# What You Must Know About Women's Hormones

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# Disclosure

- Speaker: Genova, Microbiome, PCCA, ZRT

# Objectives

- Identify the symptoms of peri-menopause and menopause
- Discuss the functions of DHEA, cortisol, estrogen, pregnenolone, progesterone and testosterone in a woman's body
- Identify the symptoms of DHEA dysfunction
- Discuss the relationship that female hormones have with insulin in the body
- Describe methods of hormone testing
- Review the medical literature concerning natural versus synthetic hormone replacement

# References


- Smith, P., What You Must Know About Women's Hormones. 2nd. Ed. Garden City Park, NY: Square One Publishing, 2022. Ahead of print.
- Smith, P., What You Must Know About Memory Loss and How You Can Stop It. Garden City Park, MY: Square One Publishing, 2014.

# 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.
- 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

# 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
- Panic attacks
- Skin feeling crawly
- Migraine headaches
- Memory lapses
- Weight gain

# 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 auto-immune 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
- Elevation of 16-OH estrone

# 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)

- Is the main estrogen the body makes postmenopausally
- High levels many researchers believe may increase a women's risk of breast cancer

# 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 (E2)

- 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)

- 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

# 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

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

# Estrogen Metabolism

- One minor pathway
  - 4-OH estrone

# 2-OH Estrone/Methylation

- Good estrogen.  It does not stimulate cell growth.
- Blocks 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.

# 2-OH Estrone/Methylation (Cont.)

- Another way of evaluating the body's ability to methylate is by measuring the homocysteine level.
- Low ratios of 2/16 hydroxy estrogen are also associated with an increased rate of developing lupus.

# 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

- 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), omega-6-fatty acid excess, and inflammatory cytokines.

# 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.
- 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

- 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

# Xenoestrogens

- There are 50 chemicals that imitate estrogen that are toxic to the body.
  - Pesticides
  - Synthetic hormones fed to animals
  - Plastics
  - Cosmetics

# 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 distractability
- 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 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 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

- 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 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.

# 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
- Helps maintain bladder function
- Maintains pregnancy

# 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
- Promotes Th2 immunity

# 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

# 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

- Called progestins
- Progestins do not reproduce the same actions of natural progesterone

# Side Effects of Progestins

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

# 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

# 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.

# References


- 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.
- Papa, V., et al., “Progestins increase insulin receptor content and insulin stimulation of growth in human breast carcinoma cells,” Cancer Res 1990; 50(24):7858-62.

# 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.

# 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.

# Side Effects of Progestins (Cont.)

- Stop 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.

# References


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

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- 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.
- 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.

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- 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.
- 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.

# 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.

# Estrogen/Progesterone Ratio

# Prolonged Use of Progesterone Without Adequate Estrogen

- Increases weight gain
- Increases total cholesterol
- Decreases HDL
- Increases LDL
- Increase triglycerides
- Causes depression
- Causes fatigue
- Decreases libido
- Increases 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 hips
- 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

- 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
- Birth control pills
- 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.

# 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

# 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.

# SHBG

- SHBG is a carrier protein for testosterone and DHT and somewhat for E2 estrogen
- If SHBG is low, more estrogen and testosterone are available for usage.
- Low SHBG may be a marker for low thyroid function.
- Low SHBG is commonly due to an increase in body weight.
  - Schindler, A., et al., "Progesterone deficiency and endometrial cancer risk," Maturitas 2009; 62(4):334-37.
- Drinking coffee, green, or black tea has been shown to raise SHBG levels.

# SHBG (Cont.)

- The results of this study suggest that the lower serum SHBG levels are associated with the risk of PCOS.
- SHBG may also play an important role in various metabolic disturbances in PCOS patients. In fact, therapeutic interventions improved SHBG levels in PCOS women which further reduced PCOS associated complications. Therefore, SHBG levels may prove to be a useful biomarker for the diagnosis and treatment of PCOS.
  - Deswal, R., et al., "Sex hormone binding globulin - an important biomarker for predicting PCOS risk: A systematic review and meta-analysis," Syst Biol Repro Med 2018; 64(1):12-24.

# SHBG (Cont.)

- If SHBG is elevated, then there is less E2 and testosterone available for use by the body.
- High insulin levels are a negative modifier for SHBG as are high prolactin levels.
- Estrogen by mouth increases SHBG by 50%.
- Equine estrogens increase SHBG by 100%.
- Elevated SHBG is commonly linked to estrogen dominance or the use of oral contraceptives or other forms of birth control that contain estrogen.
- Anorexia nervosa, hyperthyroidism, pregnancy, HIV, hepatitis, and liver disease are all associated with elevated SHBG.

# SHBG (Cont.)

- High serum SHBG is associated with an increased risk of subsequent hip fracture and high endogenous testosterone with a decreased risk, independent of each other, serum estradiol concentration, and other putative risk factors in postmenopausal women.
  - Lee, J., et al., "Associations of serum sex hormone-binding globulin and sex hormone concentrations with hip fracture risk in postmenopausal women," Jour Clin Endocrinol Metab 2008; 93(5):1796-803.

# SHBG (Cont.)

- Women with a combination of both low estradiol and high SHBG had a 7.8 times higher risk of an incident vertebral fracture.
  - Goderie-Plomp, H., et al., "Endogenous sex hormones, sex hormone-binding globulin, and the risk of incident vertebral fractures in elderly men and women: the Rotterdam Study," Jour Clin Endocrinol Metab 2004; 89(7):3261-69.

# 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
- 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

# 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.

# Reference


- 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

# Reference


- 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

- Is the only hormone in the body that increase with age.
- 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.

# 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

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

# What Elevates Cortisol

- Stress
- Depression
- High progestin intake
- Sodium depletion
- High prolactin
- Inflammation
- Cushing's disease
- Obesity

# What Lowers Cortisol

- Chronic stress
- Addison's disease
- Opioid use
- Chronic marijuana use
- Accutane
- Glucocorticoid use

# 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.

# Reference


- 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

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

# 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

- Stress reduction techniques
- Adaptogenic herbs
  - Rhodiola
  - Ginseng
  - Ashwagandha
- Adrenal extracts (if adaptogenic herbs do not work)
- Calming herbs
- 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.

# Insulin and Sex Hormones

- Estrogen, progesterone, DHEA, and thyroid hormones are all important for the regulation of glucose in the body.
- Estrogen lowers blood sugar in a women.
- Testosterone decreases blood glucose in a male.
- Progesterone raises blood sugar if not balanced with estrogen.

# Functions Of Insulin In The Body

- Counters the actions of adrenaline and cortisol in the body
- Helps the body repair
- Helps convert blood sugar into triglycerides
- Keeps blood glucose levels from elevating
- Plays a major role in the production of serotonin
- At normal levels increases development of muscle

# Levels of Insulin

- It is important that the levels of insulin in the body not be too high or too low.

# Low Insulin Levels

- Insulin is not working effectively in the body
- This is a pre-diabetes state

# Symptoms of Insulin Deficiency

- Bone loss
- Depression
- Fatigue
- Insomnia

# Causes of Insulin Deficiency

- Eliminating carbohydrates from the diet
- Not eating enough
- Over-exercising

# Excess Insulin Is Associated With

- Acne
- Aging process accelerates
- Alzheimer's disease
- Asthma
- BPH
- Breast cancer
- Colon cancer
- CVA
- Depression and mood swings
- Diabetes/insulin resistance
- Erectile dysfunction

# Excess Insulin Is Associated With (Cont.)

- Estrogen levels that are too low
- Gout
- Hearing loss
- Irritable bowel syndrome
- Memory loss not related to Alzheimer's disease
- Migraine headaches
- Heart disease/acute MI
- Heartburn
- Hypercholesterolemia
- Hypertension

# Excess Insulin Is Associated With (Cont.)

- Hypertriglyceridemia
- Infertility
- Insomnia
- Osteopenia/osteoporosis
- PCOS
- Skin tags
- Tinnitus
- Vertigo
- Weight gain/obesity

# Causes of Excess Insulin Production

- High carbohydrate diet
- Soft drinks
- Diet pills
- Eating a low-fat diet
- Intake of trans-fats
- Elevated DHEA levels
- Excess caffeine intake
- Intake of thyroid medication that is excessive or not needed

# Causes of Excess Insulin Production (Cont.)

- Excessive progesterone replacement
- Increased testosterone levels
- Insomnia
- Lack of exercise
- Low estrogen levels
- Skipping meals
- Smoking

# Causes of Excess Insulin Production (Cont.)

- Hypothyroidism
- OTC meds that contain caffeine
- Stress
- Use of natural stimulants
- Use of recreational stimulants
- Using artificial sweeteners
- Yo-yo dieting

# Causes of Excess Insulin Production (Cont.)

- Medications
  - Beta blockers
  - Birth control pills
  - Steroids
  - Thiazide diuretics
  - Some antidepressants and antipsychotics

# Pregnenolone

- Precursor to DHEA, estrogen, progesterone, and testosterone
- 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

# 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.

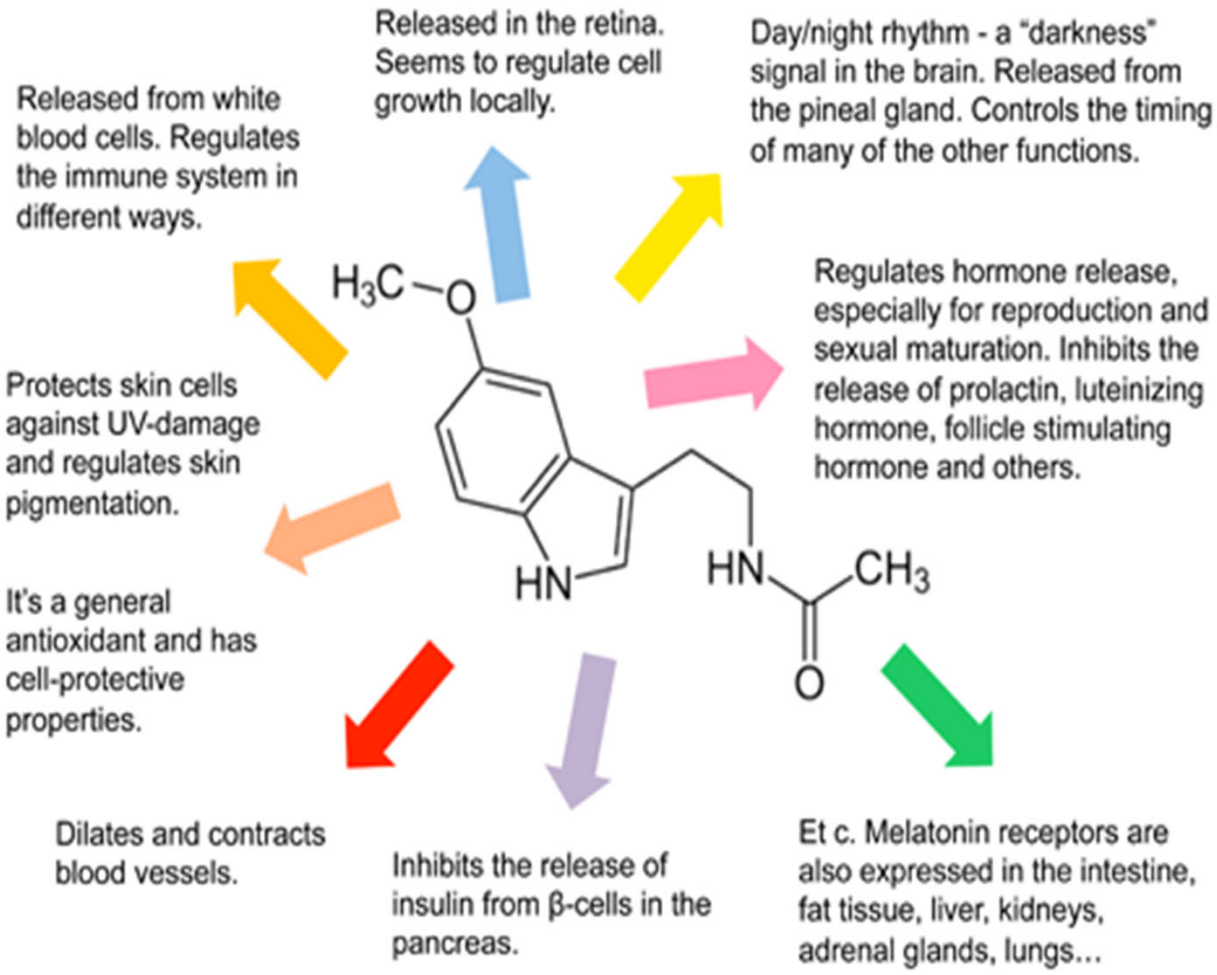
# Elevated Pregnenolone Levels Can Cause the Following Symptoms

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

# Melatonin

- Melatonin is produced by the pineal gland, retina, GI tract, and WBCs.
- It is made from tryptophan which is also used to make serotonin.
- If melatonin goes up, serotonin goes down.
- If you eat too many high glycemic index carbohydrates you will make less melatonin (more serotonin is made instead).
- The body needs vitamin B to convert melatonin from tryptophan.

## Melatonin: conductor of a large orchestra



# Functions of Melatonin

- Affects the release of sex hormones
- Aids the immune system
- Acts as an antioxidant
- Blocks estrogen from binding to receptor sites
- Decreases cortisol levels
- Helps balance the stress response
- Helps prevent cancer
- Improves mood
- Improves sleep quality
- Increases the action of benzodiazepines
- Stimulates the parathyroid gland
- Stimulates the production of growth hormone
- Cardio-protection
- Protects against GERD

# References


- Markus, R., et al., “Immune-pineal axis: acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes,” Brit Jour Pharmacol 2018; 175(16):3239-50.
- Hardeland, R., “Melatonin and inflammation: Story of a double-edged blade,” Jour Pineal Res 2018; 65(4)e12525.
- Pandi-Perumal, S., et al., “Melatonin antioxidative defense: therapeutical implications for aging and neurodegenerative processes,” Neurotox Res 2013; 23(3):267-300.
- Feng, Z., et al., “Long-term melatonin or 17-beta-estradiol supplementation alleviates oxidative stress in ovariectomized adult rats,” Free Radic Biol Med 2005; 39(2):195-204.

# References (Cont.)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- Bubenik, G., et al., "Melatonin and aging: prospects for human treatment," Jour Physiol Pharmacol 2011; 62(1):13-9.
- Wu, Y., et al., "The human pineal gland and melatonin in aging and Alzheimer's disease," Jour Pineal Res 2005; 38(3):145-52.
- Daniels, W., et al., "Melatonin prevents beta-amyloid-induced lipid peroxidation," Jour Pineal Res 1998; 24(2):78-82.
- Werbach, M., "Melatonin for the treatment of gastroesophageal reflux disease," Altern Ther Health Med 2008, 14(4):54-8.

# References (Cont.)


- Pereira, R., "Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and aminoacids: comparison with omeprazole," Jour Pineal Res 2006; 41:195–200.
- Konturek S., et al., "Protective influence of melatonin against acute esophageal lesions involves prostaglandins, nitric oxide and sensory nerves," Jour Physiol Pharmacol 2007; 58(2):361–77.
- Kandil, T., et al., "The potential therapeutic effect of melatonin in gastro-esophageal reflux disease," BMC Gastroenterology 2010; 10:7.
- Csaba, G., "The pineal regulation of the immune system: 40 years since the discovery," Acta Microbiol Immunol Hung, 2013; 60(2):77–91.

# Melatonin and Oxidative Stress

- Study showed that melatonin supplementation along with estradiol replacement in women decreased oxidative stress in lab animals.
  - Ibid., Feng.

# Melatonin and Hypertension

- Melatonin has been shown to reduce blood pressure in patients with hypertension.
  - Tordjman, S., et al., “Melatonin: pharmacology, functions and therapeutic benefits,” Curr Neuropharmacol 2017; 15(3):434-43.
  - Arangino, S., et al., “Effects of melatonin a vascular reactivity, catecholamine levels, and blood pressure in healthy men,” Amer Jour Cardiol 1999;83:1417.
  - Scheer, F., et al., “Daily night-time melatonin reduces blood pressure in male patients with essential hypertension,” Hypertension 2004; 43:192-97.

# Melatonin and Hypertension (Cont.)

- Evening controlled-release melatonin, 2 mg for 4 weeks, significantly reduced nocturnal systolic BP in patients with nocturnal hypertension in a medical trial.
  - Grossman, E., et al., "Melatonin reduces night blood pressure in patients with nocturnal hypertension," Amer Jour Med 2006; 119(10):898-902.

# Melatonin and Cardioprotection

- Patients with CAD tend to have low nocturnal serum melatonin levels.
- Melatonin has been shown to reduce hypoxia and prevent reoxygenation-induced damage in patients with cardiac ischemia and ischemic stroke.

# References


- Reiter, R., et al., “Melatonin: a novel protective agent against oxidative injury of the ischemic/reperfused heart,” Cardiovasc Res 2003; 58(1):10-9.
- Reiter, R., et al., “When melatonin gets on your nerves: its beneficial actions in experimental models of stroke,” Exp Biol Med 2005; 230(2):104-17.

# Melatonin and Cardioprotection

- Patients who have developed adverse effects post MI were shown to have lower nocturnal melatonin levels than patients without adverse effects.
  - Death
  - CHF
  - Recurrent MI

# Melatonin and Cardioprotection (Cont.)

- Functions of melatonin in cardioprotection
  - Vasodilator
  - Free radical scavenger
  - Inhibits oxidation of LDL-C
    - Dominguez-Rodriguez, A., et al., "Prognostic value of nocturnal melatonin levels as a novel marker in patients with ST-segment elevation myocardial infarction," Amer Jour Cardiol 2006; 97(8):1162-64.

# Melatonin and Cardioprotection (Cont.)

- There is an inverse correlation between melatonin levels and CRP levels after acute MI.
  - Dominguez-Rodriguez, A., et al., "Relation of nocturnal melatonin levels to C-reactive protein concentration in patients with T-segment elevation myocardial infarction," Amer Jour Cardiol 2006; 97(1):10-2.

# Melatonin and Cardioprotection (Cont.)

- MARIA study was a prospective, randomized, double-blind, placebo-controlled trial.
- Used IV melatonin in patients following an acute MI that were having angioplasty.
  - Decreased CRP and IL-6
  - Attenuated tissue damage from reperfusion
  - Decreased V tach and V fib after reperfusion
  - Attenuated cellular and molecular damage from ischemia
    - Dominguez-Rodriguez, A., et al., "Clinical aspects of melatonin in the acute coronary syndrome," Curr Vasc Pharmacol 2009; 7(3):367-73.

# Melatonin and Cardioprotection (Cont.)

- Melatonin has been shown to protect cardiac myocyte mitochondria after doxorubicin use.
  - Xu, M., et al., “Melatonin protection against lethal myocyte injury induced by doxorubicin as reflected by effects on mitochondrial membrane potential,” Jour Mol Cell Cardiol 2003; 34(1):75-9.
  - Dominguez-Rodriguez, A., et al., “Melatonin and circadian biology in human cardiovascular disease,” Jour Pineal Res 2010; 49(1):14-22.

# Melatonin and Insulin

- Melatonin is necessary for the proper synthesis, secretion, and action of insulin.
- Melatonin acts by regulating GLUT4 expression and/or triggering, via its G-protein-coupled membrane receptors, the phosphorylation of the insulin receptor and its intracellular substrates mobilizing the insulin-signaling pathway.
- Melatonin is a powerful chronobiotic meaning that it helps regulate the body's internal clock.

# Melatonin and Insulin (Cont.)

- Furthermore, melatonin is responsible for the establishment of an adequate energy balance by regulating energy flow to and from the stores and directly regulating the energy expenditure through the activation of brown adipose tissue and participating in the browning process of white adipose tissue.
- The reduction in melatonin production, with aging, shift-work or illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian changes which leads to weight gain.

# Reference


- Cipolla-Neto, J., et al., “Melatonin, energy metabolism, and obesity: a review,” Jour Pineal Res 2014; 56(4):371-81.

# Melatonin and Insulin (Cont.)

- Study using laboratory animals showed that melatonin supplementation daily at middle age decreased abdominal fat and lowered plasma insulin to youthful levels.
  - Wolden-Hanson, T., "Daily melatonin administration to middle-aged rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin: independent of food intake and total body fat," Endocrinology 2000; 141(2):487-97.

# Melatonin and Neurodegenerative Disease

- Studies have shown that low melatonin levels are associated with an increased risk of developing neurodegenerative diseases.
  - Ibid., Pandi-Perumal.
  - Gupta, Y., et al., "Neuroprotective role of melatonin in oxidative stress vulnerable brain," Indian Jour Physiol Pharmacol 2003; 47(4):373-86.
  - Bondy, S., et al., "Retardation of brain aging by chronic treatment with melatonin," Ann NY Acad Sci 2004; 1035:197-215.

# Melatonin and Alzheimer's Disease

- Some symptoms of decreased melatonin are also common to patients with Alzheimer's disease.
  - Disruption of circadian rhythm
  - Mood changes
  - Delirium
    - De Rooij, S., "Melatonin deficiency hypothesis in delirium. A synthesis of current evidence," Rejuvenation Res 2013; April 19.
    - Fredericks, S., "Melatonin: The Brain Hormone," Life Extension, September 2013, p. 40-9.

# Melatonin and Alzheimer's Disease (Cont.)

- One medical trial showed that melatonin levels in the CSF in patients over the age of 80 were ½ the level of younger/healthier patients.
- Patients in this study with Alzheimer's disease had even lower levels which were 1/5 of those in young healthy people.
  - Liu, R., et al., "Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging," Alzheimer's disease, and apolipoprotein E-epsilon 4/4 genotype," Jour Clin Endocrinol Metab 1999; 84(1):323-27.

# Melatonin and Alzheimer's Disease (Cont.)

- Studies have shown a benefit in melatonin replacement in patients with early Alzheimer's disease.
  - Cardinali, D., et al., "The use of melatonin in Alzheimer's disease," Neuro Endocrinol Lett 2002; 23(Suppl 1):20-3.
  - Cardinali, D., et al., "The use of chronobiotics in the resynchronization of the sleep/wake cycle. Therapeutical application in the early phases of Alzheimer's disease," Recent Pat Endocr Metab Immune Drug Discov 2011; 5(2):80-90.

# Melatonin and Alzheimer's Disease (Cont.)

- Melatonin supplementation has been shown to decrease the damage caused by amyloid beta proteins and tau proteins.
  - Lahiri, D., et al., "Amyloid, cholinesterase, melatonin, and metals and their roles in aging and neurodegenerative diseases," Ann NY Acad Sci 2005; 1056:430-49.
  - Wang, J., et al., "Role of melatonin in Alzheimer-like neurodegeneration," Acta Pharmacol 2006; 27(1):41-9.

# References


- Zhu, L, et al., “Effect of inhibiting melatonin biosynthesis on spatial memory retention and tau phosphorylation in rat,” Jour Pineal Res 2004; 37(2):71-7.
- Ibid., Daniels.
- Lahiri, D., et al.,, “Dietary supplementation with melatonin reduces levels of amyloid beta-peptides in the murine cerebral cortex,” Jour Pineal Res 2004; 36(4):224-31.

# Melatonin and Alzheimer's Disease (Cont.)

- Melatonin has also been shown to guard against the harmful effects of aluminum which has been shown to cause oxidative changes in the brain that are like Alzheimer's disease.
  - Ibid., Daniels.

# Melatonin and Alzheimer's Disease (Cont.)

- Studies showed that replacing melatonin in the animal model of Alzheimer's disease reduced learning and memory deficits.
  - Feng, Z., et al., "Early melatonin supplementation alleviates oxidative stress in a transgenic-mouse model of Alzheimer's disease," Free Radic Biol Med 2006; 40(1):101-09.
  - Feng, Z., et al., "Melatonin alleviates behavioral deficits associated with apoptosis and cholinergic system dysfunction in the APP 695 transgenic-mouse model of Alzheimer's disease," Jour Pineal Res 2004; 37(2):129-36.

# Melatonin and Alzheimer's Disease (Cont.)

- Study in the animal module also revealed that it was important to replace melatonin before Alzheimer's disease was clinically evident.
- In genetically predisposed mice, where melatonin was replaced early, they did not show pathological changes nor have symptoms of cognitive decline.
  - Ibid., Feng.

# Melatonin and Alzheimer's Disease (Cont.)

- Medical trials revealed that using melatonin in patients with Alzheimer's disease they had better sleep patterns, less sundowning, and slower progression of cognitive loss.
  - Cardinali, D., et al., "Clinical aspects of melatonin intervention in Alzheimer's disease progression," Curr Neuropharmacol 2010; 8(3):218-27.
  - Ibid., Cardinali, 2002.

# Melatonin and Alzheimer's Disease (Cont.)

- Studies have shown that supplementing with melatonin helps to protect against Alzheimer's disease.
  - Ibid., Pandi-Perumal.
  - Ibid., Lahiri.
  - Ma, J., et al., "Does melatonin help save dopaminergic cells in MPTP-treated mice?" Parkinsonism Relat Disord 2009; 15(4):307-14.
  - Borah, A., et al., "Melatonin inhibits 6-hydroxydopamine production in the brain to protect against experimental parkinsonism in rodents," Jour Pineal Res 2009; 47(4):293-300.

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- Reiter, R., et al., “Melatonin ameliorates neurologic damage and neurologic damage and neurophysiologic deficits in experimental models of stroke,” Ann NY Acad Sci 2003; 993:35-47.
- Ayer, R., et al., “Effects of melatonin in early brain injury following subarachnoid hemorrhage,” Actu Neurochir Suppl 2008; 102:327-30.
- Ibid., Feng.

# Melatonin and Mild Cognitive Impairment

- Mild cognitive impairment (MCI) is impairment that precedes actual dementia.
  - Cardinali, D., et al., "Therapeutic application of melatonin in mild cognitive impairment," Amer Jour Neurodegener Dis 2012; 1(3):280-91.
- 12% of people with MCI proceed to develop dementia each year.
  - Ibid., Fredericks.

# Melatonin and Mild Cognitive Impairment (Cont.)

- Studies showed that patients that supplemented with melatonin (3-24 mg) for 15-60 months did much better on cognitive tests.
  - Ibid., Cardinali, 2010.
  - Ibid., Cardinali, 2012.
  - Furio, A., et al., "Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study," Jour Pineal Res 2007; 43(4):404-09.

# Melatonin and Longevity

- Lab trials have shown that melatonin replacement increase SIRT1 which is a longevity protein. SIRT1 is activated by caloric restriction.
  - Chang, H., et al., "Melatonin preserves longevity protein (sirtuin 1): expression in the hippocampus of total sleep-deprived rats," Jour Pineal Res 2009; 47(3):211-20.

# Melatonin and Parkinson's Disease

- Melatonin replacement has been shown to decrease the risk of developing Parkinson's disease.
  - Ibid. Pandi-Perumal.
  - Ibid., Wang.
  - Ibid., Ayer.
  - Ibid., Ma.

# Melatonin and Parkinson's Disease (Cont.)

- Animal trials have shown that melatonin can prevent and to some extent may even help reverse the motor and behavior changes that are associated with Parkinson's disease.
  - Gutierrez-Valdez, A., et al., "Effects of chronic L-dopa or melatonin treatments after dopamine deafferentation in rats: dyskinesia, motor performance, and cytological analysis," ISRN Neurol 2012; 2012:360379.
  - Patki, G., et al., "Melatonin protects against neurobehavioral and mitochondrial deficits in a chronic mouse model of Parkinson's disease," Pharmacol Biochem Behav 2011; 99(4):704-11.

# Melatonin and Parkinson's Disease (Cont.)

- In Parkinson's disease there is an accumulation of a protein called alpha-synuclein.
  - Ono, K., et al., "Effect of melatonin on alpha-synuclein self-assembly and cytotoxicity," Neurobiol Aging 2012; 33(9):2172-85.

# Melatonin and Parkinson's Disease (Cont.)

- In animal studies melatonin supplementation has been shown to prevent the production of alpha-synuclein in brain cells.
- Melatonin supplementation also attacks alpha-synuclein and makes it more available to be removed by the body.
  - Ibid., Ono.
  - Sae-Ung, K., et al., "Melatonin reduces the expression of alpha-synuclein in the dopamine containing neuronal regions of amphetamine-treated postnatal rats," Jour Pineal Res 2012; 52(1):128-37.

# Melatonin and Parkinson's Disease (Cont.)

- Lab study showed that melatonin can reverse the inflammatory changes that occur in Parkinson's disease.
  - Brito-Armas, J., et al., "Melatonin prevents dopaminergic cell loss induced by lentiviral vectors expressing A3OP mutant alpha-synuclein," Histol Histopathol 2013; Feb 27.

# Melatonin and Parkinson's Disease (Cont.)

- Animal trial showed that melatonin helps to restore the normal activity of a key enzyme that is involved in the synthesis of dopamine.
  - Niranjan, R., et al., "The mechanism of action of MPTP-induced neuroinflammation and its modulation by melatonin in rat astrocytoma cells," C6 Free Radic Res 2010; 44(11):1304-16.
  - Ibid., Cardinali, 2002.

# Melatonin and Parkinson's Disease (Cont.)

- In lab studies melatonin supplementation was shown to increase the survival of dopamine-producing cells.
  - Ibid., Niranjan.
  - Ibid., Ma.
  - Ibid., Borah.

# Melatonin and CVA

- If the patient has a low melatonin level, they have an increased risk of developing a stroke.
- The odds rise more than 2% for every 1 pg/mL decline in melatonin.
  - Atanassova, P., et al., "Impaired nocturnal melatonin in acute phase of ischaemic stroke: cross-sectional matched case-control analysis," Jour Neuroendocrinol 2009; 21(7):657-63.

# Melatonin and CVA (Cont.)

- In patients with a calcified pineal gland (where melatonin is produced) the risk of developing a CVA is increased by 35%.
  - Kitkhuandee, A., et al., "Pineal calcification is associated with symptomatic cerebral infarction," Jour Stroke Cerebrovasc Dis 2013; Feb.20.

# Melatonin and CVA (Cont.)

- Melatonin supplementation has been shown to shrink the size of an infarct area in a patient with acute CVA.
- This may be due to melatonin's ability to neutralize free radical production.
  - Ibid. Pandi-Perumal.
  - Ibid., Lahiri.
  - Ibid., Feng.
  - Ibid., Niranjan.
  - Ibid., Ma.

# Reference


- Deykun, K., et al., “Modulations of behavioral consequences of minor cortical ischemic lesion by application of free radical scavengers,” Gen Physiol Biophys 2011; 30(3):263-70.

# Melatonin and CVA (Cont.)

- Melatonin may also decrease the risk of CVA by significantly lowering cholesterol and also decreasing blood pressure.
  - Sewerynek, E., et al., “Melatonin and the cardiovascular system,” Neuro Endocrinol Lett 2002; 23(Supp l):79–83.

# Melatonin and CVA (Cont.)

- Melatonin supplementation in lab animals decreased the damage after stroke and decreased seizure occurrence.
  - Manev, H., et al., "Increased brain damage after stroke or excitotoxic seizures in melatonin-deficient rats," FASEB Jour 1996; 10(13):1546-51.

# Melatonin and CVA (Cont.)

- Melatonin has been shown to increase plasticity of neurons after CVA.
  - Chen, H., et al., "Melatonin improves presynaptic protein, SNAP-25, expression and dendritic spin density and enhances functional and electrophysiological recovery following transient focal cerebral ischemia in rats," Jour Pineal Res 2009; 47(3):260-70.

# Melatonin and CVA (Cont.)

- In animal studies, melatonin reduced the damage caused by stroke by decreasing the activation of "protein-melting" enzymes.
  - Hung, Y., et al., "Melatonin decreases matrix metalloproteinase-9 activation and expression and attenuates reperfusion-induced hemorrhage following transient focal cerebral ischemia in rats," Jour Pineal Res 2008; 45(4):459-67.
  - Jang, J., et al., "Melatonin reduced the elevated matrix metalloproteinase-9 level in a rat photothrombotic stroke model," Jour Neurol Sci 2012; 15:323(1-2):221-27.

# Melatonin and CVA (Cont.)

- In animal trials of experimentally induced stroke, melatonin supplementation had the following effects.
  - Tightened the blood-brain barrier
  - Reduced tissue swelling
  - Prevented hemorrhagic transformation
    - Ibid., Reiter.
    - Ibid., Hung.
    - Ibid., Jang.
    - Reiter, R., et al., “When melatonin gets on your nerves: its beneficial actions in experimental models of stroke,” Exp Biol Med (Maywood) 2005; 230(2):104-17.

# Melatonin and CHI/TBI

- Supplementation with melatonin has been shown to minimize the brain swelling and dysfunction after a closed head injury.
  - Ibid., Pandi-Perumal.
  - Ibid., Lahiri.
  - Ibid., Feng.
  - Ibid., Niranjan.
  - Ibid., Ma.
  - Ibid., Reiter.

# Melatonin and CHI/TBI (Cont.)

- Melatonin supplementation has been shown to help protect the brain in the case of traumatic brain injury.
  - Tsai, M., et al., "Melatonin attenuates brain contusion-induced oxidative insult, inactivation of signal transducers and activators of transcription 1, and up-regulation of suppressor of cytokine signalin-3 in rats," Jour Pineal Res 2011; 51(2):233-45.
  - Ismailoglu, O., et al., "The therapeutic effects of melatonin and nimodipine in rats after cerebral cortical injury," Turk Neurosurg 2012; 22(6):740-46.

# Melatonin and CHI/TBI (Cont.)

- Studies done on lab animals have shown that giving melatonin after a TBI had the following results.
  - Maintained the integrity of the blood-brain barrier
  - Prevents dangerous brain swelling in the hours and days after the injury
  - Shrinks the size of the bruised and injured tissue
    - Ibid., Ismailoglu.

# Melatonin and CHI/TBI (Cont.)

- In other medical studies in the laboratory, melatonin supplementation reduced the mortality rate after a burst aneurysm.
  - Ibid., Ayer.
  - Ibid., Wang.

# Melatonin and Sleep

- Melatonin has been shown to synchronize the circadian rhythms, and improve the onset, duration and quality of sleep.
- Exogenous melatonin supplementation is well tolerated and has no obvious short- or long-term adverse effects.
  - Xie, Z., et al., "A review of sleep disorders and melatonin," Neurol Res 2017; 29(6):559-565.
  - Auld, F., et al., "Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders," Sleep Med Rev 2017; 34:10-22.

# Melatonin and Pre-Op Anxiety

- When compared to placebo, melatonin given as premedication (tablets or sublingually) can reduce preoperative anxiety in adults. In fact, melatonin may be equally as effective as standard treatment with midazolam in reducing preoperative anxiety in adults.
- The effect of melatonin on postoperative anxiety in adults is mixed but suggests an overall attenuation of the effect compared to preoperatively.
  - Hansen, M., et al., "Melatonin for pre-and postoperative anxiety in adults," Cochrane Database Syst Rev 2015; 2015(4):CD009861.

# Melatonin and GI Reflux

- The enterochromaffin cells of the gastrointestinal (GI) tract secrete 400 times as much melatonin as the pineal gland.
- A randomized, single-blind clinical trial of subjects with gastroesophageal reflux disease (GERD), the combination of melatonin with other natural supplements was found to be superior to omeprazole, a proton pump inhibitor (PPI).
  - Melatonin 6 mg, 5-hydroxytryptophan 100 mg, D,L-methionine 500 mg, betaine 100 mg, L-taurine 50 mg, riboflavin 1.7 mg, vitamin B6 0.8 mg, folic acid 400 microg, and calcium 50 mg. After 40 days, the PPI was withdrawn without a return of symptoms.
  - Subsequently, an attempt to reduce melatonin to 3 mg resulted in symptoms, while all other ingredients were withdrawn with minimal symptoms during 10 months of follow-up.
    - Werbach, M., "Melatonin for the treatment of gastroesophageal reflux disease," Altern Ther Health Med 2008, 14(4):54-8.

# Melatonin and the Immune System

- Melatonin is a major regulator of the immune system.
- Disease states affecting a wide range of organ systems have been reported as benefitting from melatonin administration.
  - Csaba, G., "The pineal regulation of the immune system: 40 years since the discovery," Acta Microbiol Immunol Hung, 2013; 60(2):77-91.
  - Bondy, S., et al., "Melatonin and regulation of immune function: Impact on numerous diseases," Curr Aging Sci 2020; Jull 11. doi: 10.2174/1874609813666200711153223, on-line ahead of print.

# Melatonin and Breast Cancer

- Many studies have shown that melatonin is an effective therapy for breast cancer as an adjunct to traditional care.
  - Barcelo, S., et al., "Breast cancer therapy based on melatonin," Recent Pat Endocr Metab Immune Drug Discov 2012; 6(2):108-16.
  - Cos, S., et al., "Melatonin as a selective estrogen enzyme modulator," Curr Cancer Drug Targets 2008; 8(8):691-702.
  - Sanchez-Barcelo, E., et al.," Melatonin uses in oncology: breast cancer prevention and reduction of the side effects of chemotherapy and radiation," Expert Opin Investig Drugs 2012; 21(6):819-31.

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- Proietti, S., et al., Melatonin and vitamin D3 synergistically down-regulate Akt and MDM2 leading to TGFβ-1-dependent growth inhibition of breast cancer cells," Jour Pineal Res 2011; 50(2):150-58.
- Thaiz Ferraz, B., et al., "Melatonin decreases breast cancer metastasis by modulating Rho-associated kinase protein-1 expression," Jour Pineal Res 2015; Aug 21.
- do Nascimento Gonçalves, N., "Effect of melatonin in epithelial mesenchymal transition markers and invasive properties of breast cancer stem cells of canine and human cell lines," PLoS One2 016;11(3):e0150407.

# Melatonin and COVID-19

- Melatonin is now being used as an adjuvant treatment for COVID-19 since it has been shown to limit virus-related diseases.
- It is protective against acute lung injury and adult respiratory distress syndrome caused by viruses and other pathogens due to is anti-inflammatory and anti-oxidative effects.
  - Zhang, R., et al., "COVID-10: Melatonin as a potential adjuvant treatment," Life Sci 2020; 250:117583.

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- Salles, C., “Correspondence COVID-19: Melatonin as a potential adjuvant treatment,” Life Sci 2020; 253:117716.
- Juybari, K., et al., “Melatonin potentials against viral infections including COVID-19: Current evidence and new findings,” Virs Res 2020; 287:198108.

# Melatonin and COVID-19

- Covid-19 takes a more severe course in individuals with chronic metabolic diseases such as obesity, diabetes mellitus, and hypertension.
- Since Covid-19 infection and complications involve severe inflammation and oxidative stress in people with obesity and diabetes, melaotnin is being suggested as an add-on therapy for patients that are diabetic and overweight.
  - El-Missiry, M., et al., "Melatonin is a potential adjuvant to improve clinical outcomes in individuals with obesity and diabetes with coexistence of Covid-19," Eur Jour Pharmacol 2020; 882:173329.

# Melatonin

- In Europe, melatonin is considered a medication by the European Medicines Agency.
  - Fermandez-Tresguerres Hernandez, J., et al., “Melatonin: old molecule, new medication,” Ann R Acad Nac Med (Madr) 2008; 125(4):681-96.

# Causes of Melatonin Deficiency

- Alcohol
- Caffeine
- Electromagnetic fields
- Tobacco
- Numerous medications including benzodiazepines

# Benzodiazepines and Melatonin Suppression

- Study showed that a single dose of 2 mg alprazolam at 9 pm suppressed melatonin levels all night long and even at 7 am the next morning.
  - McIntyre, I, et al., "Alterations to plasma melatonin and cortisol after evening alprazolam administration in humans," Chronobiol Int 1993; 10(3):205-13.

# Benzodiazepines and Melatonin Suppression (Cont.)

- A medical trial showed that patients that used benzodiazepines at any time in their life had a 50% greater risk for developing dementia than people that did not use benzodiazepines.
  - Billioti de Gage, BB., et al., "Benzodiazepine use and risk of dementia: prospective population based study," BMJ 2012; 345:e6231.

# Benzodiazepines and Melatonin Suppression (Cont.)

- Another study showed that for patients with benzodiazepine dependence, the risk of probable cognitive impairment was more than quintupled.
  - Potvin, O., et al., "Prevalence of psychiatric disorders in community-dwelling older men and women with cognitive impairment in dementia: results from the ESA study," Aging Ment Health 2012; 16(2):218-27.

# Symptoms of Excess Melatonin

- Daytime sleepiness/fatigue
- Depression
- Headaches
- Increase in cortisol which can lead to fat storage
- Intense dreaming/nightmares
- Suppression of serotonin which increases carbohydrate cravings
- Transient dizziness
- Hypotension
- Abdominal pain
  - Wei, S., et al., "Efficacy and safety of melatonin for sleep onset insomnia in children and adolescents: a meta-analysis of randomized controlled trials," Sleep Med 2020; 68:1-8.

# Causes of Excess Melatonin Production

- Foods
  - Bananas
  - Barley
  - Cherries
  - Ginger
  - Oats
  - Rice
  - Sweet corn
  - Tomatoes
  - Walnuts
  - Mushrooms

# Causes of Excess Melatonin Production (Cont.)

- Exercise
- St. John's wort
- Taking excess melatonin as a supplement
- Caution should be exercised in patients on multiple medications due to potential unknown interactions and in patients taking a medication that can inhibit cytochrome P450, since melatonin is mainly metabolized by this enzyme.
  - Balduini, W., et al., "Melatonin pharmacokinetics and dose extrapolation after enteral infusion in neonates subjected to hypothermia," Jour Pineal Res 2019; 66(4).
  - Besag, F., et al., "Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders: a systematic review," CNS Drugs. 2019; 33(12):1167–186.

# Dihydrotestosterone (Cont.)

- Higher DHT levels in women have been associated with increased risk of all-cause mortality.
  - Schederecker, F., et al., "Sex hormone-binging globulin, androgens and mortality: the KORA-F4 cohort study," Endocr Connect 2020; 9(4):326-36.

# Who Should Not Take Melatonin?

- Use with caution in patients with an autoimmune disease since it can stimulate the immune system
- Pregnant or breast-feeding women
- Patients taking steroids
- Use with caution in patients that are depressed
- Do not use if patient has lymphoma or leukemia

# 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
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.

# Potential Problem with Testing Testosterone Levels in Individuals of Asian Origin

Due to deletion polymorphisms in glucuronidation pathways for testosterone, some ethnic groups (prevalence > 80% in Asians) will have "apparent" low testosterone levels in urine, but normal levels in serum, saliva, and capillary blood. This could lead to a misdiagnosis of androgen deficiency and consequent inappropriate androgen supplementation.

Epi-Testosterone, the epimer of testosterone, is normal in Asians due to a different enzyme that glucuronidates Epi-Testosterone.

When testing urine for testosterone, Epi-testosterone should always be run in concert to avoid "false-low" testosterone results.

# Reference


- Jakobson, J., et al., “Large differences in testosterone excretion in Korean and Swedish men are strongly associated with a UDP-glucuronosyl transferase 2B17 polymorphism,” Jour of Clin Endocrinol and Met 2006; 91(2):687-93.

# 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 of the other hormones.
- Consequently, bio-identical, compounded, customized hormone replacement is the only way to achieve this balance.
- One size does not fit all.

# Motto To Live By

- Life should NOT be a journey to the grave with the intention of arriving safely in an attractive and well-preserved body, but rather to slide in sideways, body thoroughly used up, totally worn out, and screaming , “WOO HOO, what a ride!”