WHAT YOU MUST KNOW ABOUT WOMEN'S HORMONES

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

DISCLOSURE STATEMENT

Pamela Smith, MD, Center for Precision Medicine has financial relationships with:

- ZRT Laboratories
- PCCA
- Genova Diagnostics
- American Academy of Anti-Aging Medicine
- Microbiome Labs
- Doctors Data
- Biotics Research

All of the relevant financial relationships listed for these individuals have been mitigated.

LEARNING OBJECTIVES

At the completion of this activity, the participant will be able to:

1. identify the symptoms of peri-menopause and menopause;
2. describe the biochemistry and physiology of female hormones;
3. describe the functions of hormones such as estrogen, progesterone, DHEA, and pregnenolone ;
4. explain the science behind bio-identical hormone replacement; and
5. describe considerations for selecting compounded hormone replacement products.

REFERENCE

- Smith, P., What You Must Know About Women's Hormones. 2nd. Ed. Garden City Park, NY: Square One Publishing, 2022.

MENOPAUSE

- Menopause is the best time in a women's life if her hormones are balanced!

MENOPAUSE

Hormone response is as unique to each person as their own fingerprints.

Hormone replacement should not be considered without a thorough understanding of how all of the body's hormones interact with each other.

The normal age to go through menopause ranges from 35 to 55.

Therefore, a woman may live one half of her life without a menstrual cycle.

Cycling after the age of 55 increases a women's risk of breast cancer.

SYNTHETIC HRT: OTHER PROBLEMS

IT IS ESTIMATED THAT ONE-HALF OF WOMEN QUIT TAKING THEIR SYNTHETIC HORMONE REPLACEMENT THERAPY AFTER ONE YEAR BECAUSE THEY ARE UNABLE TO TOLERATE THE SIDE EFFECTS.

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SYNTHETIC HORMONES WASTE ENERGY BY GIVING INCOMPLETE MESSAGES TO CELLS WHICH THEN FAIL TO PRODUCE A BALANCED HORMONAL RESPONSE.

WHY CONSIDER HRT

- Relief of symptoms
- Prevention of memory loss
- Heart health
- Bone production
- Growth and repair
- Youthful appearance to the skin
- Maintaining a healthy immune system

HORMONES THAT REGULATE GROWTH AND REPAIR

- Insulin
- Growth hormone
- Testosterone
- Estrogens
- DHEA

SYMPTOMS OF MENOPAUSE

- Hot flashes
- Night sweats
- Vaginal dryness
- Anxiety
- Mood swings
- Irritability
- Insomnia
- Depression

SYMPTOMS OF MENOPAUSE (CONT.)

- Loss of sexual interest
- Hair growth on face
- Painful intercourse
- Panic attacks
- Weird dreams
- Urinary tract infections
- Vaginal itching
- Lower back pain
- Bloating

SYMPTOMS OF MENOPAUSE (CONT.)

Flatulence	Indigestion	Osteoporosis	Aching ankles, knees, wrists, shoulders, heels
Hair loss	Frequent urination	Snoring	Sore breasts

SYMPTOMS OF MENOPAUSE (CONT.)

- Palpitations
- Varicose veins
- Urinary leakage
- Dizzy spells
- Anxiety
- Skin feeling crawly
- Migraine headaches
- Memory lapses
- Weight gain

ESTROGEN

ESTROGEN

- Estrogen has 400 functions in the body, including the following:

FUNCTIONS OF ESTROGEN

- Stimulates the production of choline acetyltransferase, an enzyme which prevents Alzheimer's disease
- Increases metabolic rate
- Improves insulin sensitivity
- Regulates body temperature
- Helps prevent muscle damage
- Helps maintain muscle
- Improves sleep

FUNCTIONS OF ESTROGEN (CONT.)

- REDUCES RISK OF CATARACTS
- HELPS MAINTAIN THE ELASTICITY OF ARTERIES
- DILATES SMALL ARTERIES
- INCREASES BLOOD FLOW
- INHIBITS PLATELET STICKINESS
- DECREASES THE ACCUMULATION OF PLAQUE ON ARTERIES
- ENHANCES MAGNESIUM UPTAKE AND UTILIZATION
- MAINTAINS THE AMOUNT OF COLLAGEN IN THE SKIN

FUNCTIONS OF ESTROGEN (CONT.)

- Decreases blood pressure
- Decreases LDL and prevents its oxidation
- Helps maintain memory
- Increases reasoning and new ideas
- Helps with fine motor skills
- Increases the water content of skin and is responsible for its thickness and softness
- Enhances the production of nerve-growth factor
- Positive effect on emotions

FUNCTIONS OF ESTROGEN (CONT.)

- Increases HDL by 10 to 15%
- Reduces the overall risk of heart disease by 40 to 50%
- Decreases lipoprotein(a)
- Acts as a natural calcium channel blocker to keep arteries open
- Enhances energy
- Improves mood
- Increases concentration
- Maintains bone density
- Helps prevent glaucoma

FUNCTIONS OF ESTROGEN (CONT.)

- Increases sexual interest
- Reduces homocysteine
- Decreases wrinkles
- Protects against macular degeneration
- Decreases risk of colon cancer
- Helps prevent tooth loss
- Aids in the formation of neurotransmitters in the brain such as serotonin which decreases depression, irritability, anxiety, and pain sensitivity

REFERENCE

- Graham, B., et al., "Sex hormones are associated with rumination and interact with emotion regulation strategy choice to predict negative affect in women following a sad mood induction," Front Psychol 2018; 9:937.

SYMPTOMS OF ESTROGEN EXCESS

- Cervical dysplasia
- Depression with anxiety or agitation
- Increased risk of uterine cancer
- Weight gain (abdomen, hips, thighs)
- Water retention
- Headaches
- Poor sleep
- Panic attacks
- Swollen breasts

SYMPTOMS OF ESTROGEN EXCESS (CONT.)

Heavy periods
Increased risk of breast cancer
Increased risk of some autoimmune diseases
Hypothyroidism
Fatigue
Irritability/mood swings
Uterine fibroids
Bloating

CAUSES OF EXCESS ESTROGEN IN THE BODY

- Taking too much estrogen
- Impaired elimination of estrogen
- Lack of exercise
- Diet low in grains and fiber
- Environmental estrogens

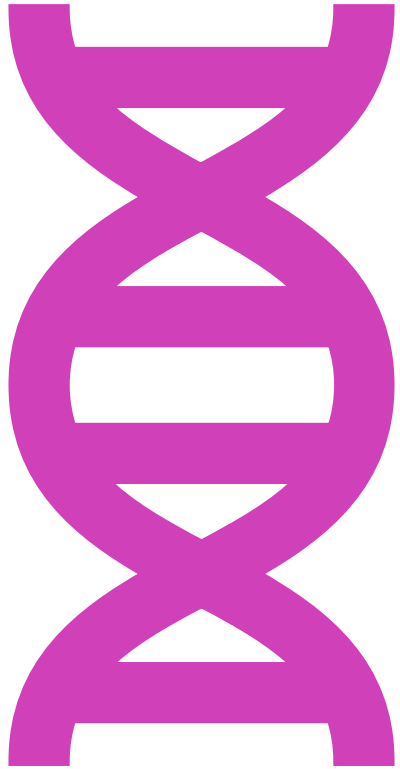
SYNTHETIC ESTROGEN

- Synthetic estrogen is not the same chemical structure of estrogen that the patient's body is born with.
- Most common synthetic estrogen available worldwide.

  Estrone

  Sodium equilin sulfate

  Concomitant components
  - 17 alpha-dihydroequilin
  - 17 alpha-estradiol
  - 17 beta-dihydroequilin



NATURAL ESTROGEN

Medically, natural estrogen means that it is the same chemical structure that the patient is born with.

It may or may not come from a plant.

Natural estrogen helps to protect against endothelial dysfunction by increasing endothelial nitric oxide.

- Novella, S., et al., "Vascular aging in women: Is estrogen the fountain of youth?" Front Physiol 2012; 3:165.

NATURAL ESTROGEN (CONT.)

Endothelial nitric oxide synthase is a crucial enzyme involved in the production of nitric oxide in endothelial cells.

Study showed that compared to natural estrogen, gene transcription of endothelial nitric oxide synthase was 30 to 50% lower in response to equine estrogens.

Novensa, L., et al., "Equine estrogens impair nitric oxide production and endothelial nitric oxide synthase transcription in human endothelial cells compared with the natural 17(beta)-estradiol," Hypertension 2010; 56(3):405-11.

NATURAL ESTROGENS (CONT.)

- E1 called estrone
- E2 called estradiol
- E3 called estriol

ESTRONE (E1)

It is the main estrogen the body makes post-menopause.

High levels many researchers believe may increase a women's risk of breast cancer.

Estrone is a major source of local bioactive estrogen formation in human bone.

ESTRADIOL (E2)

Increases HDL
Decreases LDL and total cholesterol
Decreases triglycerides
Helps maintain bone structure
Increases serotonin
Decreases fatigue
Works as an antioxidant
Helps maintain memory
Helps absorption of calcium, magnesium, zinc

ESTRADIOL (CONT.)

- Results of a new trail reveal that estradiol has a direct effect in reducing atherosclerosis by reducing cholesterol accumulation in the arterial wall.

Karim, R, et al., Abstract MP09. Presented at: American Heart Association Epidemiology, Prevention, Lifestyle and Cardiometabolic Health Scientific Sessions; March 3-6, 2020; Phoenix.

ESTRIOL (E3)

- It is 80 times weaker than E2 so has a lesser stimulatory effect.
- Considerable evidence exists to show that it protects against breast cancer.
- Experimentally E3 is being used in breast cancer patients.
- It does not have the bone, heart, or brain protection of estradiol.

FUNCTIONS OF E3 IN THE BODY

- Helps maintain pregnancy
- Benefits the vaginal lining
- Blocks E1 by occupying the estrogen receptor sites on the cells of the breasts
- Controls symptoms of menopause
- Deceases LDL
- Increases HDL

FUNCTIONS OF E3 IN THE BODY (CONT.)

- Helps reduce pathogenic bacteria
- Helps restore the proper pH of the vagina, which prevents urinary tract infections
- Helps the GI tract maintain a favorable environment for the growth of lactobacilli

FUNCTIONS OF E3 IN THE BODY (CONT.)

Emerging evidence indicates that estriol has potential immunomodulatory benefits for many disease states including autoimmune, inflammatory, and neurodegenerative conditions.

This review, discusses emerging roles for estriol in the treatment of menopausal symptoms, osteoporosis, cancer, hyperlipidemia, vascular disease, and multiple sclerosis.

- Ali, E., et al., "Estriol: emerging clinical benefits," Menopause 2017; 24(9):1081-85.

ESTROGEN RECEPTOR SITES

- Estrogen has two main receptor sites that it binds to in the body
  - Estrogen receptor alpha
    - Increases undesirable growth in reproductive tissues
  - Estrogen receptor beta
    - Decreases cell growth
    - Helps prevent breast cancer development
    - Promotes beneficial estrogenic effects on skin, bone, brain, and other tissues

Farzaneh, S., et al., "Estrogen receptor ligands: A review (2013-2015)," Sci Pharm 2016; 13:84(3):409-27.

ESTROGEN RECEPTOR SITES (CONT.)

E2 equally activates estrogen-receptors alpha and beta.

E1 activates estrogen-receptor alpha selectively in a ratio of 5:1 which increases cell proliferation.

E3 binds preferentially to estrogen-receptor beta in a 3:1 ratio which may be the reason that E3 may help prevent breast cancer.

ESTROGEN RECEPTOR SITES (CONT.)

- Siberian rhubarb has been shown to activate estrogen receptor ER-beta to a greater extent than ER-alpha receptors.

  Wober, J., et al., "Activation of estrogen receptor-beta by a special extract of Rheum rhaponticum (ERr 731), its aglycones and structurally related compounds," Jour Steroid Biochem Mol biol 2007; 107(3-5):191-201.

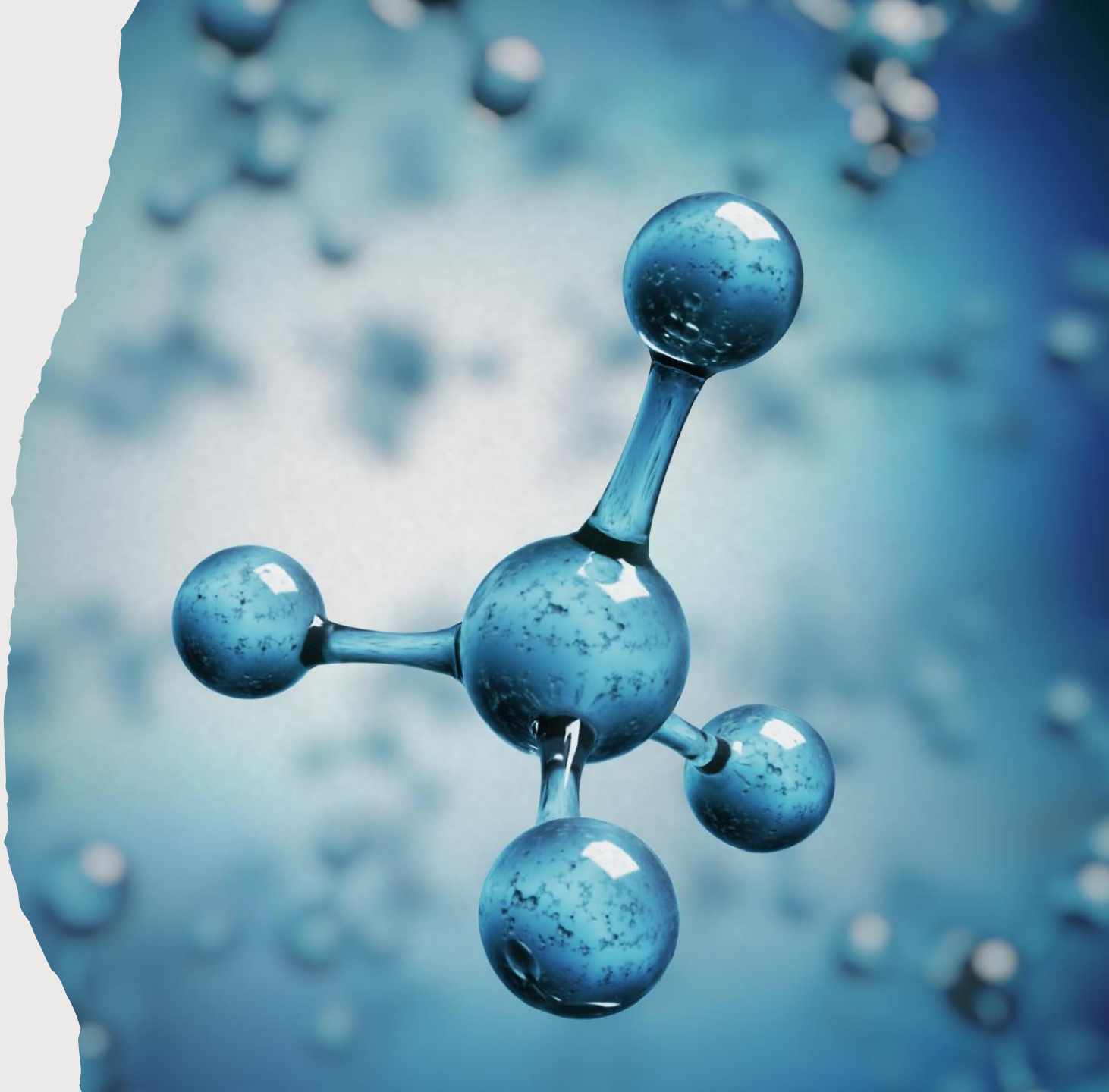
ESTROGEN METABOLISM

After menopause, the metabolism of estrogen can change.

Consequently, a women may respond differently to estrogen replacement.

ESTROGEN METABOLISM (CONT.)

- Two major competing pathways
  - 2-OH estrone
  - 16-OH estrone



2-OH ESTRONE/METHYLATION

2-OH is the "good estrogen." It does not stimulate cell growth.

It blocks the action of stronger estrogen products that may be carcinogenic.

2-OH estrone is protective against cancer when methylated by catechol-O-methyltransferase (COMT) into 2-methoxy-estrone.

The ratio of 2-methoxyestrone to 2-hydroxyestrone can be measured in the urine and is a good gauge of the body's ability to methylate.

FACTORS THAT SUPPORT METHYLATION

SAMe	Methionine	B2, B6, B12
Folic acid (also as folinic acid, 5-formyl THF, or 5-methyltetrahydrofolate--MTHF)	TMG (betaine)	Reducing catecholamine production by decreasing stress

16-OH ESTRONE

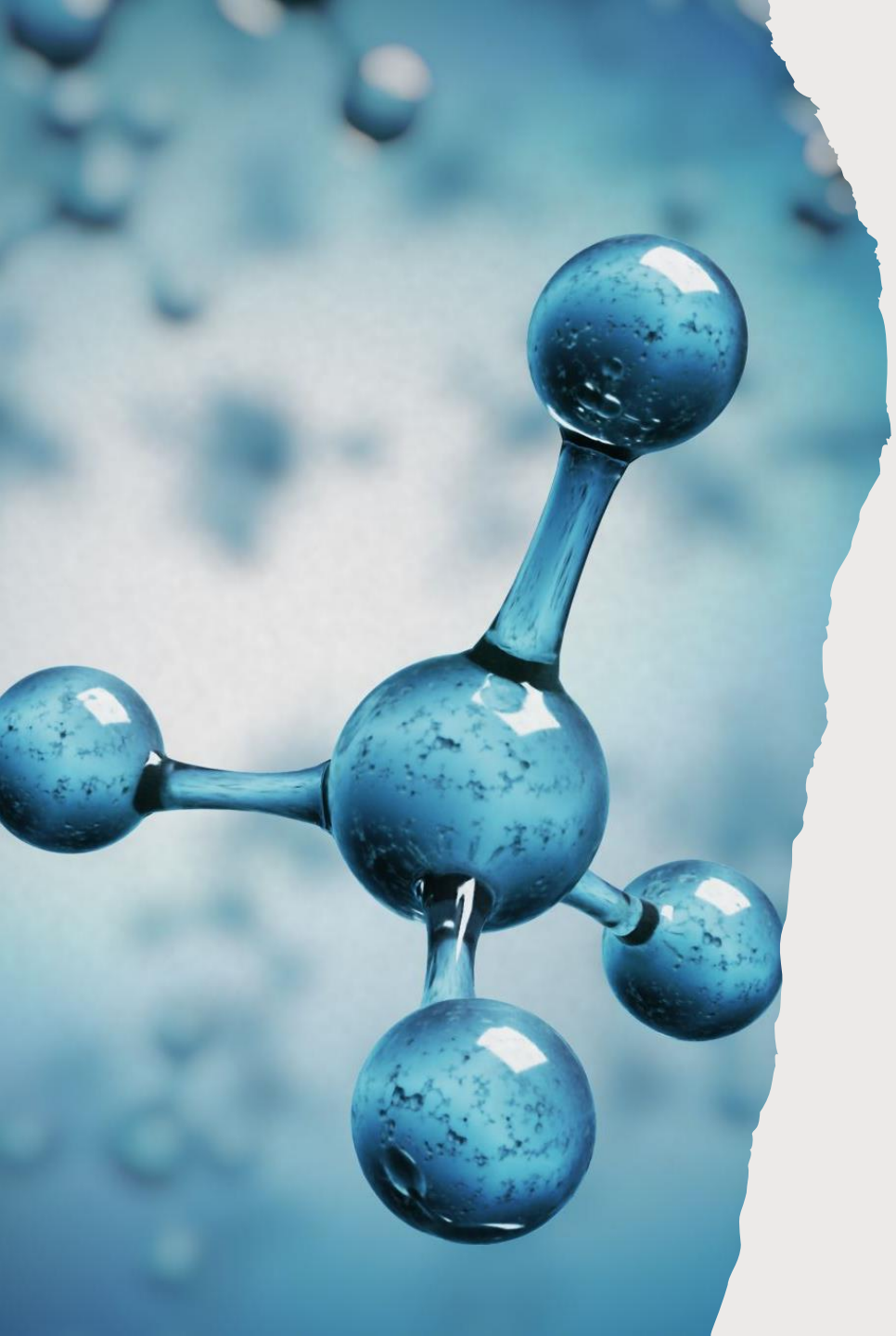
16-OH has significant strong estrogenic activity and studies show it may be associated with an increased risk of breast cancer.

High levels are associated with obesity, hypothyroidism, pesticide toxicity (organochlorines such as endosulfan, dieldrin, and DDE, a DDT metabolite), omega-6-fatty acid excess, and inflammatory cytokines.

ESTROGEN METABOLISM

- Results of this prospective study support the hypothesis that the estrogen metabolism pathway favoring 2-hydroxylation over 16alpha-hydroxylation is associated with a reduced risk of invasive breast cancer risk in premenopausal women.

  Muti, P., et al., "Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16alpha-hydroxyestrone ratio in premenopausal and postmenopausal women," Epidemiology 2000; 11(6):635-40.



ESTROGEN METABOLISM (CONT.)

- One minor pathway
  - 4-OH estrone

4-OH ESTRONE

Studies show it may directly damage DNA and cause mutations. Therefore, it is proposed to enhance cancer development.

Equine estrogens, such as Premarin, increase metabolism into 4-OH estrones.

4-OH is present in greater quantities there is a deficiency of methionine and folic acid.

People who have uterine fibroids also may have increased levels of 4-OH estrone.

HOW CAN YOU RAISE 2-OH ESTRONE?

Moderate exercise

Cruciferous vegetables

Flax

Soy

Kudzu

Broccoli derivatives: indole-3-carbinol taken as a supplement. Daily dose is 200 to 300 mg. Other derivatives of broccoli that have been shown to be effective are DIM (diindolymethane, a breakdown product of I-3-C) and sulforaphane glucosinolate.

HOW CAN YOU RAISE 2-OH ESTRONE? (CONT.)

- Omega-3-fatty acids
- B6, B12, and folate
- MTHF
- TMG
- Rosemary, turmeric
- Weight loss
- High protein diet

THERE ARE OTHER FACTORS THAT AFFECT ESTROGEN METABOLISM.

OBESITY AFFECTS ESTROGEN METABOLISM

Obesity decreases 2-OH estrone and increases 16-OH estrone.

Estrogen production and storage occurs in fat cells.

Concentrations of sex hormone binding globulin (SHBG) are decreased.

In addition, inflammatory factors found in the breast of obese women considerably impact estrogen signaling, mainly by driving changes in aromatase expression the enzyme responsible for estrogen production, and therefore promote tumor formation and progression.

- Gerard, C., et al., "Obesity and breast cancer - Role of estrogens and the molecular underpinnings of aromatase regulation in breast adipose tissue," Mol Cell Endocrinol 2018; 466:15-30.

XENOESTROGENS

What Are They and Where Are They Hiding

ALCOHOL

- Alcohol interferes with the body's ability to detoxify estrogen and increases E2 levels and the risk of breast cancer.

Scoccianti, C., et al., "Recent evidence on alcohol and cancer epidemiology," Future Oncol 2013; 9(9):1315-22.

Scoccianti, C., et al., "Female breast cancer and alcohol consumption: a review of the medical literature," Amer Jour Prev Med 2014; 46(3 Suppl 1):S:16-25.

ANTIBIOTICS

- Antibiotics found in food may be associated with an elevated risk of breast cancer by changing the gut flora involved in the enterohepatic circulation of estrogens.

ESTROGEN AND THE BRAIN

- Common comments I hear from patients are the following:
  - "I think that I am losing my mind."
  - "I feel like my body is divorcing itself."
  - "I have lost the ability to spell."
  - "I am always losing my keys."
  - "I may be getting Alzheimer's disease."

ESTROGEN AND THE BRAIN (CONT.)

- Increases blood flow
- Increases glucose and oxygen to the neurons
- Protects neurons
- Increases neurotransmitters
- Keeps the blood-brain barrier working
- Increases sensitivity to nerve growth factor
- Decreases neuronal generation of Alzheimer's beta amyloid peptides

ESTROGEN AND THE BRAIN (CONT.)

- Is a natural antioxidant
- Increases manual speed and dexterity
- Increases availability of acetylcholine
- Boosts by 30% NMDA receptors to maintain strength and durability of synapse connections involved in creating long-term memories
- Decreases distractibility
- Turns on progesterone receptors

ESTROGEN AND THE HEART

- Reports have correlated the use of estrogen for the treatment of menopausal symptoms with beneficial effects on the cardiovascular system.
- The prospective randomized Women's Health Initiative (WHI) and the Early Versus Late Intervention Trial (ELITE) showed that starting menopausal hormone treatment (MHT) within 5 to 10 years of menopause is fundamental to the success of estrogen's cardioprotection in post-menopausal women without adverse effects.

Naftolin, F., et al., "Cardiovascular health and the menopausal woman: the role of estrogen and when to begin and end hormone treatment," F1000 Res 2019; PMID 31543950.

ESTROGEN AND THE HEART (CONT.)

Presented at the American College of Cardiology Scientific Session, March 2017 in Washington D.C. by Yoav Arnson, M.D.

He looked at coronary artery calcium scanning between 1998 and 2012 of postmenopausal women.

"HRT results in lower atherosclerosis and improved survival for all age groups and for all levels of coronary calcium."

ESTROGEN AND HYPERTENSION

Menopause is accompanied by a dramatic rise in the prevalence of hypertension in women, suggesting a protective role of endogenous estradiol on blood pressure. Human clinical investigations suggest that estrogen engages several mechanisms that protect against hypertension, such as activation of the vasodilator pathway mediated by nitric oxide and prostacyclin and inhibition of the vasoconstrictor pathway mediated by the sympathetic nervous system and angiotensin.

However, oral estrogen raises blood pressure. Transdermal delivery of estrogen, which avoids the first-pass hepatic metabolism of estradiol, has a blood pressure lowering effect in postmenopausal women.

Consequently, this is another reason that estrogen should always used on the skin and not taken by mouth.

- Ashraf, M., et al., "Estrogen and hypertension," Curr Hypertens Rep 2006; 8(5):368-76.

ESTROGEN AND HYPERTENSION (CONT.)

This study highlights that estradiol plays an important role in the development of systemic HTN and target organ damage, exerting several modulatory effects.

The influence of E2 leads to alterations in mechanisms regulating the sympathetic nervous system, renin-angiotensin-aldosterone system, body mass, oxidative stress, endothelial function and salt sensitivity; all associated with a crucial inflammatory state and influenced by genetic factors, ultimately resulting in cardiac, vascular and renal damage in HTN.

Consequently, it is important to replace estradiol after menopause when E2 levels become low.

It is also paramount that estrogen be prescribed transdermally.

- Sabbatini, A., et al., "Estrogen-related mechanisms in sex differences of hypertension and target organ damage," Biol Sex Differ 2020; 11:31.

ESTROGEN AND HEART FAILURE

Studies revealed that cardiac estrogen is reduced in heart failure.

It was found that estrogen supplementation rescues pre-existing heart failure by restoring cardiac estrogen and aromatase, stimulating angiogenesis, and suppressing fibrosis.

- Iorga, A., et al., "Rescue of pressure overload-induced heart failure by estrogen therapy," Jour Amer Heart Assoc 2016; 5(1):e002482.
- Iorga, A., et al., "Estrogen rescues heart failure through estrogen receptor beta activation," Biol Sex Diff 2018; 9(1):48.

ESTROGEN AND MEMORY

- The results of this study indicate that HRT may contribute to beneficial cognitive outcomes after menopause under an obesogenic diet.

  Zimmerman, B., et al., "Longitudinal effects of immediate and delayed estradiol on cognitive performance in a spatial maze and hippocampal volume in menopausal macaques under an obesogenic diet," Front Neurol 2020; 11:539.

ESTROGEN AND BONE HEALTH

- Studies support that hormone replacement improves BMD and reduces fracture risk in women with and without osteoporosis.
- The authors of this trail propose that HRT should be considered for the primary prevention and treatment of osteoporosis in appropriate candidates and that estrogen should be transdermally applied and not orally prescribed.

Levin, V., et al. "Estrogen therapy for osteoporosis in the modern era," Osteoporos Int 2018; 29(5):1049-55.

ESTROGEN AND CATARACTS

- This study suggests that estrogen replacement has a protective effect against the development of cataracts.

Na, K-S., et al., "The ocular benefits of estrogen replacement therapy: a population-based study in postmenopausal Korean women," PLoS One 2014; 9(9):e106473.

ESTROGEN AND DIABETES

- This systemic review and meta-analysis provides evidence that postmenopausal women using low-dose combined estrogen replacement therapy have a decreased risk of developing diabetes and have better diabetic control.

  Xu, Y., et al., "Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus," Kaohsiung Jour Med Sci 2014; 30(7):350-61.

ESTROGEN DEFICIENCY

- Estrogen deficiency has been suggested to be a state of accelerated aging.

  Birge, S., "The use of estrogen in older women," Clin Geriatr Med 2003; 19(3):617-27.

ESTROGEN REPLACEMENT

- In a 2013 study: researchers estimated that over the past decade between 18,600 to 91,600 postmenopausal women, ages 50-59 years old, who had had a hysterectomy may have died prematurely because they did not take estrogen.

  Sarrel, P., et al., "The mortality toll of estrogen avoidance: An analysis of excess deaths among hysterectomized women aged 50 to 59 years," Amer Jour Public Health 2013; July 18.

ESTROGEN REPLACEMENT (CONT.)

- Another study which was a meta-analysis from 27 published studies showed a 28% reduction in mortality in menopausal women under age 60 who used hormone replacement therapy and the participants also had improved quality of life.

Salpeter, S., et al., "Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women," Amer Jour Med 2009; 22(11):1016-22.

ESTROGEN REPLACEMENT (CONT.)

Consequences of a hypo-estrogenemic duration in women's lives are poorly understood.

The Study of Women Across the Nation suggests its magnitude is greater than was previously acknowledged. We propose that the healthy user bias was the result of surgical treatment (hysterectomy with oophorectomy) for many gynecological maladies followed by pharmacological and physiological doses of estrogen to optimize patient quality of life.

The past decade of research has begun to demonstrate the role of estrogen in homeostasis.

- Tumer, R., et al., "A theory of eu-estrogenemia: a unifying concept," Menopause 2017; 24(9):1086-97.

ESTROGEN REPLACEMENT (CONT.)

The method of estrogen delivery is vital in assessing its benefits and uses.

Always prescribe estrogen transdermally or transvaginally.

For example, the use of estrogen transdermally, in stark contrast to orally, has been linked to a lower risk of deep vein thrombosis, cholecystitis, osteoporosis, and stroke.

- Valdes, A., et al., "Estrogen therapy," Stat Pearls (Internet) May 30, 2020.

ESTROGEN REPLACEMENT THERAPY (CONT.)

Patients dependent on exogenous thyroid hormone will have an increased dose requirement after the initiation of oral estrogen treatment, whereas in patients with a functional thyroid, endogenous thyroid hormone production will increase.

Transdermal estradiol has minimal effects on thyroxine-binding globulin because this route of administration circumvents the first-pass effect on the liver.

- Shifren, J., et al., "A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women," Menopause 2007;14:985-94.

ESTROGEN GIVEN BY MOUTH

- Increases blood pressure
- Increases triglycerides
- Increases estrone
- Causes gallstones
- Elevates liver enzymes
- Increases SHBG (decreases testosterone)
- Interrupts tryptophan metabolism and consequently serotonin metabolism
- Lowers growth hormone
- Increases prothrombic effects
- Increases CRP
- Increases carbohydrate cravings

ESTROGEN GIVEN BY MOUTH (CONT.)

- Study revealed that compared with no hormone therapy, use of oral conjugated equine estrogen or oral estradiol was associated with excess risk for venous thromboembolism.
- In contrast, use of transdermal estradiol (most commonly used as a patch) was not associated with excess venous thromboembolism.

Vinogradova, Y., et al., "Use of hormone replacement therapy and risk of venous thromboembolism: Nested case-control studies using the QResearch and CPRD databases," BMJ 2019; Jan 9; 364:k4810.

ESTROGEN GIVEN BY MOUTH (CONT.)

Study of over 112,000 women.

Women taking oral estrogen therapy had a 14% higher risk of developing high blood pressure compared to those using transdermal estrogen and a 19% higher risk of developing high blood pressure compared to those using vaginal estrogen creams or suppositories.

Compared to estradiol, conjugated equine estrogen was associated with an 8% increased risk of developing high blood pressure.

- Kalenga, C., et al., "Association between the route of administration and formulation of estrogen therapy and hypertension risk in postmenopausal women: A prospective population-based study," Hypertension, June 2023.

TREATMENT

- Compounded by a pharmacy
  - Dose is individualized
  - Can use any mix of different percentages of E2 and E3 (biest)
  - Only method of obtaining E3 in North America
  - Individualized therapy
  - Do not use triest

PROGESTERONE

PROGESTERONE

Progesterone is one of the sex hormones. It plays a role in menstruation, pregnancy, and the formation of embryos.

Progesterone is made in the ovaries up until menopause. After menopause, it is made in the adrenal glands.

Progesterone is made from pregnenolone and performs many functions in the body.

FUNCTIONS OF PROGESTERONE

- Acts as a diuretic
- Is anti-inflammatory
- Aids in ovulation
- Balances estrogen
- Effects the potentiation of GABA
- Enhances the action of thyroid hormones
- Has a positive effect on sleep
- Helps build bone

FUNCTIONS OF PROGESTERONE (CONT.)

- Helps prevent anxiety, irritability, and mood swings
- Helps restore proper cell-oxygen levels
- Helps the body use and eliminate fats
- Increases metabolic rate
- Increases scalp hair
- Induces conversion of E1 to the inactive E1S form
- Lowers LDL
- Modulates oxytocin receptor binding in the hypothalamus

FUNCTIONS OF PROGESTERONE (CONT.)

- Protects breast health
- Relaxes smooth muscle of the gut to aid in breaking down food
- Supports the immune system
- Helps promote implantation of the egg
- Promotes the formation of myelin sheaths
- Maintains pregnancy
- Promotes Th2 immunity
- Helps maintain bladder function

SYMPTOMS OF PROGESTERONE LOSS

- Anxiety
- Depression
- Irritability
- Mood swings
- Insomnia
- Pain and inflammation
- Osteoporosis
- Excessive menstruation

SYMPTOMS OF PROGESTERONE LOSS (CONT.)

- Hypersensitivity
- Nervousness
- Migraine headaches before cycles
- Weight gain
- Decreased libido
- Decreased HDL

CAUSES OF LOW PROGESTERONE

- Impaired production
- Low LH
- Increased prolactin production
- Stress
- Antidepressants
- Excessive arginine consumption
- Sugar
- Saturated fat
- Deficiency of vitamins A, B6, C, zinc
- Decreased thyroid hormone

SYNTHETIC PROGESTERONE

Synthetic progesterone is called progestins.

Progestins do not reproduce the same actions of natural progesterone.

POSSIBLE SIDE EFFECTS OF PROGESTINS

Increases appetite	Weight gain	Fluid retention	Irritability	Depression
Headache	Decreases energy	Bloating	Breast tenderness	Decreases sexual interest

POSSIBLE SIDE EFFECTS OF PROGESTINS (CONT.)

Acne	Hair loss	Nausea	Insomnia
Interferes with the body's own production of progesterone	Does not help balance estrogen	Remains in the body longer	Can cause spasm of coronary arteries

POSSIBLE SIDE EFFECTS OF PROGESTINS (CONT.)

- Progestins increase breast cell replication and growth due to the stimulation of estrogen receptors by progestins.

Wood, C., et al., "Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys," Breast Cancer Res Treat 2007; 101(2):125-34.

Liang, Y., et al., "Synthetic progestins induce growth and metastasis of BT-474 human breast cancer xenografts in nude mice," Menopause 2010; 17(5):1040-47.

Ory, K., et al., "Apoptosis inhibition mediated by medroxyprogesterone acetate treatment of breast cancer cell lines," Breast Cancer Res Treat 2001; 68(3):187-98.

POSSIBLE SIDE EFFECTS OF PROGESTINS (CONT.)

- Progestins increase the risk of breast cancer.

  Rossouw, J., et al., "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial," JAMA 2002; 288(3):321-33.

  Fournier, A., et al., "Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort," Int Jour Cancer 2005; 114(3):448-54.

  Porsch, J., et al., "Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (U.S.)," Cancer Causes Control 2002; 13(9):847-54.

POSSIBLE SIDE EFFECTS OF PROGESTINS (CONT.)

Estrogen plus progestin increases breast cancer incidence with cancers more commonly node positive.

Breast cancer mortality also appears to be increased with combined estrogen plus progestin use.

- Chlebowski, R., et al., "Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women," JAMA 2010; 304(15):1684-92.

POSSIBLE SIDE EFFECTS OF PROGESTINS (CONT.)

- Stops the protective effects estrogen has on the heart
- May make the symptoms of progesterone loss worse
- Increases LDL
- Decreases HDL
- Protects only the uterus from cancer
- Counteracts many of the positive effects of estrogen on serotonin

ESTROGEN PLUS PROGESTIN

Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use.

This treatment should not be prescribed for the prevention of cardiovascular disease.

Manson, J., et al., "Estrogen plus progestin and the risk of coronary heart disease," NEJM 2003; 349(6):523-34.

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS

- Helps balance estrogen
- Leaves the body quickly
- Improves sleep
- Natural calming effect
- Lowers high blood pressure
- Helps the body use and eliminate fats
- Lowers cholesterol

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS (CONT.)

- Increases scalp hair
- Helps balance fluids in the cells
- Increases the beneficial effects of estrogen on BV
- Increases metabolic rate
- Natural diuretic
- Natural antidepressant
- Is anti-inflammatory

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS (CONT.)

- Stimulates the production of new bone
- Enhances the action of thyroid hormones
- Improves libido
- Helps restore proper cell oxygen levels
- Induces conversion of E1 to the inactive E1S form
- Promotes Th2 immunity
- Is neuroprotective, promoting myelination

- Stein, D., et al., "Does progesterone have neuroprotective properties?" Ann Emer Med 2008; 51(2):164-72.
- Prior, J., "Progesterone for the prevention and treatment of osteoporosis in women," Climacteric 2018; 21(4):366-74.
- Seifert-Klauss, V., "Progesterone and bone: actions promoting bone health in women," Jour Osteoporosis 2010; 2010:845180.

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS (CONT.)

- Studies have shown that progesterone does NOT induce estrogen-stimulated breast cell proliferation.

Murkes, D., et al., "Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bel-2 protein in healthy women," Fertil Steril 2011; 95(3):1188-91.

Neubauer, H., et al., "Overexpression of progesterone receptor membrane component 1: possible mechanism for increased breast cancer risk with norethisterone in hormone therapy," Menopause 2013; 20(5):504-10.

REFERENCES

Murkes, D., et al., "Percutaneous estradiol/oral micronized progesterone has less-adverse effects and different gene regulations than oral conjugated equine estrogens/medroxyprogesterone acetate in the breast of healthy women in vivo," Gynecol Endocrinol 2012; 28(Suppl 2):12-5.

Wood, C., et al., "Transcriptional profiles of progesterone effects in the postmenopausal breast," Breast Cancer Res Treat 2009; 114(2):233-42.

Mueck, A., et al., "Comparison of the proliferative effects of estradiol and conjugated equine estrogens on human breast cancer cells and impact of continuous combined progestogen addiction," Climacteric 2003; 6(3):221-27.

Chang, K., et al., "Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo," Fertil Steril 1995; 63(4):785-91.

Foidart, J., et al., "Estradiol and progesterone regulate the proliferation of human breast epithelial cells," Fertil Steril 1998; 69(5):963-69.

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS (CONT.)

Natural progesterone has been shown to decrease the risk of developing breast cancer.

A study looked at 80,000 postmenopausal women for 8 years using different kinds of HRT.

- It found that women who used estrogen in combination with synthetic progestin had a 69% increased risk of developing breast cancer when compared to women who never took HRT.
- Women who used progesterone in combination with estrogen had no increased risk in developing breast cancer compared to women that did not use HRT and also had a decreased risk in developing breast cancer compared to the women that used progestin.

REFERENCE

Fournier, A., et al., "Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study," Breast Cancer Res Treat 2008; 107(1):103-11.

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS (CONT.)

Another study done by the same researchers found a 40% increased risk of developing breast cancer in women who used estrogen with progestin.

In women who used estrogen combined with progesterone there was a trend toward a decreased risk of developing breast cancer.

- Fournier, A., et al., "Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort," Int Jour Cancer 2005; 114(3):448-54.

NATURAL PROGESTERONE EFFECTS NOT SEEN WITH PROGESTINS (CONT.)

- A new study has found that "the relative risk of being diagnosed with breast cancer was 20% to 30% higher among women who use or recently used birth control pills with a two-hormone combination, progestogen-only pills or hormonal IUDs compared to women who did not."

Fitzpatrick, D., et al., "Combined and progestogen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis," PLOS Med 2023; 20(3):e1004188.

ESTROGEN/PROGESTERONE RATIO

PROLONGED USE OF PROGESTERONE WITHOUT ADEQUATE ESTROGEN

- Increases weight gain
- Increases total cholesterol
- Decreases HDL
- Increases LDL
- Increases triglycerides
- Causes depression
- Causes fatigue
- Decreases libido
- Decreases insulin resistance
- Increases fat storage

EFFECTS OF TOO MUCH PROGESTERONE EVEN WITH ADEQUATE ESTROGEN

- Elevates cortisol
- Increases insulin resistance
- Increases appetite and carbohydrate cravings
- Relaxes the smooth muscles of the gut: can cause bloating, fullness, and constipation. It can also contribute to gallstones.
- Causes incontinence
- Decreases growth hormone
- Causes ligaments to relax and can cause backaches, leg aches, and achy hip
- Suppresses the immune system

ADRENALINE

Adrenaline interacts with progesterone.

Adrenaline surges that occur with stress can block progesterone receptors.

This can prevent progesterone from being used effectively in the body.

TREATMENT

Compounded progesterone as a cream or as a capsule.

If the patient has insomnia as symptom, then choose P.O. which affects the GABA receptors.

Experts on HRT now suggests that for peri-menopausal women and menopausal women: progesterone PO helps prevent breast cancer better than transdermally applied progesterone.

Prometrium-- advantages and disadvantages

PROGESTERONE AND BREAST CANCER PREVENTION

Study measured blood levels of progesterone in almost 6,000 women that were premenopausal.

Women with the highest levels of progesterone who had regular cycles had a 88% reduction in the risk of developing breast cancer.

- Micheli, A., et al., "Endogenous sex hormones and subsequent breast cancer in premenopausal women," Int Jour Cancer 2004; 112(2):312-18.

PROGESTERONE AND BREAST CANCER PREVENTION (CONT.)

In another study over 1,000 women were studied for over 30 years who had treatment for infertility. The trial was done to look at subsequent breast cancer risk.

Women who were deficient in progesterone had 5.4x increased risk of developing premenopausal breast cancer and were10x as likely to die from any cancer.

- Cowan, L., et al., "Breast cancer incidence in women with a history of progesterone deficiency," Amer Jour Epidemiol 1981; 114(2):209-17.

TESTOSTERONE

TESTOSTERONE

- Increases sexual interest
- Increases sense of emotional well-being
- Increases muscle mass and strength
- Helps maintain memory
- Helps skin from sagging
- Decreases excess body fat
- Helps maintain bone strength
- Elevates norepinephrine in the brain (tricyclic affect)
- Aids with pain control

REFERENCES

Korkidakis, A., et al., "Testosterone in women: Measurement and therapeutic use," Jour Obstet Gynaecol Can 2017; 39(3):124-130.

Shufelt, C., et al., "Safety of testosterone use in women," Maturitas 2009; 63(1):63-6.

Bolour, S., et al., "Testosterone in women: a review," Int Jour Impot Res 2005; 17(5):399-408.

Hubayter, Z., et al., "Testosterone therapy for sexual dysfunction in postmenopausal women," Climateric 2008; 11(3):181-91.

Glaser, R., et al., "Testosterone therapy in women: myths and misconceptions," Maturitas 2013; 74(3):230-34.

SYMPTOMS OF TESTOSTERONE LOSS

Muscle wasting	Weight gain	Fatigue	Low self-esteem	Decreased HDL
Dry, thin skin, with poor elasticity	Thinning and dry hair	Droopy eyelids	Sagging cheeks	Thin lips
Anxiety	Memory is not as sharp			

CAUSES OF LOW TESTOSTERONE

- Menopause
- Childbirth
- Chemotherapy
- Adrenal stress or burnout
- Endometriosis
- Depression
- Psychological trauma
- Oral contraceptives
- HMG-CoA-reductase inhibitors

TREATMENT

Testosterone replacement should be transdermal.
Use the bio-identical form. Methyltestosterone has been associated with an increase in liver cancer.
If used transdermally must rotate sites.
In order for testosterone to work well, estradiol must also be optimized.
Without enough estrogen, testosterone cannot attach to brain receptors.
If testosterone is given alone, it can increase plaque formation on the vessels of the heart.

TREATMENT (CONT.)

- This study showed the safety and efficacy of using testosterone for postmenopausal women with low sexual desire with administration via non-oral routes (e.g., transdermal application) preferred because of a neutral lipid profile.

Islam, R., et al., "Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data," Lancet Diabetes Endocrinol 2019; 7(10):754-66.

TREATMENT (CONT.)

- Clinical trials suggest that exogenous testosterone enhances cognitive performance and improves musculoskeletal health in postmenopausal women.

  Davis, S., et al., "Testosterone in women—the clinical significance," Lancet Diabetes Endocrinol 2015; 3(12):980-92.

TREATMENT (CONT.)

Study showed improvement in scalp hair with testosterone use in women with low testosterone levels.

The fact that no subject complained of hair loss as a result of treatment casts doubt on the presumed role of testosterone in driving female scalp hair loss.

- Glaser, R., et al., "Improvement in scalp hair growth in androgen-deficient women tested with testosterone: a questionnaire study," Brit Jour Dermatol 2012; 166(2):274-78.

HOW ELSE CAN TESTOSTERONE LEVELS BE RAISED?

Decrease calorie intake	Increase protein in the diet	Take the amino acids arginine, leucine, glutamine	Exercise
Get enough sleep	Lose weight	Reduce stress	Take zinc if deficient. Zinc is needed for the metabolism of testosterone.

SYMPTOMS OF ELEVATED TESTOSTERONE

- Anxiety
- Depression
- Fatigue
- Hypoglycemia
- Salt and sugar cravings
- Agitation and anger
- Facial hair
- Acne
- Insulin resistance
- Weight gain
- Hair loss or unwanted hair growth
- Increased risk of heart disease

TREATMENT OF ELEVATED TESTOSTERONE

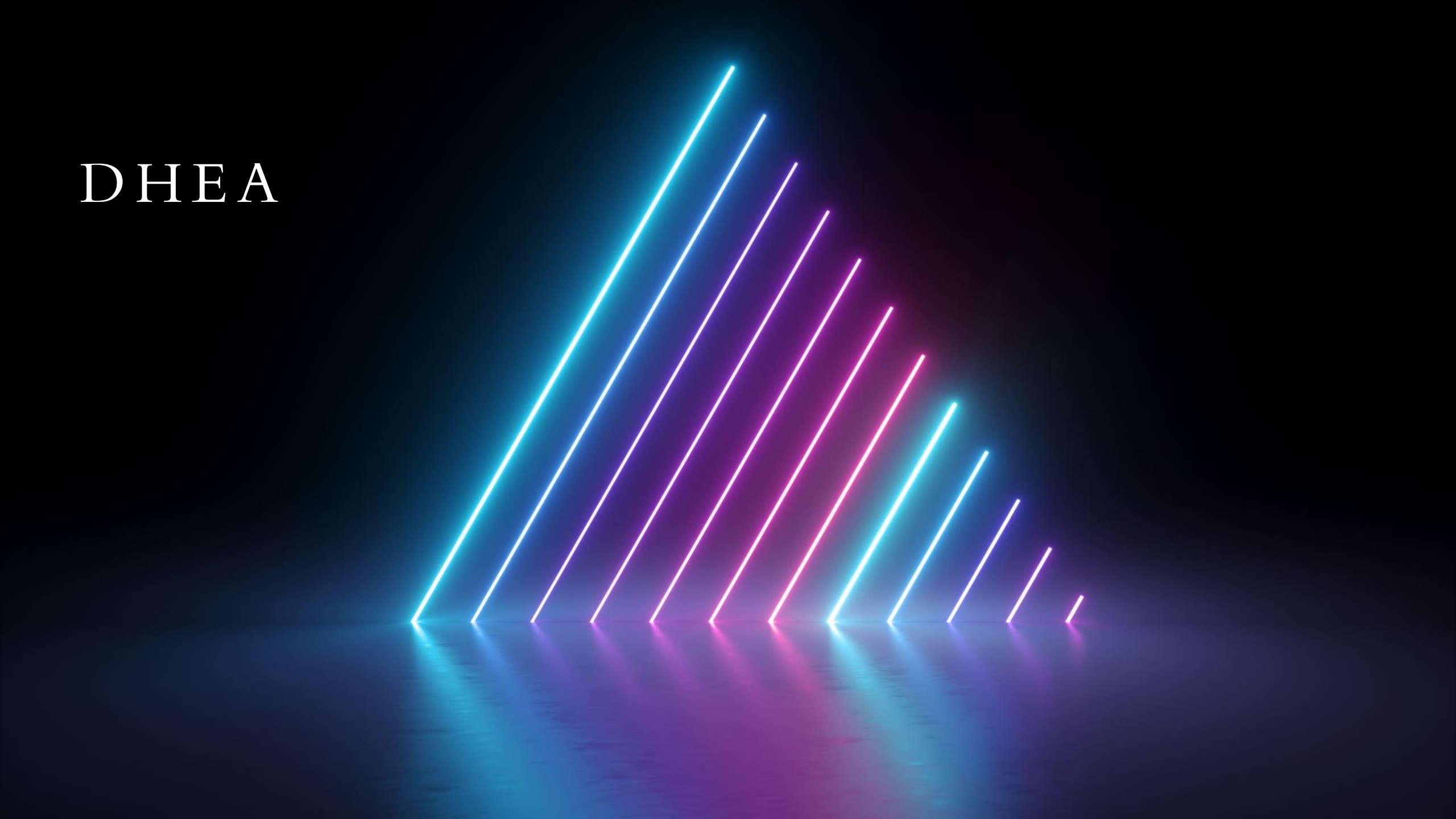
- Saw palmetto
- Metformin
- Spironolactone
- Other herbal therapies

MEASUREMENT OF TESTOSTERONE LEVELS IN WOMEN

- Androgens, both in excessive and depleted states, have been implicated in female reproductive health disorders.
- This study revealed that commercially available androgen assays have significant limitations in the female population. Furthermore, the measurements themselves are not always informative in the patient's diagnosis, treatment, or prognosis.

Korkidakis, A., et al., "Testosterone in women: measurement and therapeutic use," Jour Obstet Gynaecol Can 2017; 39(3):124-130.

DHEA



DHEA

DHEA is a hormone made by the adrenal glands.

A small amount is also made in the brain and skin.

DHEA production declines with age starting in the late twenties.

By the age of 70 the body may only make ¼ of the amount of DHEA it made earlier.

DHEA makes estrogen and testosterone in both women and men.

DHEA levels may also change when the patient has stress at any age.

FUNCTIONS OF DHEA

- Decreases cholesterol
- Decreases formation of fatty deposits
- Prevents blood clots
- Increases bone growth
- Promotes weight loss
- Increases brain function
- Increases lean body mass

FUNCTIONS OF DHEA (CONT.)

- Increases sense of well-being
- Helps one deal with stress
- Supports the immune system
- Helps the body repair itself and maintain tissues
- Decreases allergic reactions
- Lowers triglycerides
- Increases insulin sensitivity

STUDY REVIEWED FUNCTIONS OF DHEA

In the elderly, DHEA exerts an immunomodulatory action, increasing the number of monocytes, T cells expressing T-cell receptor gamma/delta (TCRγδ) and natural killer (NK) cells.

It improves physical and psychological well-being, muscle strength and bone density, and reduces body fat and age-related skin atrophy stimulating procollagen/sebum production.

STUDY REVIEWED FUNCTIONS OF DHEA (CONT.)

In adrenal insufficiency, DHEA restores DHEA/DHEAS and androstenedione levels, reduces total cholesterol, improves well-being, sexual satisfaction and insulin sensitivity, and prevents loss of bone mineral density.

In an unblinded study, it induced remission in the majority of patients with inflammatory bowel disease.

STUDY REVIEWED FUNCTIONS OF DHEA (CONT.)

- DHEA modulates cardiovascular signaling pathways and exerts an anti-inflammatory, vasorelaxant and anti-remodeling effect. Its low levels correlate with increased cardiovascular disease and all-cause mortality.
- DHEA/DHEAS appear protective in asthma and allergy. It attenuates T helper 2 allergic inflammation and reduces eosinophilia and airway hyperreactivity.
- In women, DHEA improves sexual satisfaction, fertility and age-related vaginal atrophy.

Rutkowski, K., et al., Dehydroepiandrosterone (DHEA): hypes and hopes," Drugs 2014; 74(11):1195-207.

ETIOLOGIES OF LOW DHEA

Menopause

Decreased production

Stress

Aging

Smoking (nicotine inhibits the production of 11-beta-hydroxylase which is needed to make DHEA)

REPLACEMENT OF DHEA

- Increases muscle strength and lean body mass
- Activates immune function
- Increases quality of life
- Improves sleep
- Increases feeling of wellness
- Decreases joint soreness
- Increases sensitivity of insulin
- Decreases triglycerides
- Stops the damaging effects of stress
- Elevates growth hormone levels
- Positive effect on memory

REFERENCES

Junqueira de Menezes, K., et al., "Dehydroepiandrosterone, its sulfate and cognitive functions," Clin Pract Epidemiol Ment Health 2016; 12:24-37.

Kinge, C., et al., "Dehydroepiandrosterone research: past, current, and future," Vitam Horm 2018; 108:1-28.

Clark, B., et al., "Mechanisms of action of dehydroepiandrosterone," Vitam Horm 2018; 108:29-72.

DHEA (CONT.)

DHEA in conjunction with other hormones and transmitters significantly affects some aspects of human mood and has also been shown to modify some features of human emotions and behavior.

It has been reported that its administration can increase feelings of well-being and is useful in ameliorating atypical depressive disorders.

It has neuroprotective and anti-glucocorticoid activity and modifies immune reactions. It may also have a role in degenerative brain diseases. and some authors have also reported its role in degenerative brain diseases.

- Starka, L., et al., "Dehydroepiandrosterone: a neuroactive steroid," Jour Steroid Biochem Mol Biol 2015; 145:254-60.

DHEA (CONT.)

- This study suggests that DHEA has a role in modulating recovery from PTSD.

Yehuda, R., et al., "Clinical correlates of DHEA associated with post-traumatic stress disorder," Acta Psychiatr Scand 2006; 114(3):187-93.

DOSAGE

- Women are more sensitive to the effects of DHEA and need less DHEA than men.

STATIN USE AND DHEA

- A recent study showed that patients that use statin drugs have lower SHBG levels and lower DHEA levels than controls.

  Oluleye, O., et al., "Association between statin use and sex hormones in the Multi-Ethnic Study of Artherosclerosis (MESA) cohort," Jour Clin Endo Metabol June 2019, doi:10.1210/jc.2019-00530.

SYMPTOMS OF DHEA EXCESS

Fatigue	Anger	Depression	Deepening of voice
Insomnia	Mood changes	Weight gain	Facial hair
Acne	Sugar cravings	Restless sleep	Irritability

CORTISOL

CORTISOL

Cortisol and insulin are the only hormones in the body that may increase with age.

Cortisol is made by the adrenal glands.

When one is stressed, cortisol elevates and then it should decrease. This does not always happen in today's world of 365-24-7.

Overbooking is an issue with everyone. Know how much work and responsibility to take on.

POEM BY CARL SANDBURG

- Time is the coin of your life.
- It is the only coin you have,
- And only you can determine how it will be spent,
- Be careful lest you let other people spend it for you.

FUNCTIONS OF CORTISOL

- Glucocorticoid receptors are present in almost all tissues in the body. Therefore, cortisol is able to affect nearly every organ system.
  - Nervous
  - Immune
  - Cardiovascular
  - Respiratory
  - Reproductive
  - Musculoskeletal
  - Integumentary
- Kadmiel, M., et al., "Glucocorticoid receptor signaling in health and disease," Trends Pharmacol Sci 2013; 34(9):518-30.

FUNCTIONS OF CORTISOL (CONT.)

- Balances blood sugar
- Weight control
- Immune system response
- Bone turnover rate
- Stress reaction
- Sleep
- Protein synthesis

FUNCTIONS OF CORTISOL (CONT.)

- Mood and thoughts
- Influences testosterone/estrogen ratio
- Influences DHEA/insulin ratio
- Affects pituitary/thyroid/adrenal system
- Participates with aldosterone in sodium reabsorption
- Is an anti-inflammatory

REFERENCE

Miller, W., "The hypothalamic-pituitary-adrenal axis: A brief history," Horm Res Paediatr 2018; 89(4):212-23.

CAUSES OF LOW CORTISOL LEVELS

Nutritional deficiencies
Long-term stress
Dysbiosis
Chronic inflammation
Chronic pain
Toxic exposure
Overly aggressive exercise
Hypoglycemia
Poor sleep hygiene
Depression
Severe allergies

CAUSES OF ELEVATED CORTISOL LEVELS

- Stress
- Depression
- High progestin intake
- Oral contraceptives
- Infections
- Poor sleep hygiene
- Inflammation
- Hypoglycemia
- Pain
- Toxic exposure

STRESS

- One study suggested that as many as 75% to 90% of visits to primary care doctors are stress related.

  Head, K., et al., "Nutrients and botanicals for treatment of stress: adrenal fatigue, neurotransmitter imbalance, anxiety, and restless sleep," Altern Med Rev 2009; 14(2):114-40.

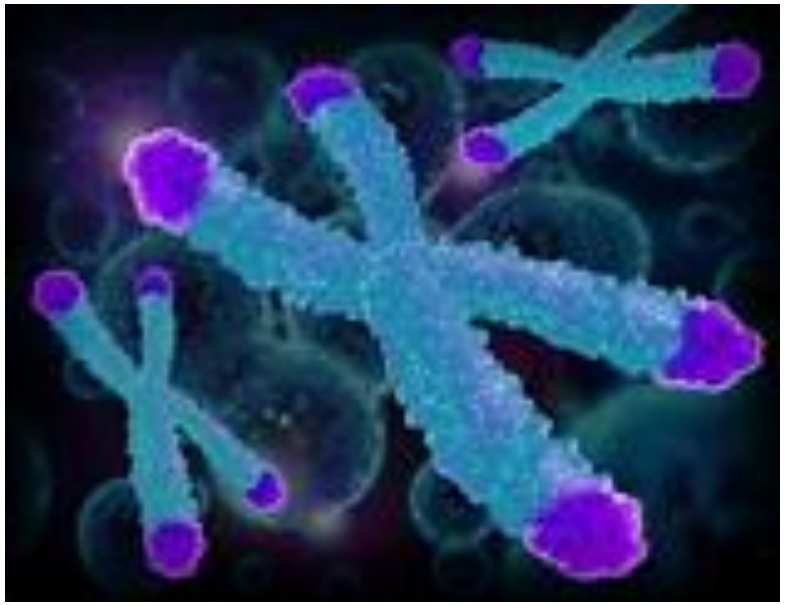
CHRONIC STRESS

- Chronic stress has been shown to contribute to accelerated aging and premature death in medical studies.

Nielsen, N., et al., "Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study," Amer Jour Epidemiol 2008; 168(5):481-91.

Carroll, B., et al., "Ageing, stress and the brain," Novartis Found Symp 2002; 242:26-36.

CHRONIC STRESS (CONT.)



- Another study revealed that chronic stress accelerated the aging process and was associated with shortened telomeres.

Wikgren, M., et al., "Short telomeres in depression and the general population are associated with a hypocortisolemic state," Biol Psychiatry 2012; 71(4):294-300.

CONSEQUENCES OF ELEVATED CORTISOL

- Compromised immune system
  - Decreases the release of antibodies
  - Causes an inhibition in the proliferation of T cells
  - Increases in inflammatory cytokines
  - Inhibits the release of some interleukins
  - Latent virus activation
  - Shift from Th1 to Th2 cytokine expression

Yaribeygi, H., et al., "The impact of stress on body function: A review," EXCLI Jour 2017; 16:1057-72.

CONSEQUENCES OF ELEVATED CORTISOL (CONT.)

- Confusion
- Shakiness between meals
- Memory is not as sharp
- Low energy
- Night sweats
- Binge eating
- Increased blood pressure
- Increased cholesterol
- Increased triglycerides
- Increased blood sugar
- Increased osteoporosis risk by increasing loss of minerals in the bones

CONSEQUENCES OF ELEVATED CORTISOL (CONT.)

- Increased insulin/insulin resistance
- Increased infections
- Thin skin
- Fatigue
- Irritability
- Sugar cravings
- Easy bruising
- Muscle weakness
- Weight gain around the middle
- Sleep disturbances
- Impaired hepatic conversion of T4 to T3
- Favors the development of leaky gut syndrome

CONSEQUENCES OF ELEVATED CORTISOL (CONT.)

There is a strong inter-relationship between activation of the HPA axis and energy homeostasis. Patients with abdominal obesity have elevated cortisol levels. Furthermore, stress and glucocorticoids act to control both food intake and energy expenditure. Glucocorticoids are known to increase the consumption of foods high in fat and sugar in animals and humans.

In women, high-cortisol individuals eat more in response to stress than low-cortisol leading to increased food intake and reduced energy expenditure and thus, predisposition to obesity. Therefore, cortisol responsiveness may be used as a marker to identify individuals who are at risk of weight gain and subsequent obesity.

REFERENCES

Hewagalamulage, S., et al., "Stress, cortisol, and obesity: a role for cortisol responsiveness in identifying individuals prone to obesity," Domest Anim Endocrinol 2016; 56(Suppl):S112-S120.

Lee, T., "High cortisol responses identify propensity for obesity that is linked to thermogenesis in skeletal muscle," FASEB Jour 2014; 28(1):35-44.

ABNORMAL CORTISOL LEVELS ARE ASSOCIATED WITH

Menopause	CFS	Fibromyalgia	Depression	Impotence
Anorexia nervosa	Insulin resistance/diabetes	Generalized memory loss	IBS	Exacerbations of multiple sclerosis

ABNORMAL CORTISOL LEVELS ARE ASSOCIATED WITH (CONT.)

- Panic disorders
- PMS
- Infertility
- Sleep disorders
- Osteoporosis
- Heart disease
- Rheumatoid arthritis
- Breast cancer
- Alzheimer's disease

REFERENCES

Wichmann, S., et al., "Cortisol stress response in post-traumatic stress disorder, panic disorder, and major depressive disorder patients," Psychoneuroendocrinology 2017; 83:135-41.

Thau, L., et al., "Physiology, cortisol," StatPearls (Internet), February 8, 2021.

ADRENAL BURNOUT (HYPOADRENALISM)

- Cortisol and DHEA levels decline.

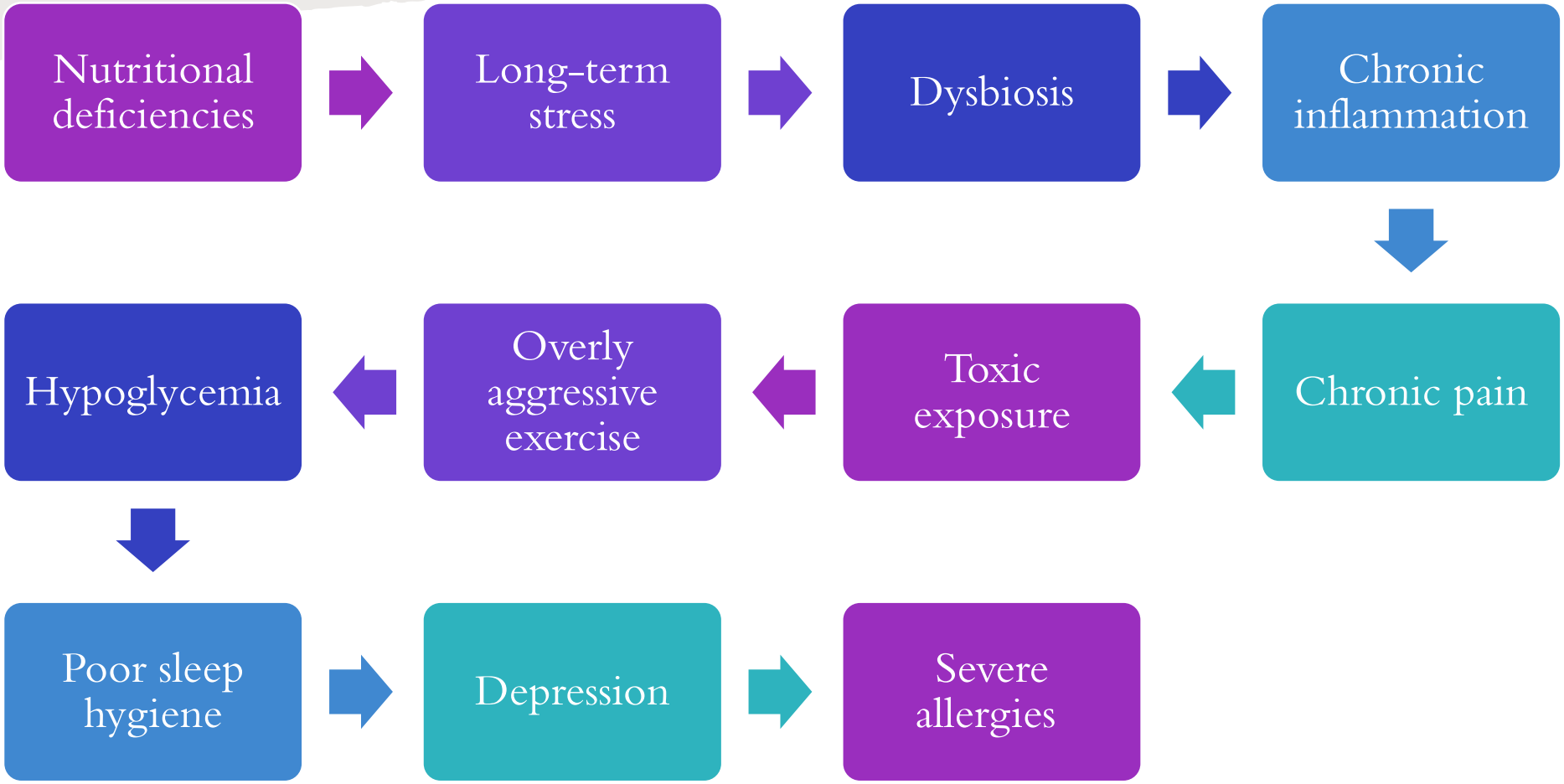
SYMPTOMS OF HYPOADRENALISM

- Fatigue
- Low blood pressure
- Sensitivity to light
- Insomnia
- Digestive problems
- Emotional imbalances/lack of motivation
- Hypoglycemia
- Decreased sexual interest

SYMPTOMS OF HYPOADRENALISM (CONT.)

Decreased immunity	Lack of stamina	Emotional paralysis	Poor wound healing
Alcoholism and drug addiction	Allergies	Unresponsive hypothyroidism (does not respond to treatment)	Feeling of being overwhelmed

CAUSES OF HYPOADRENALISM



HORMONES ARE A WEB

If cortisol is increased, it decreases the making of progesterone and its activity.

Cortisol competes with progesterone for common receptors.

When cortisol is elevated, thyroid hormone is more bound and less active.

Decreased estradiol in a women is a stressor to her body (causes decline in function of NE, serotonin, dopamine, and acetylcholine).

TREATMENT OF HYPERADRENALISM

Replacement of DHEA if it is low with adrenal support

Adaptogenic herbs

- Rhodiola
- Ginseng
- Ashwagandha

Calming herbs

Stress reduction techniques

If cortisol is high in the evening, then add phosphatidylserine 300 mg which may be taken any time of the day.

TREATMENT OF HYPERADRENALISM (CONT.)

- Nutrients
  - Vitamin C
  - B vitamins
  - Calcium
  - Magnesium
  - Zinc
  - Selenium
  - Copper
  - Sodium
  - Manganese

TREATMENT OF HYPOADRENALISM

- Replacement of DHEA if it is low with adrenal support
- Adaptogenic herbs
  - Rhodiola
  - Ginseng
  - Ashwagandha
- Calming herbs
- Stress reduction techniques
- Licorice (cannot use if the patient has hypertension)
- Cortef
  - Do not use for more than 6-9 months
  - Continue adrenal extracts while on cortef
  - Wean the patient off of cortef. Do not stop suddenly.

PREGNENOLONE

PREGNENOLONE

Precursor to DHEA, estrogen, progesterone, and testosterone

It is made from cholesterol

- If the patient's cholesterol is below 140, they may not make pregnenolone effectively.

Decreases with age

- At age 75, most people have a 65% decline compared to age 35.

FUNCTIONS OF PREGNENOLONE

Regulates the balance between excitation and inhibition in the nervous system

Increases resistance to stress

Improves energy both physically and mentally

Enhances nerve transmission and memory

Reduces pain

Blocks the production of acid-forming compounds

FUNCTIONS OF PREGNENOLONE (CONT.)

Modulates the neurotransmitter GABA

Helps to repair nerve damage

Promotes mood elevation

Improves sleep

Enhances acetylcholine transmission

Modulates NMDA receptors

- Regulates pain control, learning, memory, and alertness

FUNCTIONS OF PREGNENOLONE (CONT.)

- Pregnenolone is anti-inflammatory.

  Pregnenolone promotes ubiquitination and degradation of the TLR2/4 adaptor protein TIRAP and TLR2 in macrophages and microglial cells.

  Pregnenolone and its metabolites suppressed the secretion of tumor necrosis factor α and interleukin-6 mediated through TLR2 and TLR4 signaling.

  Pregnenolone has been reported to induce activation of cytoplasmic linker protein 170, and this protein has recently been shown to promote targeted degradation of TIRAP.

  - Murugan, S., et al., "The neurosteroid pregnenolone promotes degradation of key proteins in the innate immune signaling to suppress inflammation," Jour Biol Chem 2019; 294(12):4596-4607.

CAUSES OF LOW PREGNENOLONE LEVELS

- Aging process
- Eating too many saturated fats and trans-fats
- Low cholesterol levels
- Hypothyroidism
- Pituitary tumor
- Having a severe illness
  - Pregnenolone will make more cortisol and less of the other hormones to help the body deal with stress.

SYMPTOMS OF PREGNENOLONE DEFICIENCY

- Arthritis
- Depression
- Fatigue
- Inability to deal with stress
- Insomnia
- Lack of focus
- Memory decline

PREGNENOLONE USED IN TREATMENT

- Arthritis
- Depression including bipolar depression
- Memory loss
- Fatigue
- Moodiness
- Improves delta-wave sleep
- Prevention of memory loss
- Endometriosis
- Seizure disorders

PREGNENOLONE USED IN TREATMENT (CONT.)

- Autoimmune diseases
  - Rheumatoid arthritis
  - Ankylosing spondylitis
  - Multiple sclerosis
  - Lupus
  - Psoriasis
  - Scleroderma

PREGNENOLONE AND MEMORY

Pregnenolone and its metabolic derivatives have been shown to have beneficial effects in the brain, including enhancing memory and learning, reversing depressive disorders, and modulating cognitive functions.

A decreased level of pregnenolone has been observed in neuroinflammatory diseases, such as Alzheimer's, which emphasizes its role in neuroprotection and neuroregeneration.

- Murugan, S., et al., "The neurosteroid pregnenolone promotes degeneration of key proteins in the innate immune signaling to suppress inflammation," Jour Biol Chem 2019; 294(12):4596-4607.

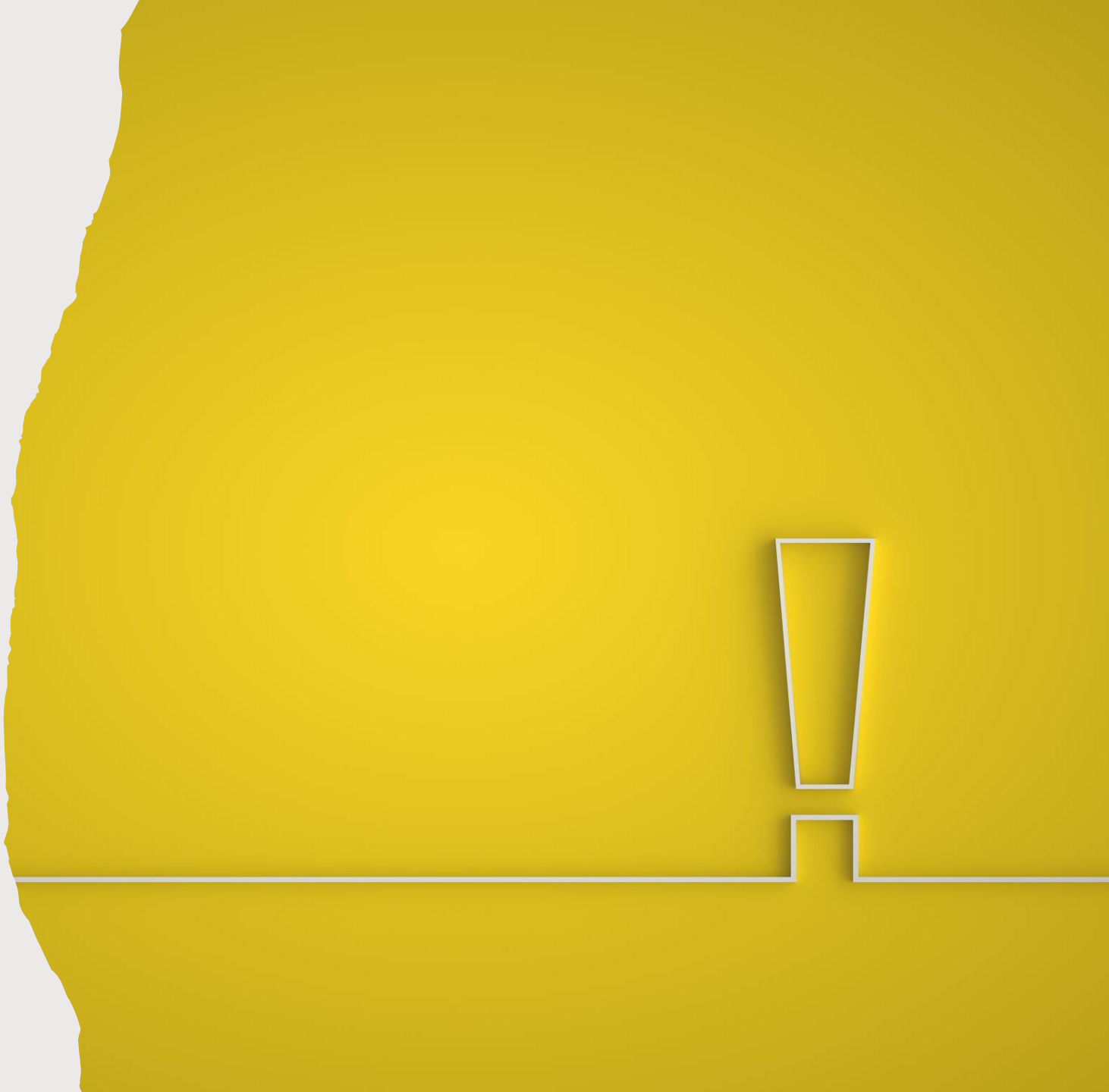
INTERESTING STUDY: USE OF PREGNENOLONE

- Pregnenolone may protect the brain from cannabis intoxication.

  Vallee, M., et al., "Pregnenolone can protect the brain from cannabis intoxication," Science 2014; 343(6166):94-8.

PREGNENOLONE

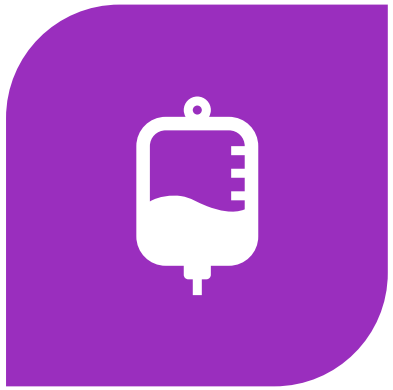
- Use pregnenolone with caution in patients with seizures since it may lower the seizure threshold.



ELEVATED PREGNENOLONE LEVELS CAN CAUSE THE FOLLOWING SYMPTOMS

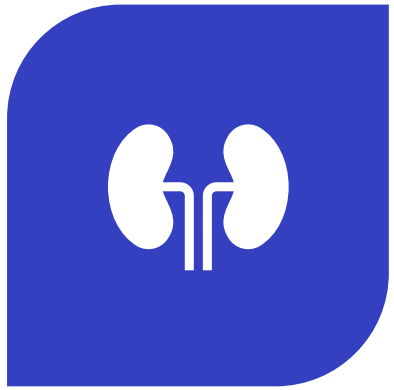
Acne	Drowsiness	Muscle aches	Fluid retention
Headache	Heart racing	Insomnia due to overstimulation	Irritability, anger, anxiety

MEASUREMENT OF HORMONES



BLOOD

SALIVA



URINE

A Guide to Steroid Hormone Testing in Different Body Fluids with Different Routes of Hormone Administration

Type of Body Fluid	None Endogenous Steroids	Oral Steroids	Topical Gels/Creams Steroids	Vaginal Steroids	Troche/ Sublingual Steroids	Transdermal Patch Occluded	Pellet/IM Steroids
Serum	Yes	Yes (1)	No (2)	Yes	Yes	Yes	Yes
Saliva	Yes	Yes	Yes (3)	Yes	No (4)	Yes	Yes
Urine	Yes	Yes (1)	No (2)	No (4)	Yes	Yes	Yes (1)
DBS	Yes	Yes	Yes (5)	Yes	Yes	Yes	Yes

1) Overestimation: Metabolites likely to interfere with immunoassays
2) Underestimation: Hormone levels not reflective of tissue uptake
3) Overestimation: Requires range adjustment
4) Overestimation: Direct contamination of body fluid (saliva/urine)
5) Overestimation: Direct contamination of capillary blood if ungloved hands used to apply topical hormones < 2 days prior to collection

REFERENCE

- Zava, D., The Pros and Cons of Different Types of Hormone Testing, Webinar January 18, 2016.

SUMMARY

SUMMARY

- Dr. K. Holtorf in his groundbreaking medical review states the following: "Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of hormone replacement therapy."

Holtorf, K., The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?" Postgrad Med 2009; 121 (1):73-85.

SUMMARY (CONT.)

All of the hormones in the body are designed to work together.

If one is altered, or deficient, it will affect the actions of all the other hormones.

Consequently, bio-identical, compounded, customized hormone replacement is the only way to achieve this balance.

One size does not fit all.

NEED MORE INFORMATION?

- Please contact me at:

  Pamela W. Smith, M.D., MPH, MS
  faafm63@yahoo.com

  Personalized Medicine Certification website:
  personalizedmedicinecertifcation.com