The Basics

Since hormones lean on nutrition and digestion and adverse illness also has some “root cause” molecules that drive it

1

Intakes

- History of Trauma first 4 years of life dictates brain/hormone cross-talk through much of life
- Gut: goal is two BMs/d many with history of hormonally driven diseases have history of severe constipation
- How do you feel after you eat? Fatigue suggests “Post prandial bacterial translocation” so assess Digestive Players and replace if needed and take some anti-oxidants to reduce pro-oxidative post prandial flush (Vitamin C + Bioflavonoids)
- How many BMs?
- See undigested food?
- Stool = large bent brown banana without foul odor
- If history/present lots of sinus issues do nares cultures (microbiologydx.com)
- If history of severe immediate bloat = SIBO
- GI Map or Genova or Doctor’s Data with h. pylori and zonulin

2

Labs

- Candida albicans Antibodies (IgG, IgA, IgM) (QuestCode 30440)
- CBC (includes Differential and Platelets) (QuestCode 6399)
- Comprehensive Metabolic Panel (CMP-14) (QuestCode 10231)
- DHEA Sulfate, Immunoassay (QuestCode 402)
- Epstein-Barr Virus Viral Capsid Antigen (VCA) Antibody (IgG) (QuestCode 8474)
- Epstein-Barr Virus Viral Capsid Antigen (VCA) Antibody (IgM) (QuestCode 8426)
- Estradiol (QuestCode 4021)
- Estriol, LC/MS/MS, Serum (QuestCode 34883)
- Estrone, LC/MS/MS (QuestCode 23244)
- Ferritin (QuestCode 457)
- FSH and LH (QuestCode 7137)
- Gamma Glutamyl Transferase (GGT) (QuestCode 482)
- Homocysteine (QuestCode 31789)
- hs-CRP (QuestCode 10124)
- Insulin (QuestCode 561)
- Iodine (QuestCode 16799)
- Iron, Total (QuestCode 571)
- Lactate Dehydrogenase (LD) (QuestCode 593)
- Lipid Panel (QuestCode 7600)
- Parathyroid Hormone (PTH), Intact and Calcium (QuestCode 8837)
- Parietal Cell Antibody, ELISA (QuestCode 15114)
- Phosphate (as Phosphorus) (QuestCode 715)
- Progesterone, Immunoassay (QuestCode 795)
- Sex Hormone Binding Globulin (SHBG) (QuestCode 30740)
- T3 (Triiodothyronine) Antibody (QuestCode 36574)
- T3, Free (FT3) (QuestCode 34429)
- T3, Reverse, LC/MS/MS (QuestCode 90963)
- T4, Free (FT4) (QuestCode 866)
- TBG (Thyroxine Binding Globulin) (QuestCode 870)
- Testosterone, Free (Dialysis) and Total LC/MS/MS (QuestCode 36170)
- TSH (Thyroid Stimulating Hormone) (QuestCode 899)
- Uric Acid (QuestCode 905)
- Vitamin B12 (Cobalamin) and Folate Panel, Serum (QuestCode 7065)
- Vitamin B6 (Pyridoxine), LC/MS/MS (QuestCode 926)
- Vitamin D, 25-Hydroxy, Total, Immunoassay (QuestCode 17306)
- Copper, RBC (QuestCode 34881)
- Magnesium, RBC (QuestCode 623)
- Manganese, RBC (QuestCode 16594)
- Selenium, RBC (QuestCode 17153)
- Zinc, RBC (QuestCode 6354)
- TMAO
- Cystatin C
- Galectin-3
- Symmetric dimethylarginine ADMA
- Assymetric dimethylaegine NDMA
- Transforming Growth Factor Beta1
- Vitamin A
- Vitamin B6
- Mercury
- Lead
- Lipoprotein (a)

3

How is liver working?

- Need a liver to be working well to process BHRT
- HRT is hormone replacement therapy
- BHRT is bioidentical hormone replacement therapy
- Wild yams cannot be made by the body into active hormones
- Want ALT and AST in teens
- Note level of HDL as it is only made in the liver
- FibroScan (liver elastography)

4

Parietal Cells

- 45% mitochondria
- Highest per volume of ANY cell in the body
- Anti-parietal cell antibodies (if highly suspicious may need to run at least 3 times) < 15 is ideal even if reference range says <20
- Anti-intrinsic cell antibodies
- Stomach Acid Challenge Test

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Stomach Acid Challenge Test (pepsin avoid high dose in those with severe GERD)

Stomach Acid Challenge by Dr. Berkson

The words "stomach acid" sounds dangerous as the word "acid" elicits something harmful.
Nothing could be further from the truth. We need stomach acid for important actions:

Reduces minerals to electrolyte state that make them useable by the body. Thus being "low" in critical nutrients, even B vitamins, might be due to insufficient HCL. This is critical for many enzymes, immune competence, growth of hair and nails, and much more.
Signals the "downstream" enzymes to secrete into the lumen of the gut to make digestion unfold, such as signaling the gallbladder to release bile and the pancreas to release pancreatic enzymes.
Thus, stomach acid has "a lot" to do with normal transit time. Often insufficient stomach acid is linked to constipation, sleeing undigested food in stool, etc.
Stomach acid helps us break down foods. Insufficient stomach acid can contribute to food reactivities, allergies, autoimmune disease, leaky gut and more.
To help keep the body alkaline (after stomach acid is released there is a post "alkaline tide" throughout the body that keep pH optimal. This helps ward off diverse illnesses and contributes to healthy functioning of the whole body).
And more.

Stomach acid is referred to in physiology as betaine hydrochloride.

Nature prioritizes "parietal cells" that make stomach acid. We know this because there are more energy packets, mitochondria, in these cells, than in any other cell in the body. More than the brain and the heart.

So, we want to figure out if you require stomach acid replacement to help you achieve optimal health.

How to do this challenge.

Note: If at any time you feel discomfort... stop. Drink 8 ounces of water. Report in the portal to your practitioner.

Meal number one:
Take an HCL capsule, after a few bites of food or toward the middle of the meal. With meal #1.
You do NOT want to take stomach acid replacement on an empty stomach or at the end of a meal. We do NOT want stomach acid to sit on top of food.

If you have no issues, you will continue with the challenge.
If immediately or within a few hours you feel pain, burning, discomfort, increased reflux more than normal, or release of stools that feel "burning", do not go further. Drink a large glass of water and stop. Drink water. Don't go further.

Meal number two:
If no issues, go to the next meal. Now take 2 HCL capsules on a few bites of food and see how you feel.

If any issues... Stop, drink water. Report in the portal.

If no issues. Continue.

Meal number three:
Take three capsules after a few bites of food. See how you feel.

If any issues... stops, drink water. Report.

If no issues go on to meal four.

Meal number four:
Take four capsules after a few bites of food.
Continue as above.

This is a high as we go for now.

Report in the portal to your practitioner:

I felt this way after challenge one_____
Or stopped.

I felt this way after challenge two_____
Or stopped.

I felt this way after challenge three_____
Or stopped.

I felt this way after challenge four_____
Or stopped.

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Clues to Digestion in Labs

- Total Protein should be in the 7's
- If in the 5's cannot make receptors (elderly in the 5's that the needle won't move may need Creon – pharmaceutical pancreatic enzymes)
- Alkaline phosphatase is a zinc dependent enzyme should be at least 50 ideally 100
- Albumin should be in the 4's as it is the most abundant carrier protein in the blood
- Pancreatic Elastase on GI map should be over 500 on or off enzyme support
- Steatorrhea – very little fat in stool is ideal to absorb many nutrients and fatty acids
- Zonulin – gives idea of (post prandial bacterial translocation)
- For hormones in the blood need to run FSH for both males and females, SHBG.
- RBC levels of minerals which ideally should be in highest quartile.

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Hormones Function & DysFunction Together So need an ideal of many hormones

- In-depth thyroid (TSH, Free T3, Free T4, rT3, TBG, iodine?
- Inflammatory markers IL-6 and a healthy gut makes lots of the anti-inflammatory cytokine Il-10
- Insulin fasting and post prandial
- Vitamin D
- Signs of low vitamin A – cracks on heels, problems with hormones like oligomenorrhea, non responsive to HRT

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RBCs (RBC levels) and or hair analysis (ticker tape read out of RBC levels)

- Zinc (zinc fingers give shape to all hormone signaling/docking)
- Magnesium (up 5o 500 enzymes)
- Manganese (bone, ligaments)
- Chromium
- Selenium
- Copper

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ER Alpha Insufficiency

- Insufficiency – anxiety, depression, memory issues, recall issues, trouble concentrating, vaginal dryness, hot flashes/sweats, irregular periods, amenorrhea, belly fat, reduced libido, fatigue, insomnia, wrinkles around mouth, loss of firmness of skin, cognitive issues (as maintains hippocampus volume), growing more polyps, gum recession/problems, bone issues, verbal issues, dry skin, tender breasts, menstrual irregularities, bone issues, brain health issues, losing skin elasticity, loss of lipid control
- In males: gynecomastica, personality changing more emotional, more central body fat
- Excess: Weight gain around middle, breasts getting larger, many of the symptoms above.
- Hyperplasia or increase in Endometrial stripe assessed by vaginal US should be in menopausal woman 5 or less mmHg > 5mm is unhealthy.

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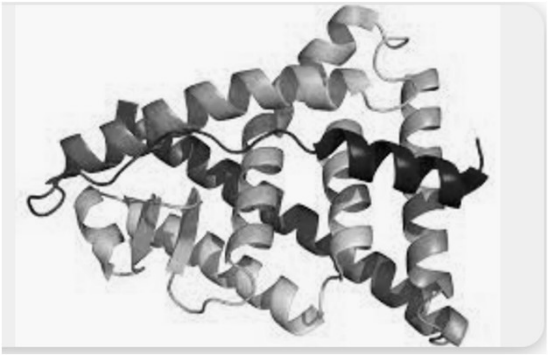
ER beta

- Insufficiency: endothelial issues, anxiety (overlaps with oxytocin receptors in brain), depression, moodiness, feeling not like oneself
- Insufficiency: anovulatory, inflammation, myelin issues,
- Leaky gut as upregulates junctional adhesive molecules A (JAM-A) that helps keeps colon cells (enterocytes) together
- Polyps in colon (growth controller so any growth out of control)
- Weight loss issues as controls mitochondria in brown fat
- Endothelial dysfunction as ER beta receptors on all epithelial tissue like blood vessels.
- Excess: Endometriosis (theory),



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Endometrial Stripe

- The thickness of the endometrial lining is rarely over 4 mm in a woman past menopause.
- n premenopausal women the thickness varies with the phase of the menstrual cycle, but the maximum thickness will be within about 20 mm even in the secretory phase, when it is greatest.
- But if not having a period, should not be > 5 mm.
- 15% of cancers occur in women without vaginal bleeding.
- In a postmenopausal woman with vaginal bleeding, the risk of cancer is approximately 7.3% if her endometrium is thick (> 5 mm) and < 0.07% if her endometrium is thin (≤ 5 mm).
- An 11-mm threshold yields a similar separation between those who are at high risk and those who are at low risk for endometrial cancer.
- In postmenopausal women without vaginal bleeding, the risk of cancer is approximately 6.7% if the endometrium is thick (> 11 mm) and 0.002% if the endometrium is thin (≤ 11 mm).
- In a postmenopausal woman without vaginal bleeding, if the endometrium measures > 11 mm a biopsy should be considered as the risk of cancer is 6.7%, whereas if the endometrium measures ≤ 11 mm a biopsy is not needed as the risk of cancer is extremely low.
- But an endometrial thickness > 5 mm suggests insufficient progesterone, iodine and possibly methylating issues as methylation promotes controlled growth.
- How thick is too thick? When endometrial thickness should prompt bi
- opsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol. 2004 Oct;24(5):558-65. doi: 10.1002/uog.1704. PMID: 15386607.

- Endometrial hyperplasia (EH) is a condition in which the innermost lining of the uterus, or endometrium, undergoes thickening usually as a result of exposure to estrogen unbalanced by progesterone. It is usually diagnosed by microscopic examination of a sample of the endometrium. There are different types of EH which are important to differentiate, because one variant is strongly associated with a high risk of uterine carcinoma.
- Most women with endometrial hyperplasia present with abnormal uterine bleeding, which could include excessive menstrual bleeding, intermenstrual bleeding (or what looks like very short menstrual cycles, less than 21 days), prolonged bleeding, or bleeding after menopause (the periods have stopped altogether for a duration equal to or more than six normal cycles, and then recurred). In postmenopausal women with abnormal uterine bleeding, over 15 of every hundred will be found to have EH.
- A woman of reproductive age who presents with abnormal vaginal bleeding may have to be evaluated for endometrial hyperplasia, among other conditions.
- But often she is insufficient in progesterone and iodine and her receptor functionality needs to be improved.
- Benign hyperplasia or hyperplasia without atypia are lesions which will resolve with conservative management (i.e., without surgery). There are no genetic changes characteristic of malignancy. On the other hand, atypical hyperplasia, EIN, or EN, is associated with existing invasive endometrial carcinoma or a high risk of such tumors within a few years, and the lesions show the characteristic mutations in tumor suppressor genes or DNA repair genes, as well as microsatellite instability. The recommended treatment for EH with atypia is total hysterectomy.

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Progesterone

- Insufficiency:
- Bleeding issues, Breast tenderness, anxiety, depression, headaches, history of miscarriages, history of severe menorrhagia, severe dysmenorrhea,
- Can't sustain pregnancy
- Lung issues such as chronic pulmonary diseases
- Demyelinating issues
- Leaky gut as up regulates adhesive proteins inbetween enterocytes

- Excess:
- Anger, Loss of libido,

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Progesterone Insufficiency Males

- Low sperm Leydig cells need progesterone to make sperm
- Depression, mood swings or anxiety.
- Low Sex Drive
- Erectile dysfunction
- Loss of muscle mass.
- Fatigue and trouble concentrating.
- Lung issues ie COPD

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Testosterone

- Insufficiency:
- Poor stamina
- Not muscle response to exercise
- Thinning bones
- Loss of libido
- Loss of memory
- Helps tamp down expression of APOE4 so loss promotes cognitive decline in vulnerable
- Not feeling like self
- Depression and Anxiety

- Excess: changes in personality, shorter fuse, anger, (tamps down oxytocin)
- Cystic acne
- Increased hair growth
- Worsening lipid picture

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Molecules of Mass Destruction

- Drive adverse tissue changes (remodeling)
- Drive cancer
- Drive Fibrosis
- Drive Disease
- Part of healing at ”Root Cause” of disease is measuring molecules that drive disease and get them in normal ranges

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Molecules of Mass Destruction

- Human Transforming Growth Factor Beta1 = if high give Taurine and check Vitamin D levels
- Gallectin-3 = if high give modified citrus pectin
- These two molecules DRIVE all fibrosis

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Knowledge is power. Recurrent fibrosis of vaginal vault. Already on BHRT. Added taurine, modified citrus pectin, 2 MEO, oxytocin. Within one week no more pain and within 3 weeks physiology was back to normal if not better.

"What did you do to this 65 year old patient? She has the vagina of a 25 year old?"

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TMAO – trimethylamine N Oxide

- Dictates diet
- Implies biome health
- Should be under 6
- Responds to changes in diet and supplements FAST.
- If higher must avoid red meat, egg yolks.
- Fish twice a week, avoid shell fish.
- If higher must avoid Carnitine, choline supplements.
- Avoid fish flesh for 10 days before testing.
- Fish flesh is high in TMAO – FISH paradox.

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TMAO – fish paradox

Give a man a fish and he will tweet over and over that it raises trimethylamine-N-oxide (TMAO). Indeed, studies indicate that eating some species of fish may acutely raise TMAO levels. As studies exist relating dietary patterns of fish consumption and favorable cardiovascular outcomes, the hundreds of studies indicating that elevated TMAO levels relate to poor health outcomes are swept aside. Fishy business indeed that conflicts with data since 2011 when researchers from the Cleveland Clinic demonstrated that meat eaters had high levels of TMAO. In those investigations, TMAO was not elevated in vegans who were asked to eat a meat meal for the purposes of the study.

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TMAO Paradox

- Deep-water animals accumulate TMAO to protect proteins, such as lactate dehydrogenase (LDH), against hydrostatic pressure stress (HPS)
- We hypothesized that TMAO exerts beneficial effects on the circulatory system and protects cardiac LDH exposed to HPS produced by the contracting heart. Male, Sprague-Dawley and Spontaneously-Hypertensive-Heart-Failure (SHHF) rats were treated orally with either water (control) or TMAO.
- In vitro, LDH with or without TMAO was exposed to HPS and was evaluated using fluorescence correlation spectroscopy.
- TMAO-treated rats showed higher diuresis and natriuresis, lower arterial pressure and plasma NT-proBNP. Survival in SHHF-control was 66% vs 100% in SHHF-TMAO.
- In vitro, exposure of LDH to HPS with or without TMAO did not affect protein structure.
- In conclusion, TMAO reduced mortality in SHHF, which was associated with diuretic, natriuretic and hypotensive effects. HPS and TMAO did not affect LDH protein structure.
- The experiments suggest that dietary TMAO may mimic the effects of heart failure treatments, which remove excess water and salt and lower pressure on the heart. More studies are needed to confirm whether TMAO has this same effect on humans.
- TMAO, a seafood-derived molecule, produces diuresis and reduces mortality in heart failure rats. Elife. 2020 Jun 8;9:e57028. doi: 10.7554/eLife.57028. PMID: 32510330; PMCID: PMC7334024.

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Kidney, Heart, Brain Disease which fish to avoid to avoid surges of TMAO?

- **Purpose:** Some species of fish and seafood are high in trimethylamine N-oxide (TMAO), which accumulates in muscle where it protects against pressure and cold.
- Fish intake is promoted for its potential cardioprotective effects.
- However, numerous studies show TMAO has pro-atherothrombotic properties.
- Here, we determined the effects of fish or seafood consumption on circulating TMAO levels in participants with normal renal function.
- **Methods:** TMAO and omega-3 fatty acid content were quantified across multiple different fish or seafood species by mass spectrometry. Healthy volunteers (n = 50) were recruited for three studies. Participants in the first study consented to 5 consecutive weekly blood draws and provided dietary recall for the 24 h preceding each draw. In the second study, TMAO levels were determined following defined low and high TMAO diets.
- Finally, participants consumed test meals containing shrimp, tuna, fish sticks, salmon or cod. TMAO levels were quantified by mass spectrometry in blood collected before and after dietary challenge.
- **Results:** TMAO + TMA content varied widely across fish and seafood species.
- Consumption of fish sticks, cod, and to a lesser extent salmon led to significant increases in circulating TMAO levels.
- Within 1 day, circulating TMAO concentrations in all participants returned to baseline levels.
- **Conclusions:** We conclude that some fish and seafood contain high levels of TMAO, and may induce a transient elevation in TMAO levels in some individuals.
- Selection of low TMAO content fish is prudent for subjects with elevated TMAO, cardiovascular disease or impaired renal function.
- Cleveland Clinic.
- Circulating trimethylamine N-oxide levels following fish or seafood consumption. Eur J Nutr. 2022 Aug;61(5):2357-2364. doi: 10.1007/s00394-022-02803-4. Epub 2022 Feb 3. PMID: 35113194; PMCID: PMC9283263.

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TMAO

- The potential role of TMAO as a marker or even a causative factor in atherosclerotic arterial disease has been appreciated for less than a decade and much more needs to be learned.
- For now, we can rest easy that fruits and vegetables, and vegetarian diets, are not raising TMAO levels.
- In some very sensitive individuals: **mushrooms, cauliflower, asparagus, soy.**

- Dietary precursors of trimethylamine in man: a pilot study. Food Chem Toxicol. 1999 May;37(5):515-20. doi: 10.1016/s0278-6915(99)00028-9. PMID: 10456680.

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TMAO paradox - Several studies have suggested negative effects of trimethylamine oxide (TMAO) on the circulatory system. However, a number of studies have shown protective functions of TMAO

- Wild-caught freshwater lake and river fish are the least likely to have high concentrations of TMAO. This includes trout and perch. Saltwater fishes however are more likely to have higher levels, including, shark, rays, mollusks, and crustaceans.
- Consumption of fish sticks, cod, and to a lesser extent farm-raised salmon led to significant increases in circulating TMAO levels.
- Circulating trimethylamine N-oxide levels following fish or seafood consumption. Eur J Nutr. 2022 Aug;61(5):2357-2364. doi: 10.1007/s00394-022-02803-4. Epub 2022 Feb 3. PMID: 35113194; PMCID: PMC9283263.
- Chronic, low-dose TMAO treatment reduces diastolic dysfunction and heart fibrosis in hypertensive rats. Am J Physiol Heart Circ Physiol. 2018 Dec 1;315(6):H1805-H1820. doi: 10.1152/ajpheart.00536.2018. Epub 2018 Sep 28. PMID: 30265149.

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Methylated Arginines

- SDMA – symmetric dimethylarginine earliest marker of renal disease
- ADMA – asymmetric dimethylarginine – earliest marker of heart disease
- Indicators of endothelial health.
- Elevations mean sick endothelium.
- Methylation of arginine residues by protein arginine methyltransferases (PRMTs) is involved in the regulation of fundamental cellular processes, including transcription, RNA processing, signal transduction cascades, the DNA damage response and liquid-liquid phase separation
- The regulation, functions and clinical relevance of arginine methylation. Nat Rev Mol Cell Biol. 2019 Oct;20(10):642-657. doi: 10.1038/s41580-019-0155-x. Epub 2019 Jul 26. Erratum in: Nat Rev Mol Cell Biol. 2019 Sep;20(9):567. PMID: 31350521.

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Methylated Arginines

- Protein arginine methyltransferases (PRMTs) are emerging as attractive therapeutic targets.
- PRMTs regulate transcription, splicing, RNA biology, the DNA damage response and cell metabolism; these fundamental processes are altered in many diseases.
- Mechanistically understanding how these enzymes fuel and sustain cancer cells, especially in specific metabolic contexts or in the presence of certain mutations, has provided the rationale for targeting them in oncology.
- Protein arginine methylation: from enigmatic functions to therapeutic targeting. Nat Rev Drug Discov. 2021 Jul;20(7):509-530. doi: 10.1038/s41573-021-00159-8. Epub 2021 Mar 19. PMID: 33742187.

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Methylated Arginines

- In recent years, protein arginine methyltransferases (PRMTs) have emerged as new members of a gene expression regulator family in eukaryotes, and are associated with cancer pathogenesis and progression.
- Cancer immunotherapy has significantly improved cancer treatment in terms of overall survival and quality of life.
- Protein arginine methylation is an epigenetic modification function not only in transcription, RNA processing, and signal transduction cascades, but also in many cancer-immunity cycle processes.
- Arginine methylation is involved in the activation of anti-cancer immunity and the regulation of immunotherapy efficacy. In this review, we summarize the most up-to-date information on regulatory molecular mechanisms and different underlying arginine methylation signaling pathways in innate and adaptive immune responses during cancer. We also outline the potential of PRMT-inhibitors as effective combinatorial treatments with immunotherapy.

- Protein Arginine Methylation: An Emerging Modification in Cancer Immunity and Immunotherapy. Front Immunol. 2022 Apr 14;13:865964. doi: 10.3389/fimmu.2022.865964. PMID: 35493527; PMCID: PMC9046588.

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More heavy metal, more methylated arginines, more cardiac/renal damage

- **Background:** In this study, we aimed to show that methylated arginines are the predictors of non-clinical atherosclerotic cardiovascular complications in metal workers exposed to Cd.
- **Methods:** The 80 Cd-exposed metal workers and 80 non-exposed workers (control) included in the study were available for measuring arginine, ADMA, SDMA, and L-NMMA levels.
- **Results:** The average urine Cd levels (CdU) found were 1.03 ± 0.8 µg/g creatinine (0.84 ± 0.65 µg/L) ranging from 0.01 to 3.00 µg/g creatinine in the control group and 5.41 ± 5.2 µg/g creatinine (4.29 ± 3.81 µg/L) ranged from 0.11 to 27.2 µg/g creatinine in metal workers.
- **Conclusions:** The present study was undertaken to investigate the relationship between cadmium exposure and methylated arginines such as ADMA/SDMA/L-NMMA parameters which is important for the early detection atherosclerotic cardiovascular diseases.
- The Relationship of Methylated Arginines with Urine Cadmium Levels. Clin Lab. 2022 Jan 1;68(1). doi: 10.7754/Clin.Lab.2021.210504. PMID: 35023667.

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ADMA

- ADMA is a post-translationally modified form of arginine that is generated in all cells during protein turnover.
- ADMA inhibits NO.
- ADMA is a very sensitive marker of "endothelial dysfunction".
- Homocysteine is a "cheap man's" ADMA marker.

- Pharmaceutical Sciences and Biomedical Analysis Journal Plasma ADMA Decrease Following a Single Bout of Physical Exercise is Related to Reduced Homocysteine Lowering. J Pharm Sci Biomed Anal. 2017; 1(1):112. protein turnover.
- Association of asymmetric dimethylarginine and endothelial dysfunction. Clin Chem Lab Med. 2003 Nov;41(11):1467-72. doi: 10.1515/CCLM.2003.225. PMID: 14656027.

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Lung = ADMA major source

- The lung plays a major role in NO metabolism and is well established as a major source of NO.
- THE LUNG IS A MAJOR SOURCE of nitric oxide (NO), be it from nitric oxide synthase (NOS) III in the endothelium of the vast pulmonary circulation, NOS II in the epithelium of the large surface area of the airways, or NOS I in the nonadrenergic noncholinergic nerves
- The lung is also a major source of the NOS inhibitor and arginine analog ADMA.
- NO produced in the lung has major roles in lung physiology, including airway and vascular smooth muscle relaxation, ventilation perfusion matching, neurotransmission, host defense and bacteriostasis, mucociliary clearance, and airway mucus secretion.
- It is also involved in the pathobiology of different lung diseases including asthma and pulmonary hypertension.
- Furthermore, as a highly diffusible molecule with strong affinity to hemoglobin, NO produced in the lung is avidly taken up by the blood in the pulmonary circulation and transported throughout the body, serving physiological functions well beyond the lungs and the pulmonary circulation.
- Measure ADMA in all lung patients including kids with asthma.

- The lung in the balance: arginine, methylated arginines, and nitric oxide. Am J Physiol Lung Cell Mol Physiol. 2007 Jan;292(1):L15-7. doi: 10.1152/ajplung.00322.2006. Epub 2006 Sep 15. PMID: 16980373.

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Lungs make NO
ADMA inhibits NO

- The lung is also a major source of the endogenous NOS inhibitor asymmetric N^GN^G-dimethylarginine (ADMA).
- This finding has significant physiological and pathological implications not only for the pulmonary circulation and the lung but also for the systemic circulation and beyond.
- The lungs make NO out of arginine.

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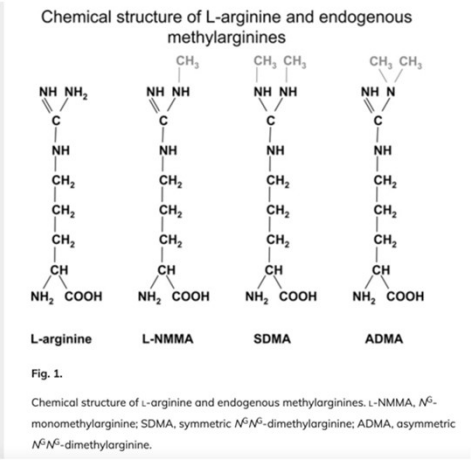
Methylarginines

- **Methylarginine** is an inhibitor of nitric oxide synthase.
- Chemically, it is methyl derivative of the amino acid
- Arginine.
- Patients with history of any respiratory issue going bad and needing antibiotics and long to heal often low in NO and higher in ADMA.



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High ADMA = Low NO

- ADMA is one of three circulating endogenous methylated analogs of L-arginine that are produced as a result of proteolysis of methylated proteins
- High levels of ADMA means that patient is low in NO
- High levels of SDMA suggest renal function but do NOT inhibit NO.
- And needs NO boosters twice a day especially if they have disease like heart or kidney.
- Excess thyroid replacement can raise ADMA (and also SHBG)
- The lung in the balance: arginine, methylated arginines, and nitric oxide. Am J Physiol Lung Cell Mol Physiol. 2007 Jan;292(1):L15-7. doi: 10.1152/ajplung.00322.2006. Epub 2006 Sep 15. PMID: 16980373.

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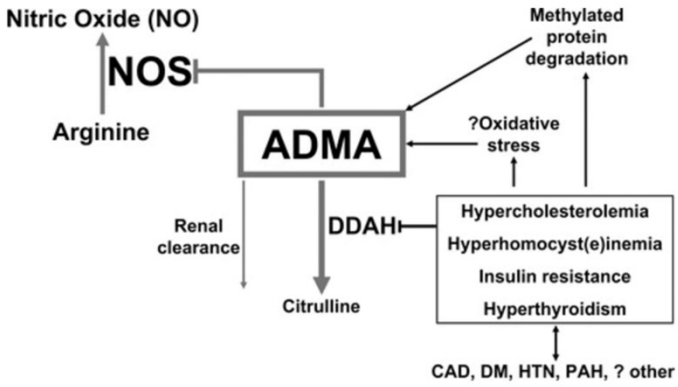
Check TSH if inhibited may be raising ADMA



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High ADMA

- Accumulation of ADMA, which has the functional effect of "NO deficiency."
- Seen in CAD, coronary artery disease; DM, diabetes mellitus; HTN, systemic hypertension; PAH, pulmonary arterial hypertension
- The lung in the balance: arginine, methylated arginines, and nitric oxide. Am J Physiol Lung Cell Mol Physiol. 2007 Jan;292(1):L15-7. doi: 10.1152/ajplung.00322.2006. Epub 2006 Sep 15. PMID: 16980373

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ADMA – shows up heart vulnerabilities long before cholesterol

- Overall, it appears that the synthesis and metabolism of endogenous methylarginines are highly regulated. Imbalance in this pathway is associated with several pathobiological consequences.
- Since elevated plasma levels were first reported in patients with renal failure, ADMA has been implicated in the pathogenesis of a variety of clinical conditions such as systemic hypertension, pulmonary hypertension, stroke, diabetes, hyperlipidemia, hyperhomocyst(e)inemia, and atherosclerosis.

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Risk

- ADMA
- Lipoprotein (a) – run on every patient
- Give you a huge idea of heart disease vulnerability

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ADMA = endothelial marker

- ADMA levels are increased in people with hypercholesterolemia, atherosclerosis, hypertension, chronic heart failure, diabetes mellitus and chronic renal failure.
- A number of studies have reported ADMA as a novel risk marker of cardiovascular disease.
- Increased levels of ADMA have been shown to be the strongest risk predictor, beyond traditional risk factors, of cardiovascular events and all-cause and cardiovascular mortality in people with coronary artery disease.
- Interventions such as treatment with L-arginine have been shown to improve endothelium-mediated vasodilatation in people with high ADMA levels.
- However the clinical utility of modifying circulating ADMA levels remains uncertain.

- The Role of Asymmetric Dimethylarginine (ADMA) in Endothelial Dysfunction and Cardiovascular Disease. Curr Cardiol Rev. 2010 May;6(2):82-90. doi: 10.2174/157340310791162659. PMID: 21532773; PMCID: PMC2892080.

38

ADMA run in early life not just seniors

- Despite the use of extensive antihypertensive therapy in patients with hypertension, little attention has been paid to early identification and intervention of individuals at risk for developing hypertension. The imbalance between nitric oxide (NO) and reactive oxygen species (ROS) resulting in oxidative stress has been implicated in the pathophysiology of hypertension.
- NO deficiency can precede the development of hypertension.
- Asymmetric dimethylarginine (ADMA) can inhibit nitric oxide synthase (NOS) and regulate local NO/ROS balance.
- Emerging evidence supports the hypothesis that ADMA-induced NO–ROS imbalance is involved in the development and progression of hypertension.
- Thus, this review summarizes recent experimental approaches to restore ADMA–NO balance in order to prevent the development of hypertension.
- Since hypertension might originate in early life, we also discuss the putative role of the ADMA–NO pathway in programmed hypertension.
- Restoration of asymmetric dimethylarginine-nitric oxide balance to prevent the development of hypertension. Int J Mol Sci. 2014 Jul 2;15(7):11773-82. doi: 10.3390/ijms150711773. PMID: 24992596; PMCID: PMC4139813.

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Cleveland Clinic

ADMA/SDMA

CPT Code **82542***
Order Code **C301**
Specimen Type **Serum**
Tube Type **Tiger Top**

Elevated levels of ADMA may identify:
- Endothelial dysfunction
- Pre-diabetes/diabetes
- Subclinical cardiovascular disease

Elevated levels of SDMA may identify:
- Reduced renal function and progressive kidney failure

Description

One of the earliest manifestations of endothelial dysfunction is nitric oxide (NO) deficiency, which promotes atherosclerosis. Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), its structural isomer, are metabolites of L-arginine, an amino acid that is catalyzed to L-citrulline and NO by nitric oxide synthase (NOS).[1,2]

Both ADMA and SDMA have distinct pathophysiologies and manifestations. ADMA is a competitive inhibitor of NOS thereby reducing NO production and promoting endothelial dysfunction. SDMA also interferes with NO production, but does so indirectly by reducing the cellular availability of arginine. ADMA is primarily cleared through enzymatic degradation in the bloodstream and its presence identifies subclinical cardiovascular disease (CVD).[1-6] Conversely, SDMA is primarily excreted in the urine and identifies reduced renal function.[5,6]

Clinical Use

ADMA/SDMA may be measured in individuals with multiple risk factors for the development of CVD.

- Elevated ADMA levels are associated with the presence of hypertension,[7] insulin resistance,[7] and hyperlipidemia.[8]
- Elevated ADMA levels are associated with subclinical atherosclerosis:
  - Increased ADMA concentrations correlate with internal carotid artery bulb intimal media thickness,[3] a hemodynamically unstable region vulnerable to NO deficiency[9] and plaque formation.
  - Elevated ADMA in young adults is associated with increased coronary artery calcification.[4]
- Individuals with established coronary artery disease and elevated ADMA levels have more than twice the risk for adverse events (myocardial infarction, stroke) than those with normal ADMA levels.[10]

Renal Significance:

- Elevated SDMA levels positively correlate with reduced renal function, as measured by estimated glomerular filtration rate[5,6] and cystatin C.[11,12]

Specimen Type

The ADMA/SDMA test should be performed on a serum specimen, and fasting is recommended, but not required.

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be monitored in individuals with hyperlipidemia, hypertension, pre-diabetes/diabetes, or those who are at moderate to high risk for developing cardiovascular disease.

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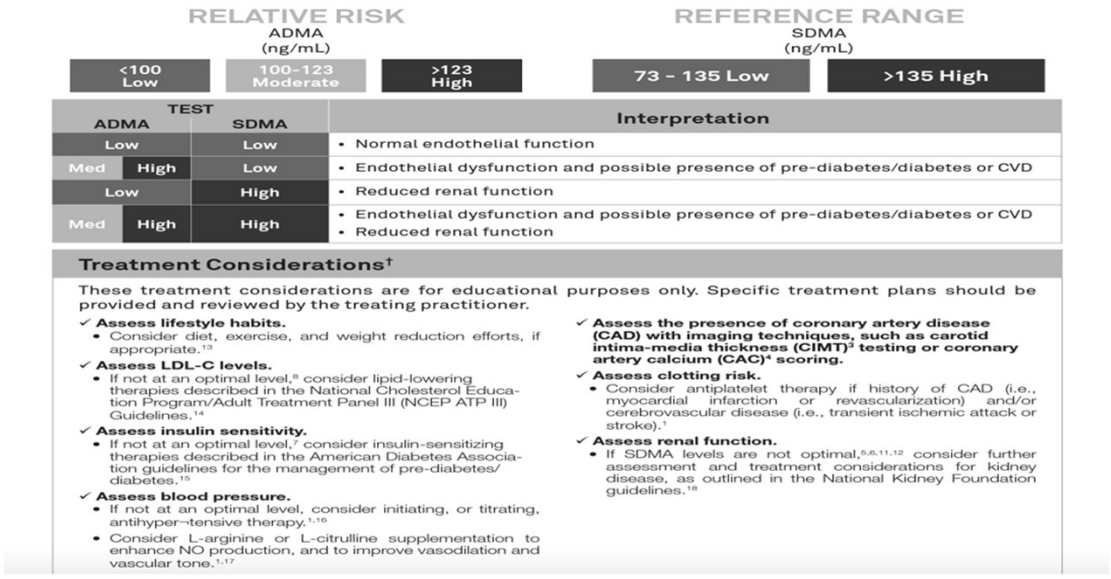

RELATIVE RISK

ADMA (ng/mL)

<100 Low	100–123 Moderate	>123 High

REFERENCE RANGE

SDMA (ng/mL)

73 – 135 Low	>135 High

TEST ADMA		TEST SDMA	Interpretation
Low		Low	• Normal endothelial function
Med	High	Low	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD
Low		High	• Reduced renal function
Med	High	High	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD • Reduced renal function

Treatment Considerations†

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ **Assess lifestyle habits.**
- Consider diet, exercise, and weight reduction efforts, if appropriate.[13]

✓ **Assess LDL-C levels.**
- If not at an optimal level,[8] consider lipid-lowering therapies described in the National Cholesterol Education Program/Adult Treatment Panel III (NCEP ATP III) Guidelines.[14]

✓ **Assess insulin sensitivity.**
- If not at an optimal level,[7] consider insulin-sensitizing therapies described in the American Diabetes Association guidelines for the management of pre-diabetes/diabetes.[15]

✓ **Assess blood pressure.**
- If not at an optimal level, consider initiating, or titrating, antihyper¬tensive therapy.[1,16]
- Consider L-arginine or L-citrulline supplementation to enhance NO production, and to improve vasodilation and vascular tone.[1,17]

✓ **Assess the presence of coronary artery disease (CAD) with imaging techniques, such as carotid intima-media thickness (CIMT)[3] testing or coronary artery calcium (CAC)[4] scoring.**

✓ **Assess clotting risk.**
- Consider antiplatelet therapy if history of CAD (i.e., myocardial infarction or revascularization) and/or cerebrovascular disease (i.e., transient ischemic attack or stroke).[1]

✓ **Assess renal function.**
- If SDMA levels are not optimal,[5,6,11,12] consider further assessment and treatment considerations for kidney disease, as outlined in the National Kidney Foundation guidelines.[18]

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References

1. Sibal L, Agarwal SC, Home PD, Boger RH. The Role of Asymmetric Dimethylarginine (ADMA) in Endothelial Dysfunction and Cardiovascular Disease. *Curr Cardiol Rev*. 2010; 6 (2): 82-90. 2. Willeit P, Freitag DF, Laukkanen JA, et al. Asymmetric dimethylarginine and cardiovascular risk: systematic review and meta-analysis of 22 prospective studies. *J Am Heart Assoc*. 2015; 4 (6): e001833. 3. Maas R, Xanthakis V, Polak JF, et al. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. *Stroke*. 2009; 40: 2715-2719. 4. Iribarren C, Husson G, Sydow K, Wang B, Sidney S, Cooke JP. Asymmetric dimethyl-arginine and coronary artery calcification in young adults entering middle age: the CARDIA Study. *Eur J Cardiovasc Prev Rehabil*. 2007; 14: 222-229. 5. Kielstein JT, Boger RH, Bode-Boger SM, et al. Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol*. 2002; 13: 170-176. 6. Kielstein JT, Salperter SR, Bode-Boeger SM, Cooke JP, Fliser D. Symmetric dimethylarginine (SDMA) as endogenous marker of renal function – a meta-analysis. *Nephrol Dial Transplant*. 2006; (21): 2446-2451. 7. Stühlinger MC, Abbasi F, Chu JW, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA*. 2002; 287: 1420-1426. 8. Böger RH, Bode-Boger Sm, Szuba A, et al. Asymmetric dimethylarginine (ADMA): A novel risk factor for endothelial dysfunction its role in hypercholesterolemia. *Circulation*. 1998; 98: 1842-1847. 9. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA*. 1999; 282: 2035-2042. 10. Schnabel R, Blankenberg S, Lubos E, et al. Asymmetric dimethylarginine and the risk of cardiovascular events and death in patients with coronary artery disease: Results from the AtheroGene study. *Circ Res*. 2005; 97: e53-e59. 11. El-Khoury JM, Bunch DR, Hu B, Payto D, Reineks EZ, Wang S. Comparison of symmetric dimethylarginine with creatinine, cystatin C and their eGFR equations as markers of kidney function. *Clin Biochem*. 2016; (49): 1140-1143. 12. Wilcken DEL, Wang J, Sim AS, Green K, Wilcken B. Asymmetric dimethylarginine in homocystinuria due to cystathionine D-synthase deficiency: Relevance of renal function. *J Inherit Metab Dis*. 2006; 29: 30-37. 13. Tanahashi K, Akazawa N, Miyaki A, et al. Plasma ADMA concentrations associate with aerobic fitness in postmenopausal women. *Life Sci*. 2014;108(1):30-3. 14. Third report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). National Institutes of Health. September 2002. *NIH Publication No*. 02-5215. 15. American Diabetes Association: Cardiovascular Disease and Risk Management: Standards of Medicare Care in Diabetes—2018. *Diabetes Care*. 2018;41(Supplement 1):S86-S104. 16. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol*. 2002;90(9):974-82. 17. Schwedhelm E, Maas R, Freese R, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. *Br J Clin Pharmacol*. 2008;65(1):51-9. 18. National Kidney Foundation: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013; 3 (1): 1-150.

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Omega 3 FATTY Acids and ADMA

- Methods
- A male population (n = 563, age 70 ± 6 yrs) with long-standing hyperlipidemia, characterized as high risk individuals in 1970–72, was included, randomly allocated to receive placebo n-3 PUFA capsules (corn oil) and no dietary advice (control group), dietary advice (Mediterranean type), n-3 PUFA capsules, or dietary advice and n-3 PUFA combined and followed for 3 years.
- Fasting blood samples were drawn at baseline and the end of the study.
- Results
- Compliance with both intervention regimens were demonstrated by changes in serum fatty acids and by recordings from a food frequency questionnaire. No influence of either regimens on ADMA levels were obtained.
- However, n-3 PUFA supplementation was accompanied by a significant increase in L-arginine levels, different from the decrease observed in the placebo group ($p < 0.05$). In individuals with low body mass index (<26 kg/m^2), the decrease in L-arginine on placebo was strengthened ($p = 0.01$), and the L-arginine/ADMA ratio was also significantly reduced ($p = 0.04$).
- Conclusion
- In this rather large randomized intervention study, ADMA levels were not influenced by n-3 PUFA supplementation or dietary counselling. n-3 PUFA did, however, counteract the age-related reduction in L-arginine seen on placebo, especially in lean individuals, which might be discussed as an improvement of endothelial function.

- Effect of diet and omega-3 fatty acid intervention on asymmetric dimethylarginine. Nutr Metab (Lond). 2006 Jan 5;3:4. doi: 10.1186/1743-7075-3-4. PMID: 16396682; PMCID: PMC1343562.

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Omega 3's but used corn oil

- The study aimed to evaluate the effects of a 3-week n-3 polyunsaturated fatty acids (n-3 PUFA) supplementation on serum nitric oxide (NO), asymmetric dimethyloarginine (ADMA), ultrasound indices of endothelial function and maximal oxygen uptake (VO2 max) of elite cyclists. The effects of dietary supplementation (n-3 PUFA at a dose of 1.3 g twice daily for 3 weeks) and placebo administration on flow-mediated dilatation (FMD), pulse wave velocity, serum markers (NO, ADMA), lipid profile, and ΔVO2max were analysed in 13 cyclists both before and after dietary protocols. Significant differences between pre- and post-intervention baseline NO levels were observed after n-3 PUFA dietary protocol (13.9 ± 4.2 vs. 23.5 ± 3.6 µmol·l(-1); $P < 0.001$). Higher post-intervention baseline NO level was observed after n-3 PUFA diet compared with placebo (23.5 ± 3.6 vs. 15.3 ± 3.0 µmol·l(-1); $P < 0.01$, respectively). The n-3 PUFA increased baseline NO concentration (ΔNO) by 6.7 ± 3.8 µmol·l(-1) and placebo by 1.6 ± 4.4 µmol·l(-1). The positive correlation was observed between baseline post-intervention NO concentration and maximal oxygen uptake ($r = 0.72$; $P < 0.01$) and also between ΔNO and ΔVO2max ($r = 0.54$; $P < 0.05$) in response to omega-3 fatty acids supplementation. There was an association between a 5.25% higher FMD ($P < 0.05$) and higherΔVO2max ($P < 0.001$) after n-3 PUFA diet compared with lower values of placebo ($r = 0.68$; $P < 0.05$). These findings suggest that an increase in NO release in response to n-3 PUFA supplementation may play a central role in cardiovascular adaptive mechanisms and enhanced exercise performance in cyclists.
- Omega-3 fatty acids supplementation improves endothelial function and maximal oxygen uptake in endurance-trained athletes. Eur J Sport Sci. 2015;15(4):305-14. doi: 10.1080/17461391.2014.949310. Epub 2014 Sep 1. PMID: 25176010.

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Diet – Finland alcohol raises ADMA, carbs lower

- Asymmetric dimethylarginine (ADMA) is an endogenous nitric oxide synthase inhibitor that participates in the regulation of vasodilatory function and is also linked to hypertension, whereas its stereoisomere, symmetric dimethylarginine (SDMA), is biologically inactive.
- It has not been published whether diet influences plasma ADMA levels.
- In this study, we investigated the impact of diet on plasma ADMA and SDMA levels.
- Thirty-four mildly hypercholesterolemic, otherwise healthy women (n = 14) and men (n = 20) with a mean age of 46.2 years (range, 35 to 62 years) participated in the study.
- The subjects were examined twice at intervals of 2 months.
- Seven-day food records were used to analyze diet and alcohol intake.
- ADMA was measured by using high-performance liquid chromatography (HPLC)-tandem mass spectrometry. In a multivariate analysis (R2 = 0.20, P < .002), low amount of energy received from carbohydrates (r = -0.31, P = .009) and high plasma triglycerides (r = 0.30, P = .01) were predictors of high ADMA plasma levels.
- Alcohol drinkers had higher plasma ADMA concentrations than abstainers (0.50 +/- 0.13 v 0.42 +/- 0.11 micromol/L, P = .04). Plasma ADMA correlated with systolic (r = 0.60, P = .005) and diastolic blood pressure (r = 0.53, P = .02) in abstainers but not in alcohol drinkers.
- Plasma SDMA was not associated with any dietary components or with blood pressure.
- In conclusion, a high amount of dietary carbohydrates is strongly associated with low levels of plasma ADMA.
- Concentration of ADMA in plasma seems to be higher in alcohol drinkers than in abstainers.
- Dietary composition as a determinant of plasma asymmetric dimethylarginine in subjects with mild hypercholesterolemia. Metabolism. 2004 Aug;53(8):1072-5. doi: 10.1016/j.metabol.2003.12.028. PMID: 15281021.

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Food ADMA

- Asymmetric dimethylarginine (ADMA) has been recognized as a marker of cardiovascular risk.
- We sought to investigate whether consumption of tea, coffee, fruit or vegetables is associated with ADMA.
- In 148 consecutive apparently healthy subjects (104 men and 44 women aged 40 to 70), daily tea, coffee, fruit and vegetable consumption was ascertained by questionnaire.
- Plasma ADMA, symmetric dimethylarginine (SDMA), and l-arginine levels were measured by high-performance liquid chromatography.
- ADMA correlated positively with coffee intake (r = 0.37, P < .0001), although these associations were less potent after adjustment for dietary factors.
- No correlation with fruit.
- Higher tea and vegetable intake is associated with lower plasma ADMA levels in healthy middle-aged subjects

- High tea and vegetable consumption is associated with low ADMA generation in older healthy subjects. Metabolism. 2012 Aug;61(8):1171-6. doi: 10.1016/j.metabol.2011.12.013. Epub 2012 Mar 3. PMID: 22386943.

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Cornelian Cherry – a species of Dogwood

- Abstract
- In our previous publication we showed that the oral administration of cornelian cherry fruits prevented feed-induced atherosclerosis.
- In this study we have examined the effect of cornelian cherry lyophilisate on proteins responsible for regulation of NO synthesis: asymmetric and symmetric dimethylarginine (ADMA, SDMA) and L-arginine in plasma, and dimethylarginine dimethylaminohydrolase (DDAH) in the liver. We have also assessed the systemic and local redox status in the blood and the aorta, and the thickness of the thoracic aorta.
- We have shown that 60-days of administering lyophilisate to rabbits fed 1% cholesterol increased the L-arginine and L-arginine/ADMA ratio, decreased ADMA and SDMA, increased DDAH activity, and had a positive impact on the redox state in the aorta but not in the blood, measured as decreased MDA, and increased glutathione, GPx, and SOD. Moreover, lyophilisate significantly decreased intima thickness and the intima/media ratio in the thoracic aorta.
- Concluding, the L-arginine-ADMA-DDAH pathway may contribute to the beneficial effects of the cornelian cherry in feed-induced atherosclerosis.
- With a long history of cultivation, there are many ways to eat and prepare Cornelian cherries. Acidic and sweet, the cherries can be eaten raw or dried, and are also commonly used in preserves and to make wine and liqueur. In Turkey, the fruits are used to flavor sherbet, as well as to make jams and marmalades.

- Cornelian cherry consumption increases the L-arginine/ADMA ratio, lowers ADMA and SDMA levels in the plasma, and enhances the aorta glutathione level in rabbits fed a high-cholesterol diet. Journal of Functional Foods Volume 34, July 2017, Pages 189-196

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ADMA = endothelial function = Raynaud's

- Secondary Raynaud's phenomenon (RP) is often the sentinel clinical finding in systemic sclerosis and may precede systemic disease by several years.
- Altered nitric oxide metabolism plays a critical role in both fibrosis and severe secondary RP phenotypes in these patients.
- Increased flux through inducible nitric oxide synthase (iNOS) drives cutaneous fibrosis.
- Failure of flux through endothelial nitric oxide synthase (eNOS) contributes to increased vasoconstriction and decreased vasorelaxation.
- The underproduction of nitric oxide by eNOS is in part due to increased levels of asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthase.
- The inhibitory effects of increased ADMA levels may be counteracted increasing serum l-arginine, which is often an effective treatment strategy in these patients.
- As such, l-arginine-based therapies should be considered in managing secondary RP, particularly given their favourable safety and tolerability profile.
- While there is no established dosing regimen, studies of oral l-arginine in secondary RP suggest that divided dosing may begin at 1-2 g/day and may be titrated up to 10 g/day. Conversely, primary RP is not associated with increased ADMA production which likely accounts for the failure of l-arginine trials to show benefit in primary RP.
- The clinical effects of l-arginine and asymmetric dimethylarginine: implications for treatment in secondary Raynaud's phenomenon. J Eur Acad Dermatol Venereol. 2019 Mar;33(3):497-503. doi: 10.1111/jdv.15180. Epub 2018 Aug 28. PMID: 30004597; PMCID: PMC6916181.

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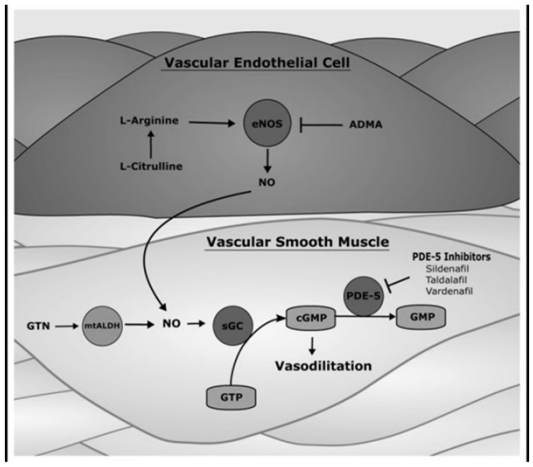
The clinical effects of l-arginine and asymmetric dimethylarginine: implications for treatment in secondary Raynaud's phenomenon. J Eur Acad Dermatol Venereol. 2019 Mar;33(3):497-503.



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Exercise

- A B S T R A C T
- This study describes as a single bout of physical exercise reduce plasma Asymmetric Dimethylarginine (ADMA) levels.
- ADMA is a naturally occurring aminoacid that aroused interest because inhibits Nitric Oxide Synthases (NOS) enhancing atherogenesis and producing sustained hypertensive damage to end organs.
- We reported experimental evidences that ADMA decrease is due to the lowering of reduced homocysteine during the physical efforts.
- High homocysteine = high ADMA or endothelial dysfunction = low NO.
- Regular physical activity may have a positive effect on healthy status since it reduces two important risk factor of vascular disease as homocysteine and ADMA.

- Plasma ADMA Decrease Following a Single Bout of Physical Exercise is Related to Reduced Homocysteine Lowering
- Pharmaceutica Science and Biomedical Analysis journal Sept 18 2017

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ADMA Estrogen Lowers

- Based on various studies, it was considered that estrogen therapy (ET) in postmenopausal women could probably reduce the higher cardiovascular risk in this group.
- Assymetric dimethylarginine (ADMA) is an endogenous methylated arginine which inhibits nitric oxide (NO) synthesis by competing with the substrate of NO, L-arginine, leading to endothelial dysfunction and, consequently, to atherosclerosis.
- It has also been found that hormone therapy (HT), and mainly oral estrogen therapy, lowers ADMA concentrations in healthy postmenopausal women.
- The effect of estrogens on ADMA levels, although small, is considered important, as physiological variation of ADMA is limited.
- Hormone therapy and asymmetrical dimethylarginine in postmenopausal women. Hormones (Athens). 2010 Apr-Jun;9(2):127-35. doi: 10.14310/horm.2002.1262. PMID: 20687396.

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ADMA Estrogens

- Estrogens inhibit the accumulation of ADMA by increasing the activation (but not expression) of DDAH and by protecting the DDAH, which is sensitive to oxidative stress.
- The fact that ADMA levels are lower in premenopausal women than in men of the same age and rise in the postmenopausal period indicates an effect of estrogens in ADMA metabolism in vivo.
- Estrogens also inhibit the accumulation of ADMA in endothelial cells cultures.

  Furthermore, ADMA levels are significantly decreased a in hyper-estrogenemic conditions such as pregnancy.
- By contrast, endothelial dysfunction in preeclampsia is characterised by high ADMA levels.
- Finally, women with polycystic ovary syndrome present higher ADMA concentrations than controls, while treatment with combined estrogens and antiandrogens significantly decrease ADMA.
- 2005 Determination of a reference value for NG, NG-dimethyl-L-arginine in 500 subjects. Eur J Clin Invest 35: 622-626.

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Estrogen ADMA

- Following a two-week subcutaneous implantation of 100mg ethynylestradiol, Holden et al showed a significant reduction (around 18%) of plasma ADMA concentration.[25]
- In the same experiment, it was found that human and murine endothelial cell lines exposed to 17β-estradiol expressed a dose-dependent decrease, in ADMA production.[25]
- This study supported retrospective and cross-sectional studies indicating that HT acts beneficially on the cardiovascular system.[93]
- (25) 2003 Estrogen stimulates dimethylarginine dimethylaminohydrolase activity and the metabolism of asymmetric dimethylarginine. Circulation 108: 1575-1580.
- (93) 2001 Oestrogen and the cardiovascular system: the good, the bad and the puzzling. Trends Pharmacol Sci 22: 152-156.

53

Estrogen lowers ADMA

- Teerlink et al demonstrated that conjugated estrogens, and raloxifene to a lesser extent, decrease ADMA levels in healthy postmenopausal women.[21]
- The study included hysterectomized women who received either conjugated equine estrogens (0.625mg/d), raloxifene or placebo.
- During the two-year treatment, there was a consistent reduction in ADMA levels only in women taking estrogens.
- The average post-baseline difference in ADMA was decreased by 8% (p=0.003).
- Interestingly, there was a trend towards a slight rise in ADMA concentrations in the placebo group throughout the two-year period, probably reflecting an effect of aging.
- Finally, reductions were also observed in the raloxifene group, although non-significant.
- 2003 Oestrogen replacement therapy lowers plasma levels of asymmetrical dimethylarginine in healthy postmenopausal women. Clin Sci 105: 67-71.

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Estrogen Types ADMA

- Research has also been focused on the type of estrogen therapy, the dose, the route of administration, and progestogens addition as to their effect on the cardiovascular system.
- Post et al conducted a study on 65 women who randomly received unopposed micronized 17β-estradiol (2 mg/d), or micronized 17β-estradiol (2 mg/d) plus either dydrogesterone (10 mg/d), or trimegestone (0.5 mg/d), or placebo during a 12-week period.[22]
- The results showed reduction in ADMA levels in all treatment groups, but not in the placebo group.
- Compared to baseline and placebo, the greater reduction in ADMA concentration was noted in the estrogen plus trimegestone group (approximately 19%) and less in the estrogen plus dydrogesterone group (almost 6.5%), while in the unopposed estrogen group the reduction was ≈4%. The same research team had shown 8% reduction with conjugated equine estrogens.[21]
- The difference in ADMA changes between the dydrogesterone and trimegestone was attributed to the stronger antiestrogenic and antiandrogenic action of the latter.
- 2003 Oestrogen replacement therapy lowers plasma levels of asymmetrical dimethylarginine in healthy postmenopausal women. Clin Sci 105: 67-71.

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Route of Administration of Estrogen ADMA

- In 2006, Verhoeven et al investigated the changes in ADMA levels according to the route of administration.[23]
- The authors randomly assigned 152 women to receive either transdermal 17β-estradiol (50µg/d), or oral micronized 17β-estradiol (1mg/d) unopposed, or oral micronized 17β-estradiol (1mg/d) plus gestodene (25µg/d), for thirteen 28-day cycles.
- They found significant reductions in all treatment groups.
- In fact, oral treatment groups presented greater reduction in ADMA levels than transdermal estrogen group.
- Compared to baseline, a 4.4% reduction was noted in the transdermal estrogen group 6.8% in the unopposed oral estrogen group and 8.5% in the oral estrogen plus gestodene group.
- The differences from baseline were similar to those found in two previous studies of the same research team.[21,22] Gestodene in contrast to trimegestone seems to minimally influence the lowering effect of estrogens.
- The difference between the transdermal and oral administration may be attributed to the fact that ADMA is metabolized in the liver.[94,95]
- 2006 Oral, more than transdermal, oestrogen therapy lowers asymmentric dimethylarginine in healthy postmenopausal women: a randomized, placebo-controlled study. J Int Med 259: 199-208.

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E and ADMA

- Verhoeven et al randomly assigned 90 healthy postmenopausal women to receive either intranasal 17β-estradiol (175μg/d) plus norethisterone (275μg/d), or oral 17β-estradiol (1mg/d) plus norethisterone (0.5mg/d), for 52 weeks.24
- They found that there was a significant reduction in ADMA levels only in the oral treatment group ($p<0.001$).
- Specifically, the mean percentage decrease in ADMA levels, compared to baseline, was approximately 1.6% in the intranasal treatment group and 6.7% in the oral treatment group.
- It should be underlined that there was a consistent decrease of around 8% in ADMA concentrations by oral estrogens in the last and in the three previous studies, conducted by the same research team.
- 2007 Effects of intranasal versus oral hormone therapy on asymmetric dimethylarginine in healthy postmenopausal women: a randomized study. Atherosclerosis 195: 181-188.

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E and ADMA

- A recent study suggested that transdermal estrogen treatment had a modulating effect on ADMA plasma levels in patients who had undergone surgery in the early premenopausal period;[97] after six months of treatment, women who received oral 17β-estradiol did not present significant reduction in ADMA concentrations, while controls (no treatment) had significantly higher ADMA levels.
- 2009 Effect of non-oral estrogen on risk markers for metabolic syndrome in early surgically menopausal women. Climact 8: 1-8.

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E and ADMA

- We have tested the hypothesis that ERT lowers plasma levels of asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of NO synthase (NOS).
- In a randomized double-blind study design, 40 hysterectomized postmenopausal women received conjugated equine oestrogen (CEE; 0.625 mg/day; n =14), the selective oestrogen receptor modulator raloxifene (150 mg/day; n =13) or placebo (n =13).
- At baseline and after 6, 12 and 24 months of treatment, plasma was analysed for levels of arginine, ADMA, and symmetrical dimethylarginine (SDMA), a stereoisomer of ADMA that does not inhibit NOS. An overall treatment effect on ADMA levels was observed in the CEE group (P =0.004 compared with placebo), but not in the raloxifene group (P =0.50).
- The decrease of ADMA levels by CEE treatment was consistent over the 2-year study period, without significant differences between the effects at 6, 12 and 24 months.
- Oestrogen replacement therapy lowers plasma levels of asymmetrical dimethylarginine in healthy postmenopausal women. Clin Sci (Lond). 2003 Jul;105(1):67-71. doi: 10.1042/CS20020309. PMID: 12625833.

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T lowers ADMA in males
T = Low NO and high ADMA in males reversed with TR

- **Methods:** In the plasma and urine of 10 hypogonadal men, we measured the major NO metabolites nitrite and nitrate and the endogenous inhibitor of NO synthase (NOS), i.e., asymmetric dimethylarginine (ADMA), before and after a 24-week testosterone treatment to normalize plasma testosterone levels. We tested potential correlations between plasma testosterone, ADMA, and $U_{NOx}R$.
- **Results:** Baseline $U_{NOx}R$ levels were low, indicating impaired nitrite-dependent renal CA activity. Baseline plasma testosterone levels were inversely correlated with creatinine-corrected urinary nitrite excretion ($r = -0.74$, $P = 0.036$) and positively with $U_{NOx}R$ ($r = 0.72$, $P = 0.044$).
- Plasma testosterone level normalization deteriorated these correlations.
- At baseline, $U_{NOx}R$ correlated inversely with urinary excretion of ADMA ($r = -0.75$, $P = 0.013$).
- **Conclusions:** Impaired testosterone synthesis in hypogonadal men favors inflammatory processes, elevates inducible NOS-mediated NO formation, and impairs CA-dependent nitrite reabsorption. Normalization of plasma testosterone reverses these processes. Pharmacological testosterone may combat atherosclerosis in hypogonadal hypogonadism.
- Associations between asymmetric dimethylarginine (ADMA), nitrite-dependent renal carbonic anhydrase activity, and plasma testosterone levels in hypogonadal men. Hellenic J Cardiol. 2018 Jul-Aug;59(4):201-206. doi: 10.1016/j.hjc.2017.10.004. Epub 2017 Nov 8. PMID: 29128547.

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TR

- **Methods:** A review of relevant literature up to September 2018 was performed via PubMed.
- **Conclusion:** Testosterone deficiency might cause endothelial dysfunction by decreasing NO levels through regulating the expression and activity of NO synthase and increasing ADMA expression.
- In addition, testosterone might affect the endothelial repair system by regulating the proliferation and migration of EPCs.
- Testosterone replacement therapy might be useful for treating endothelial dysfunction, considering that some reports have shown that this therapy improved NO bioavailability and EPC function.

- Hotta Y, Kataoka T, Kimura K. Testosterone Deficiency and Endothelial Dysfunction: Nitric Oxide, Asymmetric Dimethylarginine, and Endothelial Progenitor Cells. Sex Med Rev 2019;7:661-668.

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T deficiency raises ADMA raises ED

- **Strengths and limitations:** This study provides evidence of the influence of testosterone deficiency on endothelial function by investigating ADMA and oxidative stress.
- **Conclusion:** Testosterone deficiency increased not only ADMA levels but also oxidative stress and inflammation in castrated rats, which can cause damage to the corpus cavernosum, resulting in erectile dysfunction.
- Kataoka T, Hotta Y, Maeda Y, Kimura K. Testosterone Deficiency Causes Endothelial Dysfunction via Elevation of Asymmetric Dimethylarginine and Oxidative Stress in Castrated Rats. J Sex Med 2017;14:1540-1548.
- Testosterone Deficiency Causes Endothelial Dysfunction via Elevation of Asymmetric Dimethylarginine and Oxidative Stress in Castrated Rats. J Sex Med. 2017 Dec;14(12):1540-1548. doi: 10.1016/j.jsxm.2017.11.001. PMID: 29198509.

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Selenium lowers ADMA - PCOS

- Polycystic ovary syndrome (PCOS) is characterized by various reproductive and cardiometabolic disorders. Asymmetric dimethylarginine (ADMA) is associated with cardiovascular, metabolic, and hormonal status. Selenium, a micronutrient with antioxidant properties, could affect multiple physiological pathways. This study aimed to investigate the effect of selenium supplementation on ADMA, cardiometabolic risk factors, and hormonal status in women with PCOS.
- In this randomized, double-blind, placebo-controlled clinical trial, 66 women with PCOS, aged 18-45 years, were randomly assigned to receive either 200 µg/day selenium or placebo, for 12 weeks.
- Serum testosterone levels declined significantly in the intervention compared to the placebo group (0.01 ± 0.17 vs. - 0.08 ± 0.18 ng/ml, p = 0.038). Pre- to post-Apo-B100/Apo-A1 ratio declined considerably in the intervention group (0.72 ± 0.16 to 0.65 ± 0.16, p = 0.003). No further differences were observed in SHBG, lipid profiles, Apo-A1, Apo-B100, Apo-B100/Apo-A1 ratio, and glycemic control between the two groups at the end of the study.
- Selenium supplementation for 12 weeks had beneficial effects on reduction of circulating ADMA and total testosterone levels in women with PCOS. No significant improvements were seen in other cardiometabolic risk factors. The effects of selenium supplementation on hormonal, reproductive, and cardiometabolic disorders, considering the potential mediating role of ADMA, should be further investigated.
- Effects of Selenium Supplementation on Asymmetric Dimethylarginine and Cardiometabolic Risk Factors in Patients with Polycystic Ovary Syndrome. Biol Trace Elem Res. 2020 Aug;196(2):430-437. doi: 10.1007/s12011-019-01954-6. Epub 2019 Oct 31. PMID: 31667685.

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TR voice change

- **Objectives:** To describe voice changes as a result of the off-label use of androgen supplementation in women.
- **Methods:** A multi-institutional retrospective consecutive case series identified women taking androgen supplementation who presented to voice clinics at two institutions with a chief complaint of voice change between 2014 and 2019. Age, occupation, hormone therapy, indication, Voice Handicap Index-10, fundamental frequency, semitone pitch range, testosterone blood level, treatment undertaken, and long-term outcome were collected.
- **Results:** Nine women presented with voice change after initiation of androgen hormone supplementation.
- The mean age was 55 and three patients were performers.
- All patients underwent hormone therapy with testosterone supplementation, most commonly subcutaneous testosterone pellets.
- Six patients (67%) were being treated for menopause symptoms, one patient for decreased libido, one patient for breast cancer, and one patient who desired additional muscle gain.
- Time of symptom onset after hormone therapy initiation was highly variable, ranging from 0 to 48 months with a mean of 15 months.
- Two patients had markedly elevated serum total testosterone levels.
- Hormone therapy discontinuation and voice therapy were recommended in six (67%) patients each.
- Five patients returned for follow-up after treatment and noted some subjective benefit.
- **Conclusions:** Female patients treated with androgen supplementation may experience unintended voice changes, most prominently reduction in fundamental frequency. Although some benefit may be obtained from voice therapy and cessation of hormone therapy, voice changes may be permanent. Caution should be exercised when prescribing these medications to women.
- Voice Change Following Testosterone Supplementation in Women: A Multi-Institutional Case Series. J Voice. 2021 Nov;35(6):936.e1-936.e7. doi: 10.1016/j.jvoice.2020.03.008. Epub 2020 May 5. PMID: 32386906.

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T voice – but never day never get disclaimer from singers or consider avoiding

- **Objectives** This prospective study was designed to investigate the effect of testosterone, delivered by subcutaneous implants, on the female voice.
- **Methods** Ten women who had opted for testosterone therapy were recruited for voice analysis. Voices were recorded prior to treatment and at 3 months, 6 months, and 12 months while on testosterone therapy. Acoustic samples were collected with subjects reading a sentence, reading a paragraph, and participating in a conversation. Significant changes in the voice over time were investigated using a repeated-measures analysis of variance with the fundamental frequency (F_0) as a response variable. Demographic variables associated with characteristics of the voice were assessed.
- **Results** There were no significant differences in average F_0 related to smoking history, menopausal status, weight, or body mass index. There was no difference in average fundamental speaking frequency (sentence, paragraph, conversation) between the pre-treatment group and any post-treatment group at 3 and 12 months. There was an increase in sentence speech F_0 at 6 months. Two of three patients with lower than expected F_0 at baseline improved on testosterone therapy.
- **Conclusion** Therapeutic levels of testosterone, delivered by subcutaneous implant, had no adverse affect on the female voice including lowering or deepening of the voice.
- Effect of testosterone therapy on the female voice. Climacteric. 2016 Apr;19(2):198-203. doi: 10.3109/13697137.2015.1136925. Epub 2016 Feb 9. PMID: 26857354; PMCID: PMC4819813.

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Little ole voice

- Testosterone is derived from Leydig cells and exerts its effects on androgen receptors to influence growth, mood, voice, and several other bodily functions.
- As men age, their testosterone levels decline.
- Human immunodeficiency virus (HIV) infection has also been associated with lowered serum testosterone levels.
- Subtherapeutic levels of testosterone may lead to fatigue, loss of libido, and dysphoria.
- Issues Surrounding Testosterone Replacement Therapy. Hosp Pharm. 2016 Oct;51(9):712-720. doi: 10.1310/hpj5109-712. PMID: 27803500; PMCID: PMC5080989.

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