 10.1080/2090598X.2021.1959260. PMID: 34552788; PMCID: PMC8451690.

Risks and Monitoring Strategies for TRT

The goal of this review was to highlight the risks and summarize the current literature on safety of TRT.

Potential risk	Suggested monitoring strategies
Cardiovascular disease	Baseline blood pressure checks and repeats at 3 and 6 months, then annually thereafter. For high-risk patients, consider cardiology referral
Erythrocytosis	Obtain baseline HCT then at 3 and 6 months, then annually thereafter. If HCT is >54%, stop TRT and restart at lower dose[69]
Fluid retention	Patient history and physical exam. Stop TRT if CHF is uncontrolled[69]
BPH	Patient questionnaire and history. Refer to urologist if: IPSS+above 19 and stop TRT[69]
Prostate cancer	Obtain baseline DRE*and serum PSA then again at 3 and 6 months. Continual monitoring depending on the patient's race/age.[69] Refer to urologist if PSA rises over 4 ng/mL Abnormal DRE If PSA rises more than 1 ng/mL in the first 6 months of TRT or by more than 0.4 ng/mL/year thereafter[34] If PSA velocity is more than 0.4 ng/mL/year[69]
Acne	Patient history and physical exam. Dose adjustment and/or referral to dermatology
Hepatoxicity	Patient history and physical exam. Liver function tests are unnecessary in gel, pellet and IM preparations
Infertility	Patient history and physical exam. Reconsider alternative strategies if patient desires to father children
OSA	Baseline patient history and physical exam and again between 3 and 6 months.[20] Consider alternate causes of OSA[43]
Gynecomastia/ breast cancer	Exclude other etiologies with patient history and physical exam. Review all medications. Complete hormone evaluation may be necessary. Medications implicated to cause gynecomastia[66] Anti-androgens-finasteride, bicalutamide Antibiotics-isoniazid, ketoconazole, metronidazole Antihypertensives-amlodipine, captopril, diltiazem, verapamil, nifedipine GI agents-cimetidine, omeprazole Psychiatric-diazepam, haloperidol, tricyclic antidepressants

TRT=Testosterone replacement therapy, HCT=Hematocrit, BPH=Benign prostatic hyperplasia, DRE=Digital rectal examination, CHF=Congestive heart failure, IPSS=International prostate symptom score, PSA=Prostate-specific antigen, IM=Intramuscular, OSA=Obstructive sleep apnea, GI=Gastrointestinal,*Digital rectal examination,†International prostate symptom score

Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. Indian J Urol. 2014 Jan;30(1):2-7. doi: 10.4103/0970-1591.124197. PMID: 24497673; PMCID: PMC3897047.

Oral TRT

Starting oral testosterone treatment is associated with an increased risk of venous thromboembolism, which peaks within six months and declines thereafter.

Martinez et al Testosterone treatment and risk of venous thromboembolism: population-based case-control study *BMJ* 2016; 355 doi: https://doi.org/10.1136/bmj.i5968 (Published 30 November 2016) *BMJ* 2016;355:i5968

TRT – Dose Matters

Higher doses or doses leading to high serum levels are associated with:

1. Increased risk of blood clots and stroke due to risk of polycythemia - monitor CBC.
2. Elevated BP and arterial stiffness - monitor blood pressure.
3. High doses can cause high cholesterol: monitor cholesterol.
4. Men with a history of CVD may get worse with TRT.

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones; Connecting Cardiovascular Disease, Inflammation & Hormones | DUTCH Webinar

Therapeutic Goals in Males:

1. Total Testosterone levels in serum >500 to < 1000ng/dl
2. Serum E2 levels between 20-40pg/ml
3. Remember that serum testing is the gold standard

Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test

58 y/o Male – Low Androgens

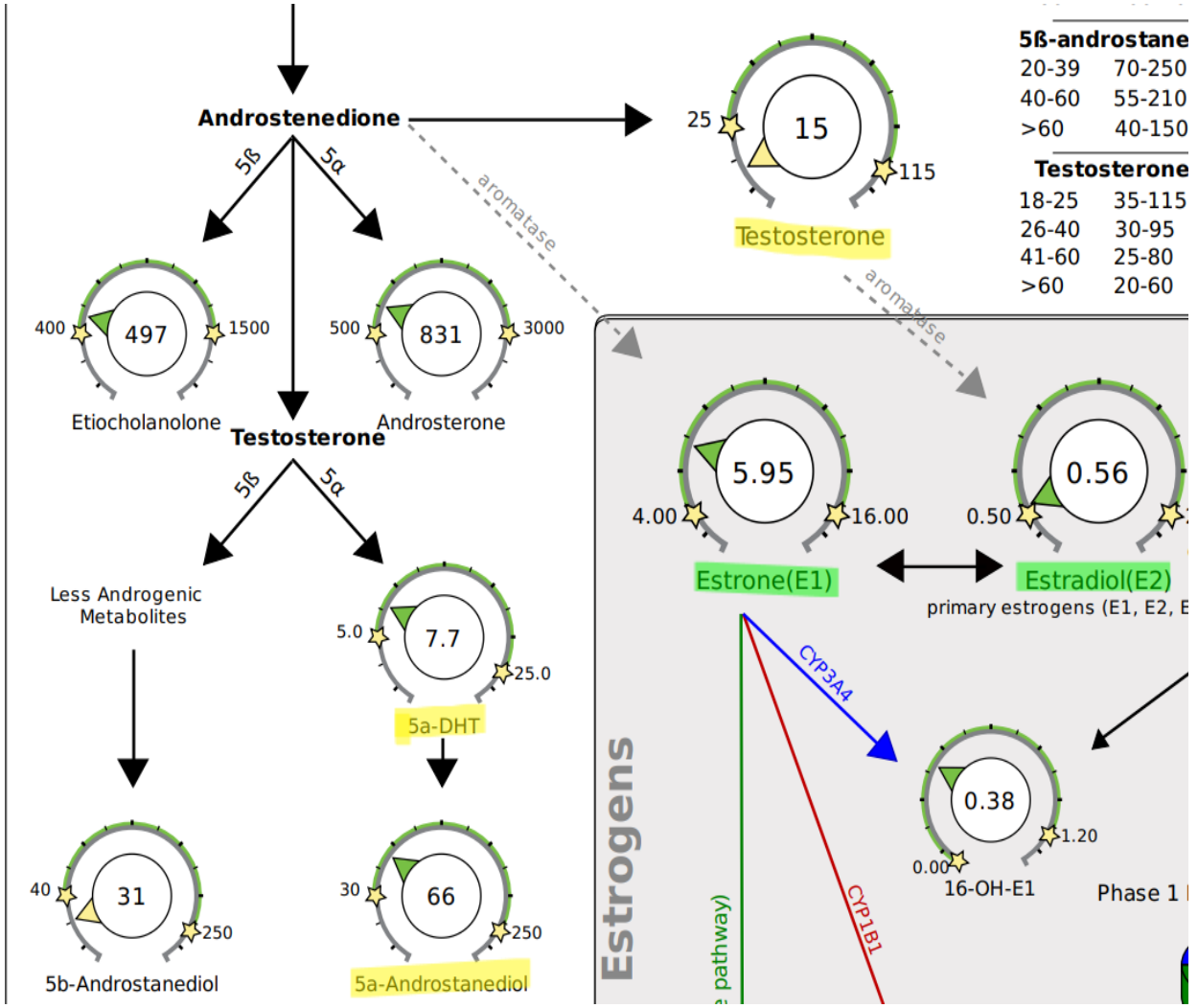
Age-Dependent Ranges

Age	DHEA-S
20-39	150-1500
40-60	60-800
>60	30-300

Etiocholanolone		Androsterone	
20-39	800-1500	20-39	1500-3000
40-60	600-1200	40-60	1000-2000
>60	400-1000	>60	500-1000

5ß-androstanediol		5α-androstanediol	
20-39	70-250	20-39	60-250
40-60	55-210	40-60	50-180
>60	40-150	>60	30-130

Testosterone		5α-DHT	
18-25	35-115	20-39	9-25
26-40	30-95	40-60	7-20
41-60	25-80	>60	5-16
>60	20-60		



58 y/o Male – High Androgens

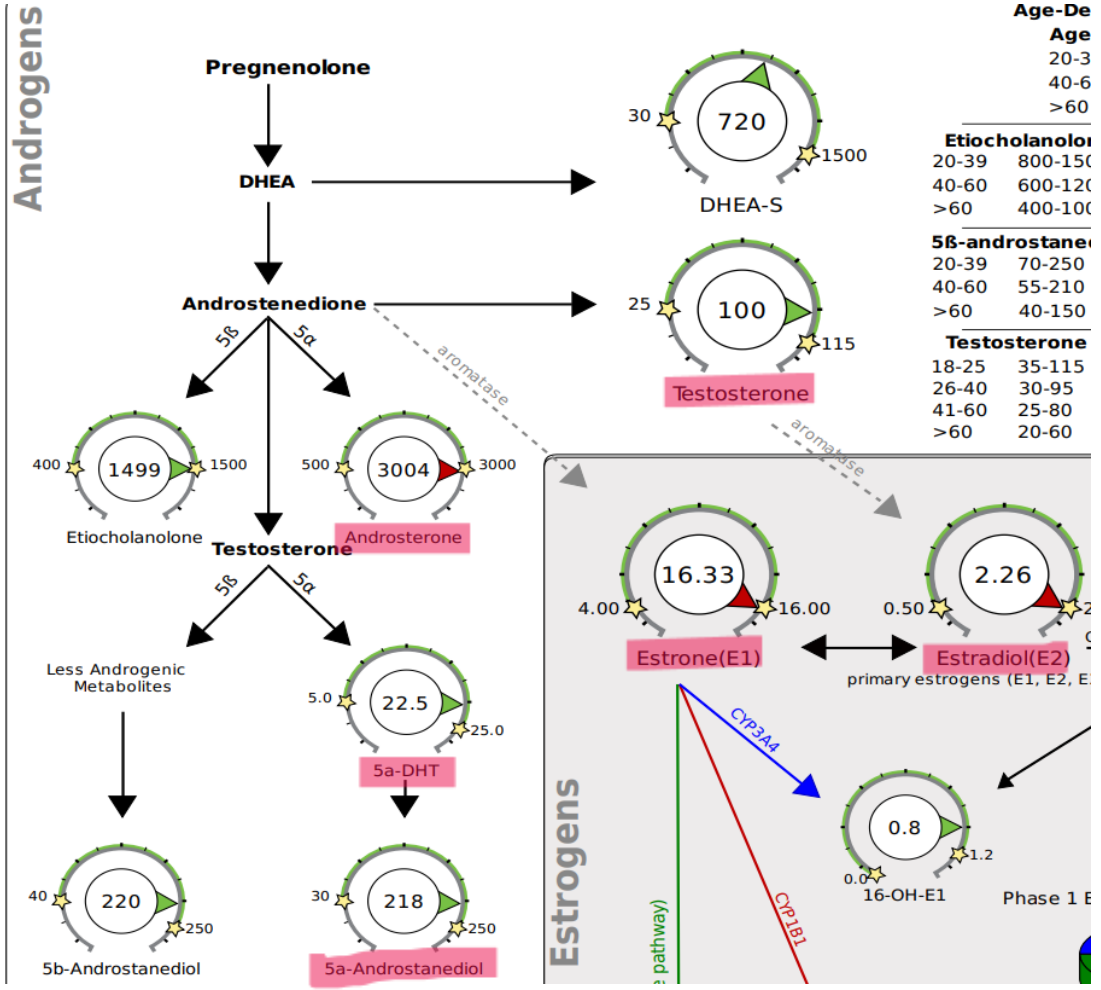
Age-Dependent Ranges

Age	DHEA-S
20-39	150-1500
40-60	60-800
>60	30-300

Etiocholanolone		Androsterone	
20-39	800-1500	20-39	1500-3000
40-60	600-1200	40-60	1000-2000
>60	400-1000	>60	500-1000

5ß-androstanediol		5α-androstanediol	
20-39	70-250	20-39	60-250
40-60	55-210	40-60	50-180
>60	40-150	>60	30-130

Testosterone		5α-DHT	
18-25	35-115	20-39	9-25
26-40	30-95	40-60	7-20
41-60	25-80	>60	5-16
>60	20-60		



Putting it all Together

1. Estrogen and testosterone are important for many reasons outside of their role in sexual function.
2. There is a plethora of evidence that suggests inflammation is at the base of cardiovascular disease and that aging in females usually concomitant with the menopausal state is associated with increased inflammation and risk for CVD.
3. The data suggests estrogen replacement therapy will improve CVD outcomes and the earlier you initiate therapy, the greater the benefits.
4. Testosterone levels decline with age and the risk for CVD increases with age.
5. Testosterone therapy supplemented within normal ranges (500-1000ng/dl in serum) improves many of the metabolic conditions associated with and causative in the process of CVD.

Introduction to HRT

Sign up to get access to Introduction to Hormone Replacement Therapy!

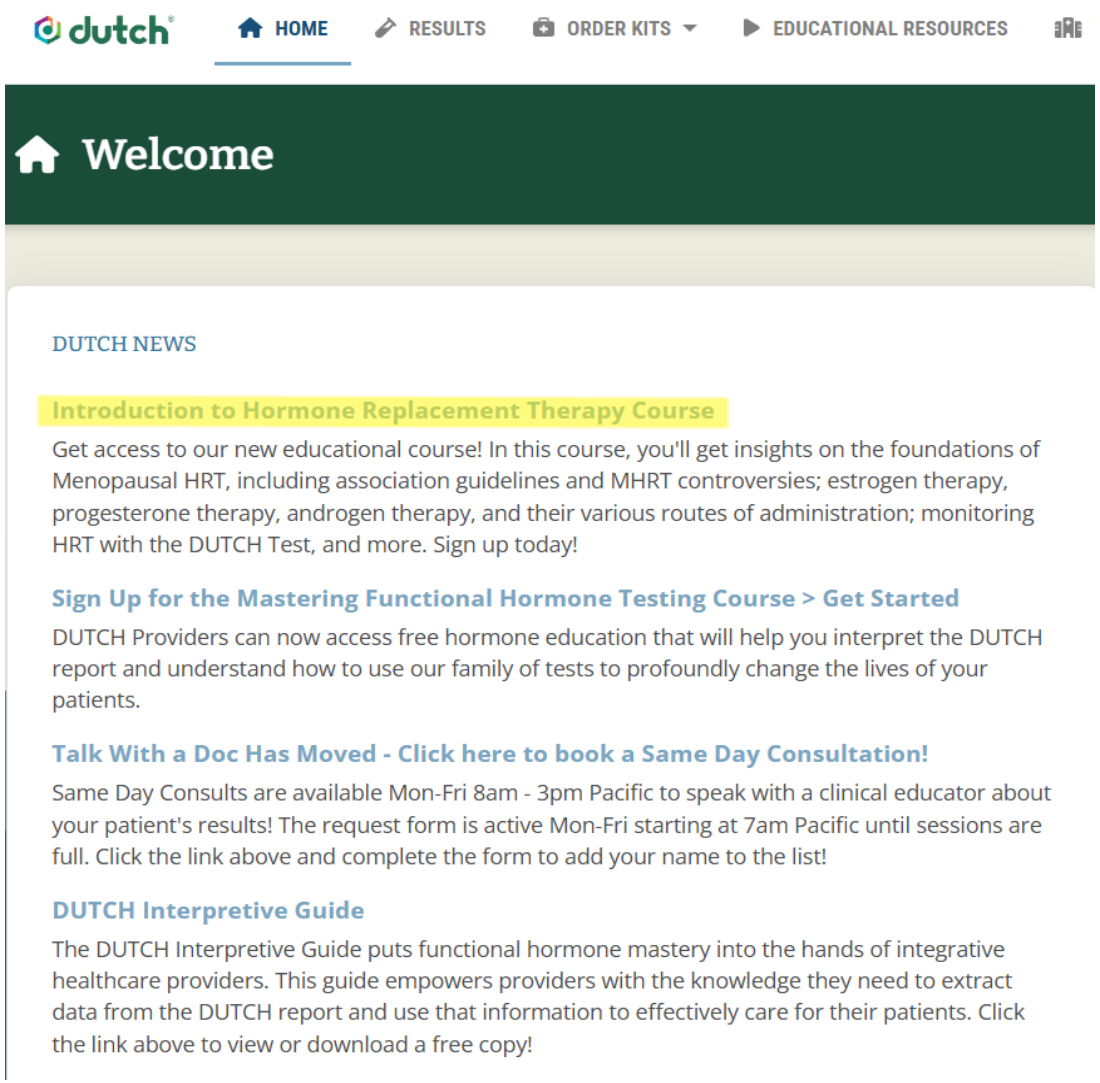
In this course, you'll get insights on:

- The foundations of Menopausal HRT, including association guidelines and MHRT controversies
- Estrogen therapy, progesterone therapy, androgen therapy, and their various routes of administration
- Proper baseline evaluation and assessment
- How to select the best prescription and dosage for your patients
- Monitoring HRT with the DUTCH Test
- **Free for registered DUTCH Providers!**

Introduction to HRT

Where to find this?

- It is located in your portal at www.dutchtest.com
- You may access it after you sign up as a provider.



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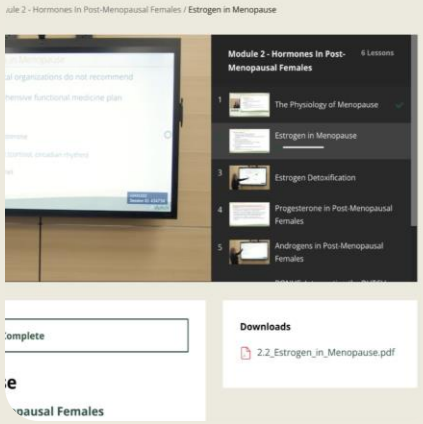
DUTCH Interpretive Guide

Mastering Functional Hormone Testing Course



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References:

- 2024-Statistics-At-A-Glance, Overview of established risk factors for cardiovascular disease - UpToDateance-final_2024.pdf
- Alemany M. Estrogens and the regulation of glucose metabolism. World J Diabetes. 2021 Oct 15;12(10):1622-1654. doi: 10.4239/wjd.v12.i10.1622. PMID: 34754368; PMCID: PMC8554369.
- Al-Zoubi RM, Yassin AA, Alwani M, Al-Qudimat A, Aboumarzouk OM, Zarour A, Al Ansari A. A systematic review on the latest developments in testosterone therapy: Innovations, advances, and paradigm shifts. Arab J Urol. 2021 Aug 8;19(3):370-375. doi: 10.1080/2090598X.2021.1959260. PMID: 34552788; PMCID: PMC8451690.
- Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, et al. (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291: 1701–1712. [DOI] [PubMed] [Google Scholar]
- Ashraf MS, Vongpatanasin W. Estrogen and hypertension. Curr Hypertens Rep. 2006, Oct;8(5):368-76. doi: 10.1007/s11906-006-0080-1. PMID.
- Babcock MC, DuBose LE, Witten TL, Stauffer BL, Hildreth KL, Schwartz RS, Kohrt WM, Moreau KL. Oxidative Stress and Inflammation Are Associated With Age-Related Endothelial Dysfunction in Men With Low Testosterone. J Clin Endocrinol Metab. 2022 Jan 18;107(2):e500-e514. doi: 10.1210/clinem/dgab715. PMID: 34597384; PMCID: PMC8764347.
- Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas. 2017 Sep;103:45-53. doi: 10.1016/j.maturitas.2017.06.025. Epub 2017 Jun 23. PMID: 28778332.
- Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones - DUTCH Test
- Colldén et al, Dietary Progesterone Contributes to Intratissue Levels of Progesterone in Male Mice, Endocrinology, Volume 164, Issue 8, August 2023, bqad103, https://doi.org/10.1210/endocr/bqad103
- Cooke PS, Nanjappa MK, Ko C, et al. Estrogens in Male Physiology. Physiol. Rev. 2017;97:995–1043. doi: 10.1152/physrev.00018.2016. [DOI] [PMC free article] [PubMed] [Google Scholar]
- Delgado BJ, Lopez-Ojeda W. Estrogen. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-Available from: https://www.ncbi.nlm.nih.gov/books/NBK538260/

References:

- Delgado BJ, Lopez-Ojeda W. Estrogen. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-Available from: https://www.ncbi.nlm.nih.gov/books/NBK538260/
- De Paoli, Monica et al. The Role of Estrogen in Insulin Resistance. The American Journal of Pathology, Volume 191, Issue 9, 1490 – 1498
- Goldštajn MŠ, Mikuš M, Ferrari FA, Bosco M, Uccella S, Noventa M, Török P, Terzic S, Laganà AS, Garzon S. Effects of transdermal versus oral hormone replacement therapy in postmenopause: a systematic review. Arch Gynecol Obstet. 2023 Jun;307(6):1727-1745. doi: 10.1007/s00404-022-06647-5. Epub 2022 Jun 17. PMID: 35713694; PMCID: PMC10147786.
- Goldštajn MŠ, et al. Arch Gynecol Obstetrics. 2022;307(6):1727-1745.
- Goodale T, Sadhu A, Petak S, Robbins R. Testosterone and the Heart. Methodist Debakey Cardiovasc J. 2017 Apr-Jun;13(2):68-72. doi: 10.14797/mdcj-13-2-68. PMID: 28740585; PMCID: PMC5512682.
- Gorgels WJ, Graaf Y, Blankenstein MA, Collette HJ, Erkelens DW, et al. (1997) Urinary sex hormone excretions in premenopausal women and coronary heart disease risk: a nested case-referent study in the DOM-cohort. J Clin Epidemiol 50: 275–281. [DOI] [PubMed] [Google Scholar]
- Gupte AA, Pownall HJ, Hamilton DJ. Estrogen: an emerging regulator of insulin action and mitochondrial function. J Diabetes Res. 2015;2015:916585. doi: 10.1155/2015/916585. Epub 2015 Mar 26. PMID: 25883987; PMCID: PMC4391691.
- Hayslett, John P, A new role for progesterone: An agonist for mineralocorticoid receptor activation and pregnancy-related hypertension, American Journal of Kidney Diseases, Volume 38, Issue 4, 893 – 895
- Hetemäki Natalia, Tomi S. Mikkola, Matti J. Tikkanen, Feng Wang, Esa Hämäläinen, Ursula Turpeinen, Mikko Haanpää, Veera Vihma, Hanna Savolainen-Peltonen, Adipose tissue estrogen production and metabolism in premenopausal women,, The Journal of Steroid Biochemistry and Molecular Biology, Volume 209, 2021,105849, ISSN 0960-0760,
- Huang Grace, Karol M Pencina, Zhuoying Li, Shehzad Basaria, Shalender Bhasin, Thomas G Travison, Thomas W Storer, S Mitchell Harman, Panayiotis Tsitouras, Long-Term Testosterone Administration on Insulin Sensitivity in Older Men With Low or Low-Normal Testosterone Levels, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 4, April 2018, Pages 1678–1685, https://doi.org/10.1210/jc.2017-02545

References:

- Hulley S, Bush T, Furberg C, Herrington D, Riggs B, et al. (1998) Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Journal of the American Medical Association 280: 605–613. [DOI] [PubMed] [Google Scholar]
- Kaur H, Werstuck GH. The Effect of Testosterone on Cardiovascular Disease and Cardiovascular Risk Factors in Men: A Review of Clinical and Preclinical Data. CJC Open. 2021 May 17;3(10):1238-1248. doi: 10.1016/j.cjco.2021.05.007. PMID: 34888506; PMCID: PMC8636244.
- Kharazmi E, Dossus L, Rohrmann S, Kaaks R (2010) Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). Heart doi: –10.1136/hrt.2010.202226: 1–6 [DOI] [PubMed] [Google Scholar].
- Kuiper GGJM, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors and α and β. Endocrinology. 1997;138:863–870. doi: 10.1210/endo.138.3.4979. [DOI] [PubMed] [Google Scholar]
- Leening M.J., Ferket, B.S., Steyerberg, E.W. et al. (2014) Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population-based cohort study BMJ349, g5992
- Lopes RA, Neves KB, Carneiro FS, Tostes RC. Testosterone and vascular function in aging. Front Physiol. 2012 Apr 10;3:89. doi: 10.3389/fphys.2012.00089. PMID: 22514541; PMCID: PMC3322529.
- Martinez et al Testosterone treatment and risk of venous thromboembolism: population-based case-control study BMJ 2016; 355 doi: https://doi.org/10.1136/bmj.i5968 (Published 30 November 2016) BMJ 2016;355:i5968
- Mair KM, Gaw R, MacLean MR. Obesity, estrogens and adipose tissue dysfunction - implications for pulmonary arterial hypertension. Pulm Circ. 2020 Sep 18;10(3):2045894020952019. doi: 10.1177/2045894020952023. PMID: 32999709; PMCID: PMC7506791.
- Moreau KL, Babcock MC, Hildreth KL. Sex differences in vascular aging in response to testosterone. Biol Sex Differ. 2020 Apr 15;11(1):18. doi: 10.1186/s13293-020-00294-8. PMID: 32295637; PMCID: PMC7161199.
- NAMS. Menopause. 2022; 29: 767-794.

References:

- Ottarsdottir K, Nilsson AG, Hellgren M, Lindblad U, Daka B. The association between serum testosterone and insulin resistance: a longitudinal study. Endocr Connect. 2018 Dec 1;7(12):1491-1500. doi: 10.1530/EC-18-0480. PMID: 30592706; PMCID: PMC6311464.
- Oettel M, Mukhopadhyay AK. Progesterone: the forgotten hormone in men? Aging Male. 2004 Sep;7(3):236-57. doi: 10.1080/13685530400004199. PMID: 15669543.
- Osadnik T, Pawlas N, Osadnik K, Bujak K, Góral M, Lejawa M, Fronczek M, Reguła R, Czarnecka H, Gawlita M, Strzelczyk JK, Gonera M, Gierlotka M, Poloński L, Gąsior M. High progesterone levels are associated with family history of premature coronary artery disease in young healthy adult men. PLoS One. 2019 Apr 15;14(4):e0215302. doi: 10.1371/journal.pone.0215302. PMID: 30986240; PMCID: PMC6464341.
- Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. Indian J Urol. 2014 Jan;30(1):2-7. doi: 10.4103/0970-1591.124197. PMID: 24497673; PMCID: PMC3897047.
- Parish SJ, Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Womens Health (Larchmt). 2021 Apr;30(4):474-491. doi: 10.1089/jwh.2021.29037. Epub 2021 Apr 1. PMID: 33797277; PMCID: PMC8064950.
- Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care. 2005 Jul;28(7):1636-42. doi: 10.2337/diacare.28.7.1636. PMID: 15983313.
- Prior JC, Elliott TG, Norman E, Stajic V, Hitchcock CL. Progesterone therapy, endothelial function and cardiovascular risk factors: a 3-month randomized, placebo-controlled trial in healthy early postmenopausal women. PLoS One. 2014 Jan 21;9(1):e84698. doi: 10.1371/journal.pone.0084698. PMID: 24465425; PMCID: PMC3897380.

References:

- Qu, Mengyuan PhD, Feng, Chenzhao MD, Wang, Xiaotong PhD, Gu, Yiqun MD, Shang, Xuejun MD, PhD, Zhou, Yuanzhong PhD, Xiong, Chengliang MD, and Li, Honggang PhD *Association of Serum Testosterone and Luteinizing Hormone With Blood Pressure and Risk of Cardiovascular Disease in Middle-Aged and Elderly Men* https://orcid.org/0000-0002-6666-8527 Journal of the American Heart Association Volume 10, Number 7 https://doi.org/10.1161/JAHA.120.019559.
- Renoux C, et al. BMJ. 2010;340(jun03 4):c2519-c2519.
- Rochira V, Carani C. Estrogens, Male Reproduction and Beyond. [Updated 2023 Mar 21]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278933/
- Ruige J. B., Mahmoud A. M., De Bacquer D., Kaufman J. M. (2011). Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. Heart 97, 870–875 10.1136/hrt.2010.210757 [DOI] [PubMed] [Google Scholar][Ref list] https://doi.org/10.1210/jcem.82.5.3958.
- Russell JK, Jones CK, Newhouse PA. The Role of Estrogen in Brain and Cognitive Aging. Neurotherapeutics. 2019 Jul;16(3):649-665. doi: 10.1007/s13311-019-00766-9. PMID: 31364065; PMCID: PMC6694379.
- Saltiel, Doreen, Connecting the Dots Between Cardiovascular Disease, Inflammation, and Hormones; Connecting Cardiovascular Disease, Inflammation & Hormones | DUTCH Webinar
- Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. Asian J Androl. 2016 May-Jun;18(3):435-40. doi: 10.4103/1008-682X.173932. PMID: 26908066; PMCID: PMC4854098.
- Stice JP, Lee JS, Pechenino AS, Knowlton AA. Estrogen, aging and the cardiovascular system. Future Cardiol. 2009 Jan;5(1):93-103. doi: 10.2217/14796678.5.1.93. PMID: 19371207; PMCID: PMC3972065
- Testosterone insufficiency in women: fact or fiction? » Sexual Medicine » BUMC
- The Safety of Testosterone Therapy in Women Al-Imari, Lina et al. of Obstetrics and Gynaecology Canada, Volume 34, Issue 9, 859 – 865

References:

- Tian, Fei et al., Ranking age-specific modifiable risk factors for cardiovascular disease and mortality: evidence from a population-based longitudinal study, eClinicalMedicine, Volume 64, 102230
- Tostes R.C., D. Nigro, Z.B. Fortes and M.H.C. Carvalho, Grupo de Pesquisa sobre Hipertensão Arterial, Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP, Brasil, Effects of estrogen on the vascular system, Braz J Med Biol Res, September 2003, Volume 36(9) 1143-1158 (Review)
- The Writing Group for the PEPI Trial (1995) Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 273: 199–208. [PubMed] [Google Scholar]
- Thomas P, Pang Y, Filardo EJ, et al. Identity of an Estrogen Membrane Receptor Coupled to a G Protein in Human Breast Cancer Cells. Endocrinology. 2005;146:624–632. doi: 10.1210/en.2004-1064. [DOI] [PubMed] [Google Scholar]
- Van Erpecum KJ, et al. Gastroenterology. 1991;100(2):482-488.
- Vecchiola, Andreaa; Uslar, Thomasa; Friedrich, Isidorab; Aguirre, Joaquinb; Sandoval, Alejandrac; Carvajal, Cristian A.a; Tapia-Castillo, Alejandraa; Martínez-García, Alejandraa; Fardella, Carlos E.a. The role of sex hormones in aldosterone biosynthesis and their potential impact on its mineralocorticoid receptor. Cardiovascular Endocrinology & Metabolism 13(3):e0305, September 2024. | DOI: 10.1097/XCE.0000000000000305.
- Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest. 1999;22(5 Suppl):110-6. PMID: 10442580.
- Yan Hui, Yang Wangbao, Zhou Fenghua, Li Xiaopeng , Pan Quan , Shen Zheng, Han Guichun, Newell-Fugate Annie, Tian Yanan , Majet Ravikumar, Liu Wenshe, Yong Xu, Chaodong Wu, Kimberly Allred, Clinton Allred, Yuxiang Sun, Shaodong Guo; Estrogen Improves Insulin Sensitivity and Suppresses Gluconeogenesis via the Transcription Factor Foxo1. Diabetes 1 February 2019; 68 (2): 291–304. https://doi.org/10.2337/db18-0638
- Thomas, Pang Yefei, Protective actions of progesterone in the cardiovascular system: Potential role of membrane progesterone receptors (mPRs) in mediating rapid effects,, Steroids, Volume 78, Issue 6, 2013, Pages 583-588, ISSN 0039-128X, https://doi.org/10.1016/j.steroids.2013.01.003

References:

- Travison TG, O'Donnell CJ, Bhasin S, Massaro JM, Hoffmann U, Vasan RS, et al. Circulating Sex Steroids and Vascular Calcification in Community-Dwelling Men: The Framingham Heart Study. J Clin Endocrinol Metab. The Endocrine Society; 2016; 101: 2160–7. https://doi.org/10.1210/jc.2015-4299 PMID: 26930184
- Turner EC, Kinsella BT. Estrogen increases expression of the human prostacyclin receptor within the vasculature through an ERalpha-dependent mechanism. J Mol Biol. 2010 Feb 26;396(3):473-86. doi: 10.1016/j.jmb.2010.01.010. Epub 2010 Jan 11. PMID: 20070947.
- Yassin, A., Nettleship, J. E., Talib, R. A., Almehmadi, Y., & Doros, G. (2016). Effects of testosterone replacement therapy withdrawal and re-treatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters. The Aging Male, 19(1), 64–69. https://doi.org/10.3109/13685538.2015.1126573.

Thank You!

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