The Science Behind BHRT For Women

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Reference

- Smith, P., What You Must Know About Women's Hormones. 2nd Edition. Garden City Park, NY: Square One Publishers, 2022. (ahead of print).

Reasons to Start and Continue BHRT

- There are many reasons a women should consider starting and taking natural hormone therapy.
- In addition, BHRT should be considered as a life-long therapy.
- The key to effective hormone replacement therapy, in summary, is individuality. Fixed doses do not allow for customized, tailor-made treatment. Having hormonal therapy personalized, at any age, helps the patient achieve and maintain the optimal hormonal symphony for their body.

Twelve Reasons to Take BHRT

- Bone production (prevention of osteoporosis)
- Growth and repair
- Heart health
- Improvement in sleep hygiene
- Improvement of skin health
- It can be tailored to the patient's needs

Twelve Reasons to Take BHRT (Cont.)

It is a safe method of hormone replacement when prescribed in physiological doses.

Management of menopausal symptoms

Prevention of memory loss

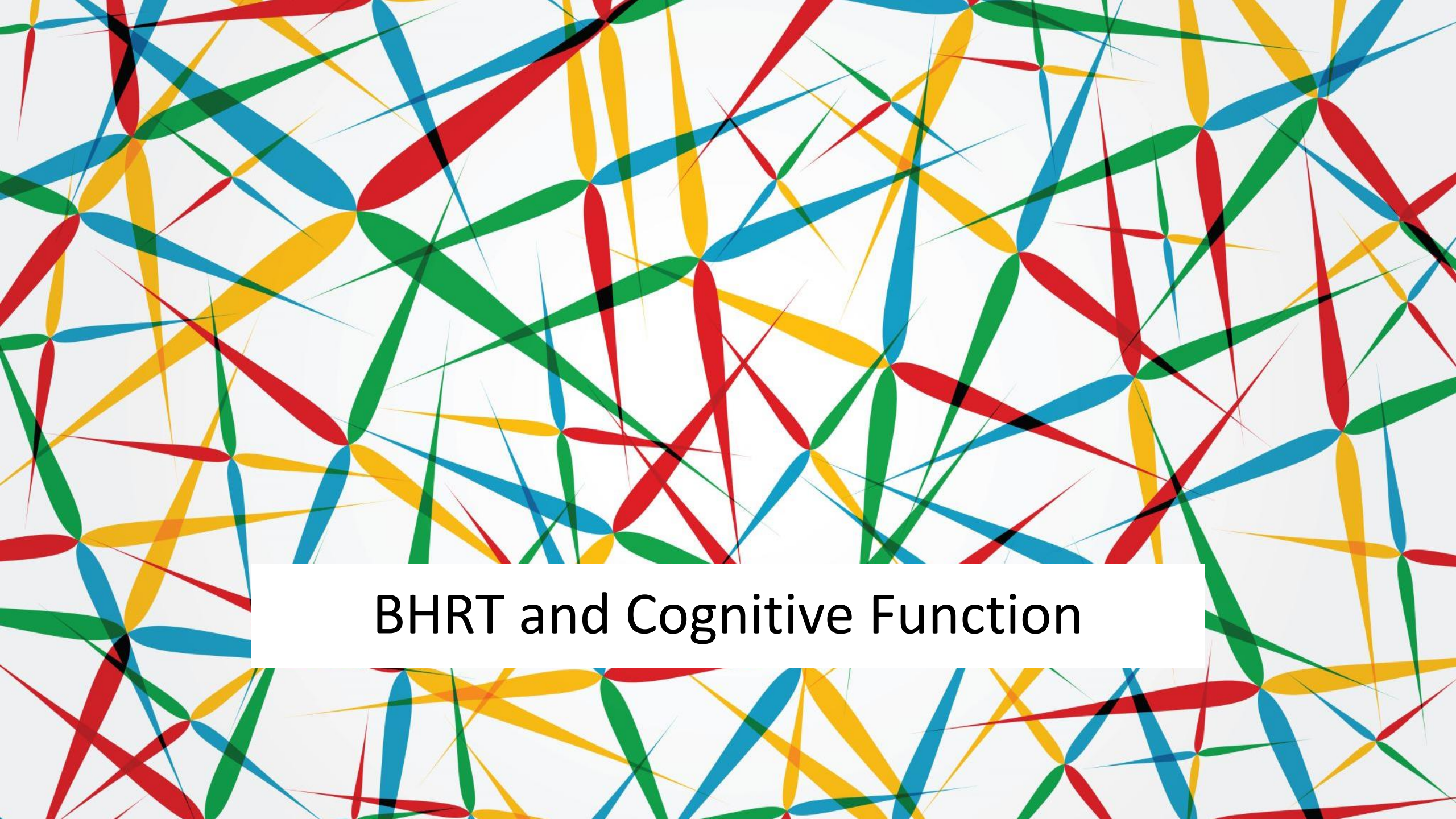
Reduction of inflammation

Longevity

Immune system support

Reasons to Start and Continue BHRT

- This seminar will discuss three of them.
  - BHRT and Cognitive Function
  - BHRT and Heart Disease
  - BHRT and Anti-Aging Skin Care


BHRT and Cognitive Function

Estrogen Affects The Work Tone Of The Brain

- Estrogen stimulates and promotes the function of
  - The brain's cholinergic projecting system
  - The serotonergic projecting system
  - The dopaminergic projecting system
  - The adrenergic projecting system
  - The neurotransmitter projecting system that depends on the neurotransmitter GABA

Estrogen Increases The Neuronal Plasticity Of The Brain

- Regulates the formation and breakdown of synapses and branches
- Facilitates the response to injury after stroke
- Orchestrates the turning on of different genes

Estrogen Is Neuroprotector

- Is a natural antioxidant
- Boosts the body's own natural antioxidant system
- Protects brain cells from beta-amyloid plaque deposits
- Helps brain cells survive deprivation of vital classes of substances longer
- Increases the expression of more nerve growth factor receptors
- Recruits the aid of nerve growth factors
- Decreases the toxicity excitotoxins such as glutamate
- Is anti-inflammatory

Estrogen Boosts The Metabolic Function Of The Brain

- Increases the availability of glucose to the brain
- Increases cerebral blood flow and preventing ischemia
- Maintains the elasticity of blood vessels
- Increases the resting rate of metabolism of the body

Estrogen Acts As An Activator And Performance Enhancer

- Increases speed of rapid limb-coordinated movements
- Increases finger-tapping skills and manual speed and dexterity
- Increases verbal fluency, speech articulation agility, syllable repetition, speeded counting, word reading
- Increases sensory perception: hearing, smell, visual signal detection, and fine touch
- Maintains central processing motor integration in such tasks as driving
- Increases short-term memory

Estrogen As An Activator And Performance Enhancer (Cont.)

- Boosts metabolic activity of many areas of the brain and spinal cord within hours of administration
- Acts as an “upper” to increase feelings of energy and well-being, mood, feelings of elation, and euphoria
- Boosts attention to tasks
- Decreases distractibility
- Increases the reaction time in premenopausal women during estrogen-dominant stage of cycle
- Increases performance and speed of learning in animals on sensorimotor tasks

Estrogen Acts As A Neuromodulator

- Turns on many but not all progesterone receptors
- Boosts neurotransmitter response
- Amplifies the sensitivity of a nerve cell
- Strengthens the electrical pathways for memory retention for at least six to eight hours
- Makes neurons more sensitive to a helpful protein substance believed to play a role in growth of dendrites and axons

Estrogen Is A Gene Modulator

- By hooking up with estrogen receptors in the cell's nucleus, estrogen can turn on or change the expression of a host of genes inside the nucleus
- By modulating the expression of the apolipoprotein E gene, estrogen may decrease the risk of developing Alzheimer's disease

Estrogen Affects Learning, Memory And Old Knowledge

- Boosts by 30 percent NMDA receptors in the hippocampus believed to be important in maintaining the strength or durability of synapse connections involved in creating longer-term memories or learning
- Has positive effects on the hippocampus
- Builds and maintains synapses
- Maintains verbal memory and spatial memory

References

- Wise, P., et al., “Minireview: neuroprotective effects of estrogen-new insights into mechanisms of action,” Endocrinol 2001; 142(3):969-73.
- Puder, J., et al., “Estrogen modulates the hypothalamic-pituitary-adrenal and inflammatory cytokine responses to endotoxin in women,” Jour Clin Endocrinol Metab 2001; 86(6):2403-08.
- Lopez-Jaramillo, P., et al., “Improvement in functions of the central nervous system by estrogen replacement therapy might be related with an increased nitric oxide production,” Endothelium 1999; 6(4):263-66.
- Simpkins, J., et al., “Estrogen and memory protection,” Jour Soc Obstet Gyn Canada 1997; Supplement: 14-19.
- Bruce, A., et al., “Estrogen attenuates and corticosterone exacerbates excitotoxin oxidative injury and amyloid beta-peptide toxicity in hippocampal neuron,” Jour Neurochem 1996; 66(5):1836-44.

References (Cont.)

- Yaffe, K., et al., “Estrogen therapy in postmenopausal women: effects on cognitive function and dementia,” JAMA 1998; 279(9):688-95.
- Strivastava, R., et al., “Apolipoprotein E gene expression in various tissues of mouse and regulation by estrogen,” Biochem Mol Biol Int 1996; 38:91-101.
- Yaffe, K., et al., “Apolipoprotein E phenotype and cognitive decline in a prospective study of elderly community women,” Arch Neuro 1998; 54:1110-14.
- Duka, T., et al., “The effects of 3-week estrogen hormone replacement on cognition in elderly healthy females,” Psychopharmacol 2000; 149(2):129-39.
- Liune, V. et al., “Immuno-chemical demonstration of increased choline acetyltransferase concentration in rat preoptic area after estradiol administration,” Brain Res 1980; 191(1):273-7.

References (Cont.)

- Henderson, V., et al., “Estrogen replacement therapy in older women. Comparisons between Alzheimer’s disease cases and nondemented control subjects,” Arch of Neur 1994; 51(9):896-900.
- Sherwin, B., et al., “Estrogen use and verbal memory in healthy post-menopausal women,” Obstet Gyn 1994; 83(6):979-83.
- Phillips, S., et al., “Effects of estrogen on memory function in surgically menopausal women,” Psycho Neuroendo 1992; 17(5):485-95.
- Drake, E., et al., “Associations between circulating sex steroid hormones and cognition in normal elderly women,” Neurology 2000; 54(3):599-603.
- Paganini-Hill, A., et al., “Alzheimer’s disease in women,” The Female Patient, 1998; 23:10-20.

References (Cont.)

- Di Paolo, T., et al., “Modulation of brain dopamine transmission by sex steroids,” Rev Neurosci 1995; 5:27-41.
- Williams, G.V., et al., “Modulation of memory fields by dopamine D1 receptors in prefrontal cortex,” Nature1995; 376(6541):572-75.
- Paganini-Hill, A., et al., “Does estrogen replacement therapy protect against Alzheimer’s disease? Osteoporosis Int 1997; Supp 1:S12-17.
- Shaywitz, S., et al., “Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks,” JAMA 1999; 281(13):1197-202.
- Poehlman, E., et al., “Changes in energy balance and body composition at menopause: a controlled longitudinal study,” Ann of Int Med 1995; 123(9):673-75.

References (Cont.)

- Paganini-Hill, A., et al., “Estrogen replacement therapy and risk of Alzheimer’s disease,” Arch Int Med 1996; 156(19):2213-17.
- Henderson, V., et al., “Estrogen replacement therapy for the prevention and treatment of Alzheimer’s disease,” CNS Drugs 1997; 5:343-51.
- Asthana, S., et al., “Transdermal estrogen improves memory in women with Alzheimer’s disease (abstract), Neurosci Abstr 1996; 22:200.
- Henderson, V., et al., “Cognitive skills associated with estrogen replacement in women with Alzheimer’s disease, “ Psychoneuroendocrinol 1996; 21(4):421-30.
- Simpkins, J., et al., “Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer’s disease,” Amer Jour Med 1997; 103(3A):19S-25S.

Estrogen And Memory

- In an animal study, eight weeks of estrogen deprivation was found to induce hippocampus-dependent memory impairment.
  - Tao, X., et al., “Effects of estrogen deprivation on memory and expression of related proteins in ovariectomized mice,” Ann Transl Med 2020; 8(6):356.

Estrogen And Memory (Cont.)

- Researchers in this 1996 study found a 54 percent reduction in the risk of developing Alzheimer's disease in those who had taken estrogen. These women had been tracked for up to sixteen years.
  - Morrison, A., et al., "A prospective study of ERT and the risk of developing Alzheimer's disease in the Baltimore longitudinal study of aging," Neurol 1996:46:A435-36.

Estrogen and Memory (Cont.)

- In another 1996 study scientists found that estrogen reduced by 50%, not only the risk of developing Alzheimer's disease, but delayed the onset of the disease, even in those at increased hereditary risk of developing Alzheimer's disease.
  - Tang, M., et al., "Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease," Lancet, 1996; 348(9025):429-32.

Estrogen and Memory (Cont.)

- Yet another study conducted on 1,889 older women in Utah revealed that women who had taken ERT were 40% less likely to develop Alzheimer's disease. Furthermore, the longer they were on hormone replacement therapy the lower was their risk.
  - Zandi, P., et al., "Hormone replacement therapy incidence of Alzheimer's disease in older women," JAMA 2002; 288 (17):2123-29.

Estrogen and Memory (Cont.)

- Many studies over the years have suggested that estrogen has a role in many cognitive functions including learning and memory.
- Estrogen not only influences memory formation and maintenance processes in some situations, but also affects the learning strategies employed to resolve a task, therefore altering what and how information is learned, and thus not only how much is learned, e.g., the strength of the memory.
  - Pompili, A., et al., “Effects of sex steroid hormones on memory,” Acta Neurobiol Exp 2020; 80:117-28.

Estrogen and Memory (Cont.)

- Estrogen replacement therapy has been shown to be most effective to maintain cognition if taken during the onset of menopause and the first few years afterward.
  - Gibbs, R., et al., “Estrogen and cognition: applying preclinical findings to clinical perspectives,” Jour Neurosci Res 2003; 74(5):637-43.
  - Henderson, V., et al., “Postmenopausal hormone therapy and Alzheimer’s disease risk: interaction with age,” Jour Nerol Neurosurg Psychiatr 2005; 76:103-05.
  - Zandi, P., et al., “Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study,” JAMA 2002; 288:2123-39.

Summary

- Estrogen is needed to help women maintain cognitive function.

Progesterone

- Progesterone is made in the brain, spinal cord, and peripheral nerves from pregnenolone and in the ovaries.
- Progesterone promotes the formation of myelin sheaths.
- Progesterone also exerts a neuroprotective role which can be effective to counteract the cognitive decline related to aging.
- Scientists are now looking at progesterone as an alternative for the prevention of memory decline.
  - Schumacher, M., et, al., “Local synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination,” Growth Horm IGF Res 2004; Jun; (Suppl):AS18-S33.
  - Morali, G., et al., “Neuroprotective effects of progesterone and allopregnanolone on long-term cognitive outcome after global cerebral ischemia,” Restor Neurol Neurosci 2011; 29(1):1-15.

Testosterone and Memory

- A small pilot study suggests that testosterone replacement might protect the memory of healthy aging women.
- Transdermal testosterone spray was used in this trial.
  - Davison, S., Endocrine Society 93rd annual meeting 2011, Abstract P1-314.

DHEA and Memory

- Low DHEA levels are often caused by stress and the aging process and can lead to cognitive decline.
- In one study, researchers found that patients with Alzheimer's disease had DHEA levels that were 48 percent lower than those of their normal counterparts.
  - Grimley, E., et al., "Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people," Cochrane Database Syst Rev 2006; 4:CD006221.

DHEA and Memory (Cont.)

- A double-blind, placebo-controlled, crossover study in which DHEA was given to postmenopausal women.
- The study showed a large benefit of DHEA replacement therapy on mental rotation, subject-ordered pointing, fragmented picture identification, perceptual identification, and same-different judgment.
  - Stangl, B., et al., “Administration of dehydroepiandrosterone (DHEA) enhances visual-spatial performance in postmenopausal women,” Behav Neuroci 2011; 125(5):742-52.

DHEA and Memory (Cont.)

- Overall, the results of this study suggest that in women DHEA may oppose cortisol effects reducing distraction and that a higher DHEA response may enhance working memory at the electrophysiological level.
  - do Vale, S., et al., “The relationship between dehydroepiandrosterone (DHEA), working memory and distraction--a behavioral and electrophysiological approach,” PLoS One 2014; 9(8):e104869.

Cortisol

- This study showed stress can rewire the emotional circuits of the brain.
- Stress can destroy nerve connections.
- Cortisol at high levels impairs the function of the hippocampus and can result in atrophy and death of neurons.
  - Carpi, J., et al., “Stress: It’s worse than you think,” Psychology Today, Jan. 1, 1996.

Cortisol (Cont.)

- Stress increases the production of IL-6 which is an inflammatory marker that is increased in the brain of patients with Alzheimer's disease.
- Old but great book: Why Zebras Don't Get Ulcers by Robert Sapolsky.
- It emphasizes how stress can affect the entire body.

Pregnenolone

- Pregnenolone is the hormone of memory in the body.
  - It makes DHEA, estrogen, progesterone, and testosterone
  - Decreases with age
  - At age 75, most people have a 65% decline compared to age 36.

Pregnenolone (Cont.)

- 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
- Directly influences acetylcholine release
- Reduces pain and inflammation
- Blocks the production of acid-forming compounds

Pregnenolone (Cont.)

- Pregnenolone promotes new nerve growth factor.
  - Mayo, W., et al., “Pregnenolone sulfate enhances neurogenesis and PSA-NCAM in young and aged hippocampus,” Neurobiol Aging 2005; 26(1):103-14.
  - Mayo, W., et al., “Individual differences in cognitive aging: implication of pregnenolone sulfate,” Prog Neurobiol 2003; 71 (1):43-8.

Pregnenolone (Cont.)

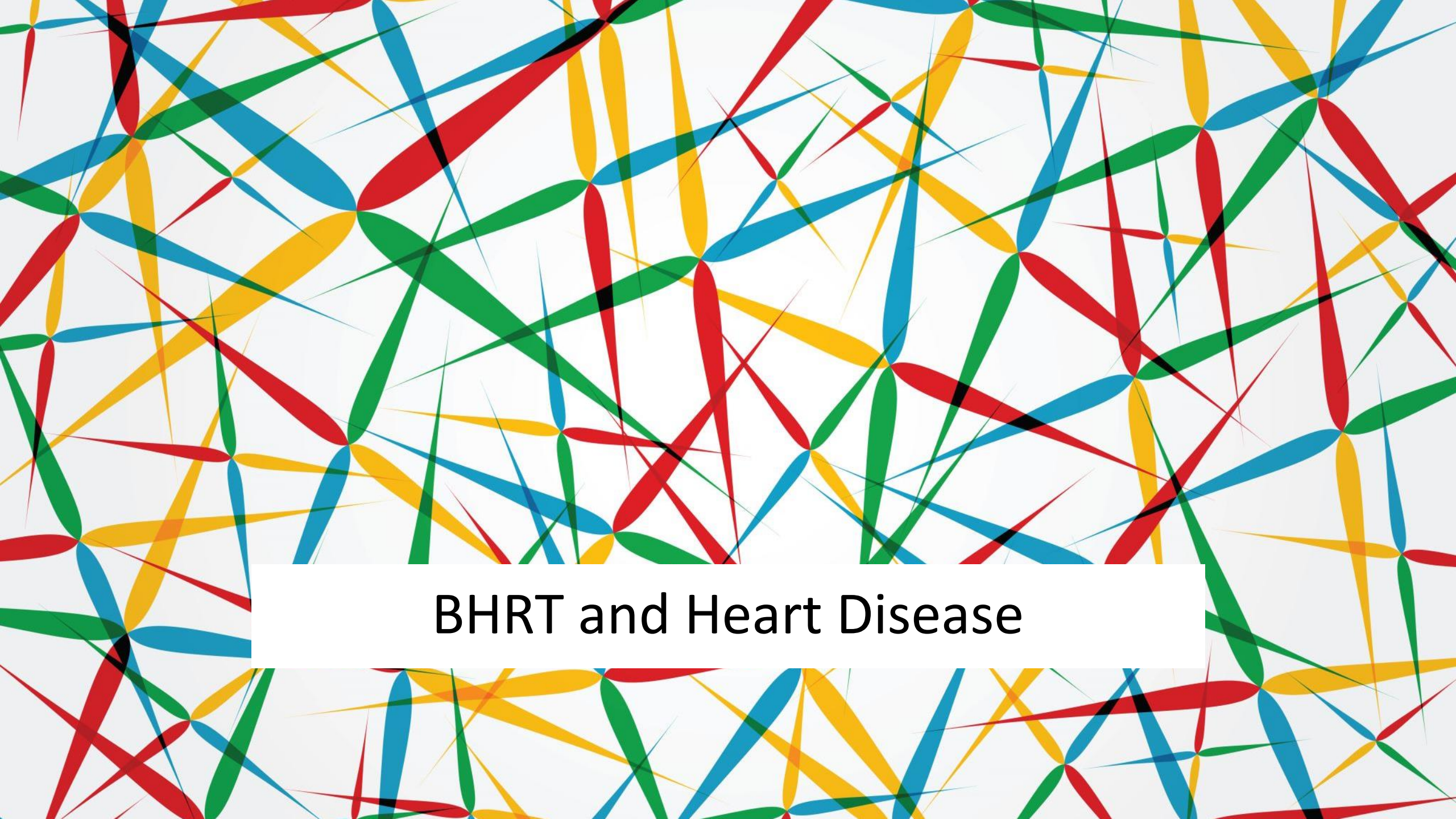
- In addition to serving as the precursor for other steroid hormones, pregnenolone exerts its own effect as an anti-inflammatory molecule to maintain immune homeostasis in various inflammatory conditions. All forms of memory loss are inflammatory in nature.
- Pregnenolone and its metabolic derivatives 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, which emphasizes its role in neuroprotection and neuroregeneration.
    - 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):4596-607.

Pregnenolone (Cont.)

- Anti-inflammatory effects of pregnenolone
  - 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.
    - Ibid., Murugan.

Pregnenolone (Cont.)

- 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.


BHRT and Heart Disease

Great Review Articles

- McCrohon, J., et al., “Effects of hormone replacement therapy on the cardiovascular system,” in Estrogens and Progestogens in Clinical Practice. Fraser, J. ed., New York: Harcourt Publishers, 2000, p. 711-25.
- Miller, V., et al., “Vascular effects of estrogen and progesterone,” in Estrogens and Progestogens in Clinical Practice. Fraser, J. Ed., New York: Harcourt Publishers, 2000, p. 215-23.
- Miller, V., et al., “Vascular actions of estrogens: functional implications,” Pharmacological Reviews 2008; 60(2):210-41.

BHRT and Heart Disease

- Before menopause, women have a lower risk of coronary heart disease than men of the same age. After menopause, women start having an increased risk of developing heart disease.
- This is due to estrogens produced by the body since they are important regulators of cardiovascular homeostasis in premenopausal women and delay the development of hypertension and coronary artery disease.

References

- Henderson, B., et al., “Estrogen replacement therapy and protection from acute myocardial infarction,” Amer Jour Obst Gyn 1988; 159:312-17.
- Stampfer, M., et al., “Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses’ Health Study,” NEJM 1991; 325:756-62.
- Grodstein, F., et al., “Postmenopausal hormone therapy and mortality,” NEJM 1997; 336(25):1769-75.

Estrogen and the Heart

- Studies have shown a 40-50% reduction in cardiovascular morbidity and mortality with hormone replacement therapy.
  - Bush, T., “Extraskeletal effects of estrogen and the prevention of atherosclerosis,” Osteoporosis International 1991; 2:3-11.
- There are many mechanisms by which estrogen is cardioprotective.

Estrogen and the Heart (Cont.)

- Estrogen replacement has a beneficial effect on the lipid profile.
  - Nabulsi, A., et al., “Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women,” NEJM 1993; 328:1069-75.
  - Bush, R., et al., “Cardiovascular mortality and non-contraceptive estrogen use in women: results from the Lipid Research Clinics Program follow-up study,” Circulation 1987; 75:1102-09.

Lipid Profile After Menopause

- Menopause (natural or surgical) is associated with a change in lipid profile for the worse.
  - Elevation of LDL
  - Higher total cholesterol
  - Triglyceride levels increase
  - Lower HDL
  - LDL/HDL ratio moves to a non-favorable ratio even if the total cholesterol level does not change.
    - Ibid., Nabulsi.

Lipid Profile with Estrogen Replacement

- Increase in large VLDL particles
- Lower remnant VLDL levels
- LDL levels are decreased due to an increase in clearance by induction of hepatic LDL receptors
- Raises HDL-2
    - Ibid., Nabulsi.

Estrogen and the Heart (Cont.)

- Lipoprotein (a) levels have been shown to be lowered by 15 percent with estrogen replacement therapy.
  - Soma, M., et al., “Plasma Lp (a) concentration after oestrogen and progestogen in postmenopausal women,” Lancet 1991; 337:612.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect

- Studies reveal that estrogen may improve arterial function independent of lipid effects.
  - Williams, J., et al., “Short-term administration of estrogen and vascular responses of atherosclerotic coronary arteries,” Jour of the American College of Cardiology 1992; 20:454-57.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen stimulates endothelial nitric-oxide synthase (eNOS) in vascular endothelial cells.
  - Moriarty, K., et al., "Mini review: estrogen receptor-mediated rapid signaling," Endocrinology 2006; 147:5557-63.
- This enhances endothelial dependent vasodilatation mediated by NO.
  - Li, L., et al., "Variant estrogen receptor-c Src molecular interdependence and c-Src structural requirement for endothelial NO synthase activation," Proc Natl Acad Sci USA 2007; 104:16468-73.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen has numerous effects on post-transcriptional and translation modulation of proteins and enzymes.
  - Glycosylation
  - Phosphorylation
  - Methylation

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen
  - Decreases turnover of growth factor-induced ornithine decarboxylase which increases cell proliferation
    - Huber, M., et al., “Posts-translational cooperactivity of ornithine decarboxylase induction by estrogens and peptide growth factors in human breast cancer cells,” Mol Cell Endocrinol 1996; 117:211-18.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen (cont.)
  - Activates secretion of MMP-7 which increases paracellular permeability
    - Gorodeski, G., et al., “Estrogen decrease in tight junctional resistance involves matrix-metalloproteinase-7-mediated remodeling of occludin,” Endocrinology 2007; 148:218-31.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen (cont.)
  - Alters synthesis of glycosyltransferases which increases paracellular permeability
    - Ulloa-Aguirre, A., et al., “Endocrine regulation of gonadotropin glycosylation,” Arch Med Res 2001; 32:520-32.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen (cont.)
  - Increases phosphorylation of telomerase which increases cell proliferation
    - Kawagoe, J., et al., “Reloxifene inhibits estrogen-induced up-regulation of telomerase activity in a human breast cancer cell line,” Jour Biol Chem 2003; 278:43363-72.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen (cont.)
  - Increases expression of propyl hydroxylase domain 1 which decreases cellular sensitivity to hypoxia
    - Tian, Y., et al., “Characterization of different isoforms of the HIF prolyl hydroxylase PHD1 generated by alternative initiation,” Biochem Jour 2006; 397:179-86.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen (cont.)
  - Increases protein binding to mRNA for AT1 receptors which decreases expression of AT1 receptors
    - Wu., Z., et al., “Estrogen regulates adrenal angiotensin AT1 receptors by modulating AT1 receptor translation,” Endocrinology 2003; 144:3251-61.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Post-translational actions of estrogen (cont.)
  - Coordination of phosphorylation and sumoylation of steroid receptor coactivators which has cell specific control of ligand-dependent nuclear transcription
    - Wu, H., “Coordinated regulation of A1B1 transcriptional activity by sumoylation and phosphorylation,” Jour Biol Chem 2006; 281:21848-56.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen has actions on the mitochondria and therefore it can affect mitochondrial function in the vascular endothelium.
  - Stirone, C., et al., “Estrogen increases mitochondrial efficiency and reduces oxidative stress in cerebral blood vessels,” Mol Pharmacol 2005; 68:959-65.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria
  - Increases oxidative phosphorylation while lowering ROS production
    - Which decreases the rate of accumulation of mitochondrial DNA mutations over a lifetime
    - Which means that estrogen would protect against future mitochondrial damage but would not reverse any damage that is already present before estrogen replacement

References

- Miller, V., et al., “Vascular Actions of Estrogens: Functional Implications,” Pharmacol Rev 2008; 60: 210-241.
- Duckles, S., et al., “Estrogen and mitochondria: a new paradigm for vascular protection?” Mol Interv 2006; 6:26-35.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria (cont.)
  - Decreases mitochondrial superoxide production
    - Ibid., Duckles.
  - Decreases hydrogen peroxide production
  - Increases levels of manganese superoxide dismutase
  - Does not affect levels of glutathione peroxidase or catalase
    - Ibid., Stirone.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria (cont.)
  - The targets in the mitochondria for estrogen are unknown.
  - Levels of nuclear respiratory factor-1, a major regulator of nuclear-encoded mitochondrial genes, increases after ERT.
    - Ibid., Stirone.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria (cont.)
  - Estrogen may also have a direct effect on the mitochondrial genome since estrogen receptors are present in the mitochondria.
    - Yang, S., et al., "Mitochondrial localization of estrogen receptor B," Proc Natl Acad Sci USA 2004; 101:4130-35.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria (cont.)
  - Several genes for mitochondrial proteins encoded by either nuclear or mitochondrial DNA are regulated by estrogen receptor alpha (ER-alpha) or estrogen receptor beta (ER-beta).
    - O'Lone, R., et al., "Estrogen receptors alpha and beta mediate distinct pathways of vascular gene expression, including genes involved in mitochondrial electron transport and generation of reactive oxygen species," Mol Endocrinol 2007; 21:1281-96.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria (cont.)
  - The production of ROS by the mitochondria plays a large role in oxidative stress.
    - Madamanchi, N., et al., "Mitochondrial dysfunction in atherosclerosis," Circ Res 2007; 100:460-73.
  - Estrogen may therefore have an important impact on vascular oxidative stress.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen's other actions on the mitochondria (cont.)
  - Also, when ROS production remains low and its system is not overwhelmed, it's signaling pathways by ROS may be maintained.
    - Gutierrez, J., et al., "Free radicals, mitochondria, and oxidized lipids: the emerging role in signal transduction in vascular cells," Circ Res 2006; 99:924-32.
    - Lyle, A., et al., "Modulation of vascular smooth muscle signaling by reactive oxygen species," Physiology (Bethesda) 2006; 21:269-80.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen also suppresses ROS through other mechanisms than the mitochondria.
  - ERT reduces angiotensin II-induced free radical production in vascular smooth muscle cells.
    - Strehlow, K., et al., “Modulation of antioxidant enzyme expression and function by estrogen,” Circ Res 2003; 93:170-77.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen also suppresses ROS through other mechanisms than the mitochondria (cont.)
  - Estrogen decreases NADPH-stimulated superoxide production by mouse cerebral arteries.
    - Miller, A., et al., “Effect of gender on NADPH-oxidase activity, expression, and function in the cerebral circulation: role of estrogen,” Stroke 2007; 38:2142-49.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen also suppresses ROS through other mechanisms than the mitochondria (cont.)
  - Estrogen also decreases strain-increased NADPH oxidase activity and intracellular generation of ROS in human umbilical vein endothelial cells.
    - Juan, S., et al., “17 beta –estradiol inhibits cyclic strain-induced endothelin-1 gene expression within vascular endothelial cells,” Amer Jour Physiol Heart Circ Physiol 2004; 287:H1254-H1261.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen also suppresses ROS through other mechanisms than the mitochondria (cont.)
  - Estrogen in vascular smooth muscle cells increases protein levels of both manganese superoxide dismutase (SOD) and extracellular SOD by increasing transcription rate.
    - Ibid., Stirone.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- The most prominent effects of estrogen on vascular reactivity are through its ability to influence endothelial function.
  - Miller, V., et al., “Sex steroids and endothelial function: translating basic science to clinical practice,” Trends Pharmacol 2007; 28:263-70.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Animal studies show that estradiol increases cardiac output by causing systemic vasodilatation.
  - Killam A., et al., “Effects of estrogens on blood flow of oophorectomized ewes,” Amer Jour of Obst and Gynecol 1973; 115:1045-52.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Many studies in humans have shown that estrogen promotes vasodilation through an eNOS-dependent mechanism.
  - Estrogen stimulated increase in plasma concentrations of NO
  - Increases in reactive hyperemia after ERT
  - Changes through the menstrual cycle reflective of an estrogenic effect
    - Ibid., Miller.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Several studies have shown that women getting ERT have more flow-mediated vasodilation if they have received ERT in the past or all along.
    - Sherwood, A., et al., “Age moderates the short-term effects of transdermal 17B estradiol on endothelium-dependent vascular function in postmenopausal women,” Arterio Thromb Vasc Biol 2007; 27:1782-87.
    - Vitale, C., et al., “Time since menopause influences the acute and chronic effect of estrogens in endothelial function,” Arterio Thromb Vasc Biol 2008; 28:348-52.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen also affects production of other endothelial factors.
  - ERT increases prostacyclin (also called prostaglandin 12 or PG12) synthesis by elevating levels of cyclooxygenase-1 and prostacyclin synthase which results in a shift from cyclooxygenase-dependent vasoconstriction to vasodilation after ERT.
  - Prostacyclin inhibits platelet activation and is also an effective vasodilator.
    - Ospina, J., et al., "17B-estradiol decreases vascular tone in cerebral arteries by shifting COX-dependent vasoconstriction to vasodilation," Amer Jour Physiol Heart Circ Physiol 2003; 285:H241-H250.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen increases the release of endothelium-derived relaxing factor(s) in postmenopausal woman.
  - Lieberman, E., et al., “Estrogen improves endothelium-dependent flow-mediated vasodilation in postmenopausal women,” Ann Int Med 1994; 121:936-41.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogens stimulate muscarinic and B-adrenergic cardiac receptors in animals and humans.
  - Maddox, Y., et al., “Endothelium-dependent gender differences in the response of the rat aorta,” Jour of Pharm and Experimental Therapeutics 1980; 40:452-57.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estradiol decreases arterial impedance in the carotid and uterine arteries in postmenopausal women.
  - Ganger, K., et al., “Pulsatility index in internal carotid artery in relation to transdermal oestradiol and time since menopause,” Lancet 1991; 338:839-42.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Left ventricular systolic flow measurements are increased on hormone replacement therapy.
- This reflects an increase in stroke volume and preserved myocardial contractility.
  - Prelevic, G., et al., “The effect of oestrogen and progestogen replacement therapy on systolic flow velocity in healthy postmenopausal women,” Maturitas 1994; 20:37-44.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- This study revealed that women that used ERT in the past or present have a lower incidence of subclinical cardiac disease.
- Women also had reduced LV mass on ECG and better E/A ratios on doppler assessment of mitral inflow which is a measure of cardiac diastolic function on ERT.
  - Manolio, T., et al., "Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women," Circulation 1993; 88: 2163-71.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen is a calcium channel blocker.
- Estrogens affect the regulation of intracellular calcium through hyper-polarization of the membrane of smooth muscle cells and inhibition of voltage-gated calcium channels.
  - Sudhir, K., et al., "Mechanisms of estrogen-induced vasodilatation: in vivo studies in canine coronary conductance and resistance arteries," Jour of the Amer College of Cardiology 1995; 26:807-14.
- Estrogen may also regulate intracellular calcium through enhancement of calcium efflux.
  - Ibid., Miller.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- In women with coronary heart disease, estrogen receptors are absent in areas of atherosclerotic plaque.
- Estrogen may limit the progression of fibrofatty lesions through inhibition of proliferation of smooth muscle by receptor-mediated processes.
  - Losordo, D., et al., "Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women," Circulation 1994; 89:1501-10.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen replacement limits neointimal formation following arterial injury and transplant associated acceleration of atherosclerosis in humans and animals.
  - Foegh, M., et al., “Estradiol inhibition of arterial neointimal hyperplasia after balloon injury,” Jour of Vascular Surgery 1994; 19(4):722-26.
  - O’Keefe, J., et al., “Estrogen replacement therapy after coronary angioplasty in women,” Jour of the Amer College of Cardiology 1997; 29(1):1-5.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen may also limit the progression of atherosclerotic plaque formation by the following mechanisms.
  - Cytokine-induced adhesion of leukocytes
    - Caulin-Glaser, T., et al., “Effects of 17 beta-estradiol on cytokine-induced endothelial cell adhesion molecule expression,” Jour of Clin Investigation 1996; 98:36-42.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen may also limit the progression of atherosclerotic plaque formation also by the following mechanisms (cont.)
  - Fibroblast migration
    - Shi, Y., et al., “Adventitial myofibroblasts contribute to neointimal formation in injured porcine coronary arteries,” Circulation 1996; 94:1655-64.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen may also limit the progression of atherosclerotic plaque formation also by the following mechanisms (cont.)
  - Uptake/degradation of lipids
    - Wagner, J., et al., “Estrogen and progesterone replacement therapy reduces low density lipoprotein accumulation in the coronary arteries of surgically postmenopausal cynomolgus monkeys,” Jour of Clin Investigation 1991; 88(6):1995-2002.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen helps with the rapid repair of vascular wounds by increasing endothelial regrowth with release of endothelium-derived factors, such as NO, which inhibit smooth muscle proliferation consequently decreasing the development of intimal hyperplasia.
  - Krasinski, K., et al., “Estradiol accelerates functional endothelial recovery after arterial injury,” Circulation 1997; 95:1768-72.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Furthermore, estrogen helps with the rapid repair of vascular wounds by modulating hematopoiesis in the bone marrow of endothelial progenitor cells.
    - Horner, S., et al., “A statistically significant sex difference in the number of colony-forming cells from human peripheral blood,” Ann Hematol 1997; 74:259-63.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen, in addition, helps with the rapid repair of vascular wounds also by slowing the senescence of the progenitor cells through elevated telomerase activity and increased proliferation through activation of ER alpha.
    - Masuda, H., et al., “Estrogen-mediated endothelial progenitor cell biology and kinetics for physiological postnatal vasculogenesis,” Cir Res 2007; 101:598-606.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estriol replacement prevents coronary hyperreactivity in vascular smooth muscle.
  - Mishra, R., et al., “Metabolite ligands of estrogen receptor-beta reduce primate coronary hyperreactivity,” Amer Jour Physiol Heart Circ Physiol 2006; 290(1):H295-H303.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Studies of carotid arteries have shown a consistent reduction in carotid intimal medial thickness in postmenopausal women using estrogen replacement compared to controls.
  - Sator, M., et al., "The effect of hormone replacement therapy on carotid arteries: measurement with a high frequency ultrasound system," Maturitas 1998; 30:63-8.
  - Karim, R., et al., "Relationship between serum levels of sex hormones and progression of subclinical atherosclerosis in postmenopausal women," Jour Clin Endocrinol Metab 2008; 93:131-38.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Positive modulation of the quantity of arterial calcification and intimal hyperplasia show the effects of estrogen on components of the vascular wall.
  - Feletou, M., et al., “Endothelial dysfunction: a multifaceted disorder (The Wiggers Award Lecture). Amer Jour Physiol Heart Circ Physiol 2006; 291:H985-H1002.
  - Bush, D., et al., “Estrogen replacement reverses endothelial dysfunction in postmenopausal women,” Amer Jour Med 1998; 104:552-58.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen replacement has been shown to suppresses the stress response to both physical and emotional stresses.
  - Dayas, C., et al., “Effects of chronic oestrogen replacement on stress-induced activation of hypothalamic-pituitary-adrenal axis control pathways,” Jour Neuroendocrinol 2000; 12:784-94.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- There is much less information known on estrogen's effects on veins than on arteries.
- This animal study suggests that the presence of ovarian hormones affect endothelial production of inhibitory prostanoids in veins as well as arteries.
  - Lewis, D., et al., "Genome and hormones: gender differences in physiology selected contribution: effects of sex and ovariectomy on responses to platelets in porcine femoral veins," Jour Appl Physiol 2001; 91:2823-30.
- Prostanoids are a subclass of eicosanoids consisting of the prostaglandins (mediators of inflammatory and anaphylactic reactions, the thromboxanes (mediators of vasoconstriction), and the prostacyclins (active in the resolution phase of inflammation).

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Likewise, estrogen lowers blood pressure by several mechanisms.
  - Studies have shown that HRT decreases serum ACE activity by 20%.
    - Proudler, A., et al., “Hormone replacement therapy and serum angiotensin-converting-enzyme activity in postmenopausal women,” Lancet 1995; 346:89-90.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen lowers blood pressure by several mechanisms (cont.)
  - Estrogen down-regulates angiotensin 1 receptors
    - Nickenig, G., et al., “Estrogen modulates AT1 receptor gene expression in vitro and in vivo,” Circulation 1998; 97:2197-2201.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen lowers blood pressure by several mechanisms (cont.)
  - Inhibition of the renin-angiotensin system by reducing transcription of angiotensin-converting enzyme in endothelial cells
    - Gallagher, P., et al., “Estrogen regulation of angiotensin-converting enzyme mRNA,” Hypertension 1999; 33:323-28.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen lowers blood pressure by several mechanisms (cont.)
  - Up-regulation of endothelium-derived vasodilator factors with simultaneous down-regulation of vasoconstrictor factors like endothelin-1
    - Barber, D., et al., “Endothelin receptors are modulated in association with endogenous fluctuations in estrogen,” Amer Jour Physiol 1996; 271:H1999-H2006.
    - Dubey, R., et al., “Estradiol metabolites inhibit endothelin synthesis by an estrogen receptor-independent mechanism,” Hypertension 2001; 37:640-44.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen lowers blood pressure by several mechanisms (cont.)
  - Depletion of estrogen with a rise in androgens in women reduces local inhibitory signals while elevating procontractile signals at the vascular wall. This leads to increased peripheral resistance and blood pressure in the absence of a decrease in sympathetic tone.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen lowers blood pressure by several mechanisms (cont.)
  - Furthermore, estrogen depletion elevates sympathetic tone and circulating levels of NE which result in an elevation of blood pressure especially if the person is under stress.
    - Wyss, J., et al., "Effects of hormone replacement therapy on the sympathetic nervous system and blood pressure," Curr Hypertens Rep 2003; 5:241-46.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen lowers blood pressure by several mechanisms (cont.)
  - Estrogen depletion is also associated with withdrawal of inhibitory tone (such as imparted by the parasympathetic system) which increases peripheral resistance and lowers heart rate variability.
  - ERT in this study restored heart rate variability.
    - Mercuro, G., et al., “Evidence of a role of endogenous estrogen in the modulation of autonomic nervous system,” Amer Jour Cardiol 2000; 85:787-89.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen regulates adrenergic neurotransmission through several mechanisms.
  - Modulates neuronal activity through binding to estrogen receptors
  - Regulates through effects on catecholamine reuptake at the synaptic cleft
    - Herbison, A., et al., “Oestrogen modulation of noradrenaline neurotransmission,” Novartis Found Symp 2000; 230:74-85; discussion 85-93.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen regulates adrenergic neurotransmission through several mechanisms (cont.)
  - Genomic regulation of alpha-adrenergic receptors
    - Ibid., Herbison.
  - Competes with NE for adrenergic binding sites
    - Ball, P., et al., “Formation, metabolism, and physiologic importance of catecholestrogens,” Amer Jour Obstet Gynecol 1990; 163:2163-70.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Women on ERT had coronary calcifications scores lower than women not on ERT.
    - Budoff, M., et al., “Effects of hormone replacement on progression of coronary calcium as measured by electron beam tomography,” Jour Women’s Health 2005; 14:410-17.
    - Mackey, R., et al., “Hormone therapy, lipoprotein subclasses, and coronary calcification: the Healthy Women Study,” Arch Intern Med 2005; 165:510-15.
    - Manson, J., et al., “Estrogen therapy and coronary-artery calcification,” NEJM 2007; 356:2591-2602.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Oral estrogen replacement therapy is proinflammatory since hepatic metabolism of 17 beta-estradiol produces proinflammatory metabolites in higher concentrations than may be produced by the transdermal application of estrogen.
    - Brosnan, J., et al., “Haemostatic activation in postmenopausal women taking low-dose hormone therapy: less effect than with transdermal administration?” Thromb Haemost 2007; 97:558-65.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Transdermal application of estrogen has an anti-inflammatory effect.
    - Seed, M., et al., “The effect of hormone replacement therapy and route of administration on selected cardiovascular risk factors in post-menopausal women,” Fam Pract 2000; 17:497-507.
    - Chen, F., et al., “Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on cardiovascular risk factors,” Menopause 2001; 8:347-52.

References

- Vehkavaara, S., et al., “Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women,” Thromb Haemost 2001; 85:619-25.
- Strandberg, T., et al., “Differing effects of oral and transdermal hormone replacement therapy on cardiovascular risk factors in healthy postmenopusal women,” Amer Jour Cardiol 2003; 92:212-14.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- ERT reduces infiltration of leukocytes to arteries after endothelium denudation and cytokine-induced gene transcription in smooth muscle.
    - Xing, D., et al., “Estrogen modulates TNF-alpha induced inflammatory responses in rat aortic smooth muscle cells through estrogen receptor-B activation,” Amer Jour Physiol Heart Circ Physiol 2007; 292:H2607-H2612.
    - Wang, D., et al., “Estrogen treatment abrogates neointima formation in human C-reactive protein transgenic mice,” Arterioscler Thromb Vasc Biol 2005; 25:2094-99.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen therefore modulates inflammation through the following mechanisms
  - Through controlling inflammatory proteins produced by the liver
  - Direct effects on the vascular wall
  - Indirectly through the hypothalamic-pituitary-adrenal axis including stimulating the release of corticotropin-releasing hormone and corticosteroid hormone release
  - Transdermal E2 decreases IL-6, TNF-alpha, IL-1

Reference

- Puder, J., et al., “Estrogen modulates the hypothalamic-pituitary-adrenal and inflammatory cytokine responses to endotoxin in women,” Clin Endocrinol Metab 2001; 86(6):2403-08.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen and blood sugar regulation
  - Estrogen actions in hypothalamic nuclei differentially control food intake, energy expenditure, and white adipose tissue distribution.
  - Estrogen actions in skeletal muscle, liver, adipose tissue, and immune cells are involved in insulin sensitivity as well as prevention of lipid accumulation and inflammation.
  - Estrogen actions in pancreatic islet β-cells also regulate insulin secretion, nutrient homeostasis, and survival.
  - Estrogen deficiency promotes metabolic dysfunction predisposing to obesity, metabolic syndrome, and type 2 diabetes.
    - Mauvais-Jarvis, F., et al., "The role of estrogens in control of energy balance and glucose homeostasis," Endocr Rev 2013; 34(3):309-38.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen and blood sugar regulation (cont.)
  - Estradiol improved insulin sensitivity in women with coronary heart disease.
  - Adding medroxyprogesterone nullified the beneficial effects of estradiol.
    - Os, I., et al., “Insulin sensitivity in women with coronary heart disease during hormone replacement therapy,” Jour Women Health (Larchmt) 2005; 14(2):137-45.

Mechanisms By Which Estrogen May Have A Cardioprotective Effect (Cont.)

- Estrogen has positive effects on coagulation.
  - ERT/HRT lowers fibrinogen levels.
    - Kannel, W., et al., “Fibrinogen and the risk of cardiovascular disease: the Framingham Study,” JAMA 1987; 258:1183-86.
  - ERT/HRT lowers PAI-1.
    - Gebara, O., et al., “Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study,” Circulation 1995; 91:1952-58.

Role of Estrogen Receptors in Heart Disease

- The effects of estrogen on cardiovascular function are mediated by nuclear and membrane estrogen receptors (ERs), including estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G-protein-coupled ER (GPR30 or GPER).
- This study discusses current reports on the underlying molecular mechanisms of the ERs in regulating vascular pathology, with a special emphasis on hypertension, pulmonary hypertension, and atherosclerosis, as well as in regulating cardiac pathology, with a particular emphasis on ischemia/reperfusion injury, heart failure with reduced ejection fraction, and heart failure with preserved ejection fraction.
    - Aryan, L., et al., "The role of estrogen receptors in cardiovascular disease," Int Jour Mol Sci 2020; 21(12):4314.

Risks

- Interesting,
  - The risk of an average women after menopause dying of heart disease is about 40%.
  - Her risk of developing breast cancer is at most 5.5% with approximately a 1% chance of expiring from breast cancer.
    - Ibid., McCrohon.

Risks (Cont.)

- This study showed no increased risk of CVA or venous thrombosis with transdermal estrogen use.
  - Speroff, L, “Transdermal hormone therapy and the risk of stroke and venous thrombosis,” Climacteric 2010; 13(5):429-32.

Risks (Cont.)

- Other studies showed no risk with transdermal estrogen use and venous thromboembolism.
- Oral estrogen use was associated with an increased risk.
  - Canonico, M., et al., “Hormone therapy and venous thromboembolism among postmenopausal women,” Circulation 2007; 115:840-45.
  - Scarabin, P., et al., “Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women: A randomized controlled trial,” American Heart Association 1997; 17(11):3071-78.

The Importance of the Hormonal Symphony

- Maintaining the hormonal symphony in the body is one of the keys to optimal health.
- The relationship between free 17B-estradiol, free testosterone, and sex hormone-binding globulin may be more predictive of changes in carotid intimal thickening than concentrations of any of these hormones by themselves.
  - Karim, R., et al., "Relationship between serum levels of sex hormones and progression of subclinical atherosclerosis in postmenopausal women," Jour Clin Endocrinol Metab 2008; 93:131-38.

Summary of Estrogen's Effects on the CV System

- In review of the studies presented here in both humans and animals, ERT has a significant beneficial effects upon the cardiovascular system.
- Timing of the ERT dose appear to matter. The ability for ERT to prevent or slow the progression of vascular remodeling or plaque formation may be somewhat limited if not begun at the time of menopause.
- The same concept holds true for the actions of estrogen on the mitochondria.

Future

- In the future, IV estrogen my be used to treat an acute MI due to its antiarrhythmic effect.
  - Philip, K., et al., “Greater antiarrhythmic activity of acute 17beta-estradiol in female than male anaesthetized rats: correlation with Ca2+ channel blockade,” Brit Jour Pharmacol 2006; 149(3):233-42.

Progesterone and the Heart

- Progesterone and progestins have different effects on smooth muscle cell proliferation.
  - Medroxyprogesterone (MPA) has been shown to increase proliferation of coronary artery smooth muscle cells.
  - Progesterone inhibits smooth muscle cell proliferation.
    - Carmody, B., et al., “Progesterone inhibits human infragenicular arterial smooth muscle cell proliferation induced by high glucose and insulin concentrations,” Jour Vasc Surg 2002; 36(4):833-38.

Progesterone and the Heart (Cont.)

- Progesterone inhibits vascular cell adhesion molecule-1 (VCAM-1) expression in human vascular endothelial cells.
- MPA does not inhibit vascular cell adhesion molecule-1 (VCAM-1) expression in human vascular endothelial cells.
  - Otsuki, M., et al., “Progesterone, but not medroxyprogesterone, inhibits vascular cell adhesion molecule-1 expression in human vascular endothelial cells,” Arteriosclero Thromb Vasc Biol 2001; 21(2):243-48.

Progesterone and the Heart (Cont.)

- In postmenopausal women, progesterone and not MPA enhances the beneficial effect that estrogen has on exercise-induced myocardial ischemia.
  - Rosano, G., et al., “Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women,” Jour Amer Coll Cardiol 2000; 36(7):2154-59.

Progesterone and the Heart (Cont.)

- Progesterone was shown to lower blood pressure in this study.
  - L'hermite, M., et al., "Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review," Maturitas 2008; 60:185-201.

Progesterone and the Heart (Cont.)

- An animal study showed that low doses of progesterone prevented coronary hyperreactivity in both nonatherosclerotic primates and in pre-atherosclerotic primates.
  - Hermsmeyer, R., et al., “Prevention of coronary hyperreactivity in preatherogenic menopausal rhesus monkeys by transdermal progesterone,” Arteriosclero Thromb Vasc Biol 2004; 24(5):955-61.

Progesterone and the Heart (Cont.)

- Results from the PEPPI trial showed that micronized progesterone yields a more favorable elevation of HDL than other progesterone medications.
  - Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 1996; 275(5):370-75.

Testosterone and the Heart

- This study discusses testosterone deficiency as being a key risk factor in the increased risk of developing heart disease in women following a hysterectomy.
  - Rako, S., “Testosterone deficiency: a key factor in the increased cardiovascular risk to women following hysterectomy or with natural aging?” Jour Women’s Health 1998; 7(7):825-59.

Testosterone and the Heart (Cont.)

- Testosterone replacement has been shown to decrease symptoms of angina.
  - Sarrel, P., Cardiovascular aspects of androgens in women," Semin Reprod Endocrinol 1998; 16(2):1221-28.

Testosterone and the Heart (Cont.)

- Testosterone replacement has been shown to relax rabbit coronary arteries.
  - Yue, P., t al., “Testosterone relaxes rabbit coronary arteries and aorta,” Circulation 1995; 91(4):1154-60.

Testosterone and the Heart (Cont.)

- In another study, testosterone replacement in postmenopausal women was found to lower lipoprotein (a) levels by up to 65%. Elevated lipoprotein (a) is a major risk factor for heart disease.
  - Alber, J., et al., “Reduction of lecithin-cholesterol acyltransferase, apolipoprotein D and the Lp(a) lipoprotein with the anabolic steroid stanozol,” Biochim Biophys Acta 1984; 795:293-303.

Testosterone and the Heart (Cont.)

- Only replace testosterone in women if they have their own estrogen or if they are on estrogen replacement therapy.
- Otherwise, women have an increased risk in developing heart disease if only testosterone is replaced, and estrogen remains low.

DHEA and the Heart

- Age-related decline of plasma DHEA levels may be associated with an increased risk of cardiovascular disease in women.
  - Akishita, M., et al., “Association of plasma dehydroepiandrosterone-sulfate levels with endothelial function in postmenopausal women with coronary risk factors,” Hypertens Res 2008; 31(1):69-74.

DHEA and the Heart (Cont.)

- A study of postmenopausal women with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia revealed lower DHEA-S levels were linked with higher cardiovascular mortality and all cause mortality.
  - Shufelt, C., et al., “DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health: National Heart, Lung, and Blood Institute (NHLBI) sponsored Women’s Ischemia Syndrome Evaluation (WISE),” Jour Clin Endocrinol Met 2010; 95(11):4985-92.

DHEA and the Heart (Cont.)

- This study showed that DHEA levels are inversely associated with diverse carotid atherosclerosis regardless of endothelial function.
  - Yoshida, S., et al., “Dehydroepiandrosterone sulfate is inversely associated with sex-dependent diverse carotid atherosclerosis regardless of endothelial function,” Atherosclerosis 2010; 212(1):310-5.

DHEA and the Heart (Cont.)

- DHEA replacement has been shown to have anti-remodeling and vasorelaxant drug effects, consequently having a role in prevention of cardiovascular disease.
  - Savineau, J., et al., “Role of DHEA in cardiovascular diseases,” Biochem Pharm 2013; 85(6):718-26.

DHEA and the Heart (Cont.)

- In addition, DHEA was shown to inhibit vascular inflammation which is a known risk factor for heart disease.
  - Altman, R., et al., “Inhibition of vascular inflammation by dehydroepiandrosterone sulfate in human aortic endothelial cells: roles of PPARalpha and NF-kappaB,” Vascular Pharmacol 2008; 48(2-3):76-84.

DHEA and the Heart (Cont.)

- A study showed that replacement of DHEA improved indices of arterial stiffness.
  - Weiss, E., et al., “Dehydroepiandrosterone replacement therapy in older adults improves indices of arterial stiffness,” Aging Cell 2012; 11(5):876-84.

DHEA and the Heart (Cont.)

- Another trial concluded that DHEA given orally may help treat systemic vascular remodeling including restenosis. The mechanism proposed is inhibition of the Akt axis.
  - Bonnet, S., et al., “DHEA reverses systemic vascular remodeling through the inhibition of the Akt/GSK3-(beta)/ NFAT axis,” Circulation 2009; 12(13):123-40.

Cortisol and the Heart

- Abnormal cortisol levels are associated with many risk factors for heart disease including the following:
  - Perivascular coronary artery inflammation
  - Endothelial dysfunction
  - Hypertension
  - Insulin resistance
  - Dyslipidemias
  - Obesity
  - Hypercoagulability: elevated fibrinogen, high von Willebrand factor, high homocysteine, elevated levels of factor XII, XI, IX, VIII, plasminogen, 2-antiplasmin, and plasminogen activating factor

Reference

- Black, P., et al., “Stress, inflammation, and cardiovascular disease,” Jour Psychosom Res 2002; 52(1):1-23.

Cortisol and the Heart (Cont.)

- Helping your patients improve and normalize their cortisol level is a great way to decrease their risk of heart disease.
- We all have stress. It is about mitigating what causes us stress which reduces inflammation and lowers the risk of developing heart disease.
- Improving cortisol also helps to regulate blood sugar and improve the patient's lipid profile which decreases their risk as well.

BHRT and Anti-Aging Skin Care

BHRT and Anti-Aging Skin Care

- This section of the seminar focuses on perimenopausal and menopausal women and the effects of hormones on the skin during this time in a woman’s life. The skin, the largest organ of the body, is the organ in which changes associated with aging are most visible. The skin is a target organ for various hormones, and sex steroids have a profound influence on the aging process.
- Aging of the skin is associated with thinning skin, atrophy, dryness, wrinkling, and delayed wound healing. Many of these changes are due to hormone decline or deficiency. A decrease in sex steroids induces a reduction of those skin functions that are under hormonal control.
- Keratinocytes, Langerhans' cells, melanocytes, sebaceous glands, collagen content, and the synthesis of hyaluronic acid, for example, are under hormonal influence.
- Let’s take a closer look at the intricacies of the endocrine system and its relationship to skin aging through the lens of hormonal function.

References

- Shu, Y., et al., “Estrogen and skin: therapeutic options,” Amer Jour Clin Dermatol 2011; 12(5):297-311.
- Shah, M., et al., “Estrogen and skin. An overview,” Amer Jour Clin Dermatol 2001; 2(3):143-50.
- Brincat, M., et al., “Estrogens and the skin,” Climacteric 2005; 8(2):110-23.
- Sator, P., et al., “Skin aging and sex hormones in women -- clinical perspectives for intervention by hormone replacement therapy,” Exp Dermatol 2004; 13(Suppl 4):36-40.
- Calleia-Agius, J., et al., “The effect of menopause on the skin and other connective tissues,” Gynecol Endocrinol 2012; 28(4):273-77.

Estrogen and the Skin

- Cutaneous aging manifests itself as a progressive reduction in function and reserve capacity of skin tissue. Collagen atrophy is a major factor in skin aging. There is a strong correlation between skin collagen loss and estrogen deficiency due to the menopause.
- Skin aging is associated with a progressive increase in extensibility and a reduction in elasticity. With increasing age, the skin also becomes more fragile and susceptible to trauma, leading to more lacerations and bruising. Furthermore, wound healing is impaired in older women.
- Estrogen deficiency following menopause results in atrophic skin changes and the acceleration of skin aging. Skin thickness is reduced by 1.13 percent and collagen content is reduced by 2 percent per postmenopausal year in menopausal women.
  - Calleia-Agius, J., et al., “Skin Ageing,” Menopause Int 2007; 13(2):60-4.

Estrogen and the Skin (Cont.)

- The effects of aging on the skin of older females correlate with the period of estrogen deficiency rather than chronological age.
- Another study of postmenopausal women indicated that estrogen deprivation is associated with dryness, atrophy, fine wrinkling, poor healing, and hot flashes. Epidermal thinning, declining dermal collagen content, diminished skin moisture, decreased laxity, and impaired wound healing have also been reported in postmenopausal women.
  - Brincat, M., et al., “Estrogens and the skin,” Climacteric 2005; 8(2):110-23.

Skin Manifestations of Estrogen Deficiency

- Decreased elastin
- Decreased skin firmness and elasticity
- Impaired wound healing
- Increased collagen
- Increased number and depth of wrinkles
- Increased oxidative stress
- Protection against skin photoaging
- Skin dryness
- Thinner skin

Estrogen and the Skin (Cont.)

- The good news is that estrogen use after menopause increases collagen content and dermal thickness, elasticity, and decreases the likelihood of dry skin.
  - Brincat, M., et al., “Skin collagen changes in post-menopausal women receiving different regimens of estrogen therapy,” Obstet Gynecol 1987; 70:123-27.
  - Varila, E., et al., “The effect of topical oestradiol on skin collagen of postmenopausal women,” Brit Jour Obstet Gynaecol 1995; 102:985-89.
  - Calleia-Agius, J., et al., “Effects of hormone replacement therapy on connective tissue: why is this important?” Best Pract Res Clin Obstest Gynecol 2009; 23(1):121-27.

References

- Borda, L., et al., “Bioidentical hormone therapy in menopause: relevance in dermatology,” Dermatol Online Jour 2019; 25(1):1.
- Shu, Y., et al., “Estrogen and skin: therapeutic options,” Amer Jour Clin Dermatol 2011; 12(5):297-311.
- Liu, T., et al., “Recent advances in the anti-aging effects of phytoestrogens on collagen, water content, and oxidative stress,” Phytother Res 2020; 34(3):435-47.
- Archer, D., “Postmenopausal skin and estrogen,” Gynecol Endocrinol 2012; 28(Supp 2):2-6.
- Stevenson, S., et al., “Effect of estrogens on skin aging and the potential role of SERMs,” Clin Interv Aging 2007; 2(3):283-97.

Estrogen and the Skin (Cont.)

- Estrogen has many positive effects on skin aging. In fact, one study suggested that estrogen therapy has long-term benefits on skin and supports the use of early and continuous HRT in preventing detrimental skin changes. Let's examine how estrogen replacement benefits each manifestation of estrogen deficiency.
  - Naftolin, F., "Prevention during the menopause is critical for good health: skin studies support protracted hormone therapy," Fertil Steril 2005; 84:293-94.

Oxidative Stress

- Estrogen deficiency is strongly linked to an altered oxidative state. Estrogen is a potent direct antioxidant and indirect inducer of antioxidant enzymes. Oxidative stress decreases procollagen I synthesis in human fibroblasts, while estrogen significantly increases the synthesis of procollagen I.
- Estrogen can increase the viability of fibroblasts and keratinocytes, which are affected by H_2O_2. Furthermore, estrogen counteracts H_2O_2-mediated lipoperoxidation and DNA oxidative damage in skin cells. The physiological concentration of estrogens also increases cell viability, which is reduced by reactive oxygen species (ROS) and protects human skin cells by decreasing oxidative damage.
    - Bottai, G., et al., “17β-Estradiol protects human skin fibroblasts and keratinocytes against oxidative damage,” Jour Eur Acad Dermatol Venereol 2012; 27:1236-43.

Collagen

- A difference in collagen subtypes has also been documented in post-menopausal women. When evaluated by immunohistochemistry, compared with premenopausal women, postmenopausal women demonstrate a decrease in collagen types I and III and a reduction in the type III/type I ratio within the dermis. Types I and III skin collagens are thought to decrease by as much as 30 percent in the first five years after menopause.
- The use of topical estrogen has also been shown to increase skin collagen and has been demonstrated to promote an increase in collagen synthesis, as shown by increased type I and type III procollagen levels. Current studies have also shown that estrogen treatment prevents the loss of the collagen I peptide and increases the expression of type III collagen. Also, estrogen increased tropoelastin and fibrillin, which may be associated with an increase in elastic fibers.
    - Savvas, M., et al., “Type III collagen content in the skin of postmenopausal women receiving oestradiol and testosterone implants,” Brit Jour Obstet Gynaecol 1993; 100:154-56.

Collagen (Cont.)

- Transforming growth factor β (TGF-β) is a growth factor that stimulates fibroblast proliferation and extracellular matrix (ECM) secretion, which can affect angiogenesis and epithelialization of the skin. TGF-β improves skin aging by enhancing the production of subcutaneous VEGF and thereby increasing the thickness of collagen. Estrogen can enhance the expression of TGF-β to delay skin aging through these mechanisms.
  - Hosokawa, M., et al., “Estrogen induces different responses in dermal and lung fibroblasts: special reference to collagen,” Connect Tissue Res 1981; 9:115-20.
  - Son, E., et al., “Topical application of 17beta-estradiol increases extracellular matrix protein synthesis by stimulating tgf-Beta signaling in aged human skin in vivo,” Jour Invest Dermatol 2005; 124:1149-61.

Collagen (Cont.)

- Matrix metalloproteinases (MMPs) induce skin aging by degrading (breaking down) collagen. There is increasing evidence that the expression of MMPs is controlled by tissue inhibitor of metalloproteinase (TIMP). TIMP is a tissue inhibitor of MMPs and thereby inhibits collagen degradation. In addition to its inhibitory effects on most known MMPs, the encoded TIMP proteins are capable of promoting cell proliferation in a variety of cell types and may also have anti-apoptotic functions. Estrogen can upregulate the expression of TIMPs to downregulate the expression of MMPs, which reduces the breakdown of collagen to protect the skin.
    - Voloshenyuk, T., et al., “Estrogen improves TIMP-MMP balance and collagen distribution in volume-overloaded hearts of ovariectomized females,” Amer Jour Physiol, Regulatory Integrative Comparative Physiol, 2010; 299:R683–R693.

Water Content

- Research has shown that the positive effects of estrogens on the water content of the skin may be due to dermal and epidermal components. Estrogen maintains skin moisture by increasing acid mucopolysaccharides and hyaluronic acid in the skin and possibly maintaining stratum corneum barrier function.
- Dryness is also alleviated through increased water-holding capacity, increased sebum production, and improved barrier function of the skin. The increased hydration is believed to be due in part to an increase in the water-holding capacity of the stratum corneum.
    - Pierard-Franchimont, C., et al., “Skin water-holding capacity and transdermal estrogen therapy for menopause: a pilot study,” Maturitas 1995; 22:151-54.

Skin Thickness

- Epidermal thinning is associated with aging, and topical estradiol has been shown to reduce epidermal thinning in aging skin and maintain skin thickness. Estrogens have moreover been shown to influence skin thickness by stimulating collagen synthesis, maturation, and turnover in animal trials.
- Topical estrogens have been shown to improve skin thickness in clinical trials. Topical application is an efficient method, since estrogen easily penetrates the stratum corneum of the skin. In one study, it demonstrated an increase in keratinocyte proliferation and epidermal thickness in response to only two weeks of topical estrogen in the skin of elderly females.
    - Maheux, R., et al., “A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness,” Amer Jour Obstet Gynecol 1994; 1(7):642-49.

Sebum

- Sebum levels are higher in postmenopausal women receiving hormone replacement therapy, which helps maintain skin moisture.
- In addition, postmenopausal aging affects the sebum production, but HRT does not significantly control the complex process of seborrhea.
- However, HRT mitigates the progressive enlargement of the openings of the sebum follicular reservoir.
  - Pierard-Franchimont, C., et al., “Postmenopausal aging of the sebaceous follicle: a comparison between women receiving hormone replacement therapy or not,” Dermatology 2002; 204(1):17-22.

Wrinkling

- Skin wrinkling is synonymous with aging. It is also affected by environmental and hormonal factors. Wrinkling occurs due to decreased skin elasticity as a result of elastic degeneration and loss of connective tissue. It has been reported that estrogen is effective in the treatment of aging skin, and improvement in skin elasticity and wrinkle depth was observed after six months of treatment in premenopausal women with skin aging symptoms in one trial. In another study of early postmenopausal women monitored for five years, skin elasticity was shown to have decreased by 1.5 percent per year, a change not seen in women on HRT. This led to the suggestion that estrogen deficiency plays a role in wrinkle formation.
- In a large cohort study, it was shown that wrinkling is reduced in postmenopausal women who were administered estrogen. Skin wrinkling may benefit from estrogen as a result of the effects of the hormone on the elastic fibers and collagen, and it enhances the morphology and synthesis of elastic fibers, collagen type III, and hyaluronic acid.

Reference

- Wolff, E., et al., “Long-term effects of hormone therapy on skin rigidity and wrinkles,” Fertil Steril 2005; 84:285-88.

Photoaging

- Ultraviolet (UV)-B exposure is associated with upregulation of matrix metalloproteinase (MMP) production, leading to an increase in collagen breakdown, and is also thought to decrease type I and type III collagen synthesis. Estrogen replacement therapy has been shown to offer some degree of protection against skin photoaging.
  - Tsukahara, K., et al., “Ovariectomy accelerates photoaging of rat skin,” Photochem Photobiol 2001; 73:525-31.
  - Tsukahara, K., et al., “Ovariectomy is sufficient to accelerate spontaneous skin ageing and to stimulate ultraviolet irradiation-induced photoageing of murine skin,” Brit Jour Dermatol 2004; 2004; 151:984-94.

Vascularization

- Changes to the cutaneous vascular reactivity are noted following menopause. Capillary blood flow velocity decreases significantly in postmenopausal women.
- Estrogen has been shown to enhance the level of vascularization in the skin. Treatments administered for menopause, in particular hormone replacement therapy, appear to alter its effects on the basic components of the skin as well as the more complex structures residing in the skin, consequently retarding the skin aging process.
  - Raine-Fenning, N., et al., “Skin aging and menopause: implications for treatment,” Amer Jour Clin Dermatol 2003; 4(6):371-78.

Wound Healing

- Estrogen increases and improves cutaneous wound healing by regulating the levels of a cytokine. Furthermore, estrogen modulates local inflammation, granulation, re-epithelialization, and possibly wound contraction, which accelerate wound healing at the expense of forming lower quality scars.
- In wound healing models, estrogen reduces wound size and stimulates matrix deposition in both human and murine skin, highlighting the effects of estrogens on dermal fibroblasts.
- Likewise, physiologic studies on estrogen and wound healing suggest that hormone replacement therapy may play a beneficial role in cutaneous injury repair.

References

- Emmerson, E., et al., “The role of estrogen deficiency in skin ageing and wound healing,” Biogerontology 2012; 13:3–20.
- Ashcroft, G., et al., “Potential role of estrogens in wound healing,” Amer Jour Clin Dermatol 2003; 4:737-43.
- Calleia-Agius, J., et al., “Skin Ageing,” Menopause Int 2007; 13(2):60-4.

Estrogen and the Skin (Cont.)

- As you have seen, skin changes of aging can be reversed by estrogen replacement, which increases keratinocyte proliferation, epidermal thickness, epidermal hydration, and skin elasticity; reduces skin wrinkles; augments the content and quality of collagen; and increases the level of vascularization.
- In addition, estrogen increases epidermal hydration, skin elasticity, and skin thickness. Estrogens can significantly modulate skin physiology, targeting keratinocytes, fibroblasts, melanocytes, hair follicles, and sebaceous glands, and improve angiogenesis, wound healing, and immune responses.
  - Thorton, M., et al., “Estrogens and aging skin,” Dermatoendocrinol 2013; 5(2):264-70.

Estrogen and the Skin (Cont.)

- This author found that both systemic and topical estrogens appear to have positive effects on hormonal aging, increasing skin collagen content, thickness, elasticity and hydration. Estrogen therapies may also improve wound healing and reduce the incidence of wound complications.
- This review explores the potential for targeted estrogen replacement as a therapeutic option for long-term skin management in postmenopausal women.
  - Archer, D., “Postmenopausal skin and estrogen,” Gynecol Endocrinol 2012; 28(Supp 2):2-6.

Progesterone and the Skin

- The positive impact of topically applied progesterone cream on markers of skin aging may be due to the suppressive effect of progesterone on tissue-degrading enzymes known as matrix metalloproteinases (MMPs).
- For example, progesterone has been found to decrease the expression and activity of MMP-1 and MMP-9, the most important conductors of photoaging (aging of the skin due to exposure to the sun) and chronological aging, by binding to their receptors. In addition, epidermal hydration has been shown to improve with oral micronized (natural) progesterone therapy.
  - Gasser, S., “Impact of progesterone on skin and hair in menopause - a comprehensive review,” Climacteric 2021; 24(3);229-35.

Progesterone and the Skin (Cont.)

- In a double-blind study, 40 perimenopausal and postmenopausal women were treated with either topically applied 2 percent progesterone cream or placebo cream every evening to the face and neck.
- After sixteen weeks, there was a significant increase of skin elasticity in the women treated with the topical progesterone cream but not in the control group.
    - Holzer, G., et al., “Effects and side-effects of 2% progesterone cream on the skin of peri- and postmenopausal women: results from a double-blind, vehicle-controlled, randomized study,” Brit Jour Dermatol 2005; 153:626–34.

Testosterone and the Skin

- Hormonal treatment is not usually the first option to treat female acne.
- However, some acne patients (30 to 80 percent) showed various degree of hyperandrogenemia (high testosterone and other androgens).
- Both natural therapies and/or metformin to lower testosterone levels will help decrease acne if it is related to elevated testosterone levels.
  - Henze, C., et al., “Incidence of increased androgen levels in patients suffering from acne,” Dermatology 1998;196(1):53–4.

References

- Slayden, S., et al., “Hyperandrogenemia in patients presenting with acne,” Fertil Steril 2001; 75(5):889–92.
- Lai, J-J., et al., “The role of androgen and androgen receptor in the skin-related disorders,” Arch Dermatol Res 2012; 304(7):499-510.
- Cibula, D., et al., “The role of androgens in determining acne severity in adult women,” Brit Jour Dermatol 2000; 143(2):399-404.

DHEA and the Skin

- A placebo-controlled, randomized, prospective study was performed with 75 postmenopausal women applying DHEA twice a day, for 13 weeks, in varying doses.
- The data suggest the possibility that topical DHEA could be used as an efficient and physiological anti-aging skin agent.
  - El-Alfy, M., et al., “Skin responses to topical dehydroepiandrosterone: implications in antiageing treatment?” Brit Jour Dermatol 2010; 163(5):968-76.

DHEA and the Skin (Cont.)

- In another study, DHEA formulation (1%) or a placebo was topically applied for four months to facial and hand skin, in two groups of twenty menopausal women.
- DHEA treatment increased the rate of sebum, which was considered positively by the menopausal population usually affected with a declining sebum level. In addition, topical DHEA improved skin brightness, counteracting the papery appearance of skin and epidermal atrophy, a characteristic feature of hormone-related skin aging. Topical DHEA also reduced wrinkles.
  - Nouveau, S., et al., “Effects of topical DHEA on aging skin: a pilot study,” Maturitas 2008; 59(2):174-81.

DHEA and the Skin (Cont.)

- Moreover, DHEA may be related to the process of skin aging through the regulation and degradation of extracellular matrix protein.
- A study demonstrated that DHEA can increase procollagen synthesis and inhibit collagen degradation by decreasing matrix metalloproteinases (MMP)-1 synthesis and increasing tissue inhibitor of matrix metalloprotease (TIMP-1) production in cultured dermal fibroblasts. DHEA was found to inhibit ultraviolet (UV)-induced MMP-1 production and the UV-induced decrease of procollagen synthesis.
- DHEA (5%) also induced the expressions of transforming growth factor-beta1 and connective tissue growth factor mRNA in cultured fibroblasts and aged skin. The authors suggested the possibility of using DHEA as an anti-skin aging agent.

Reference

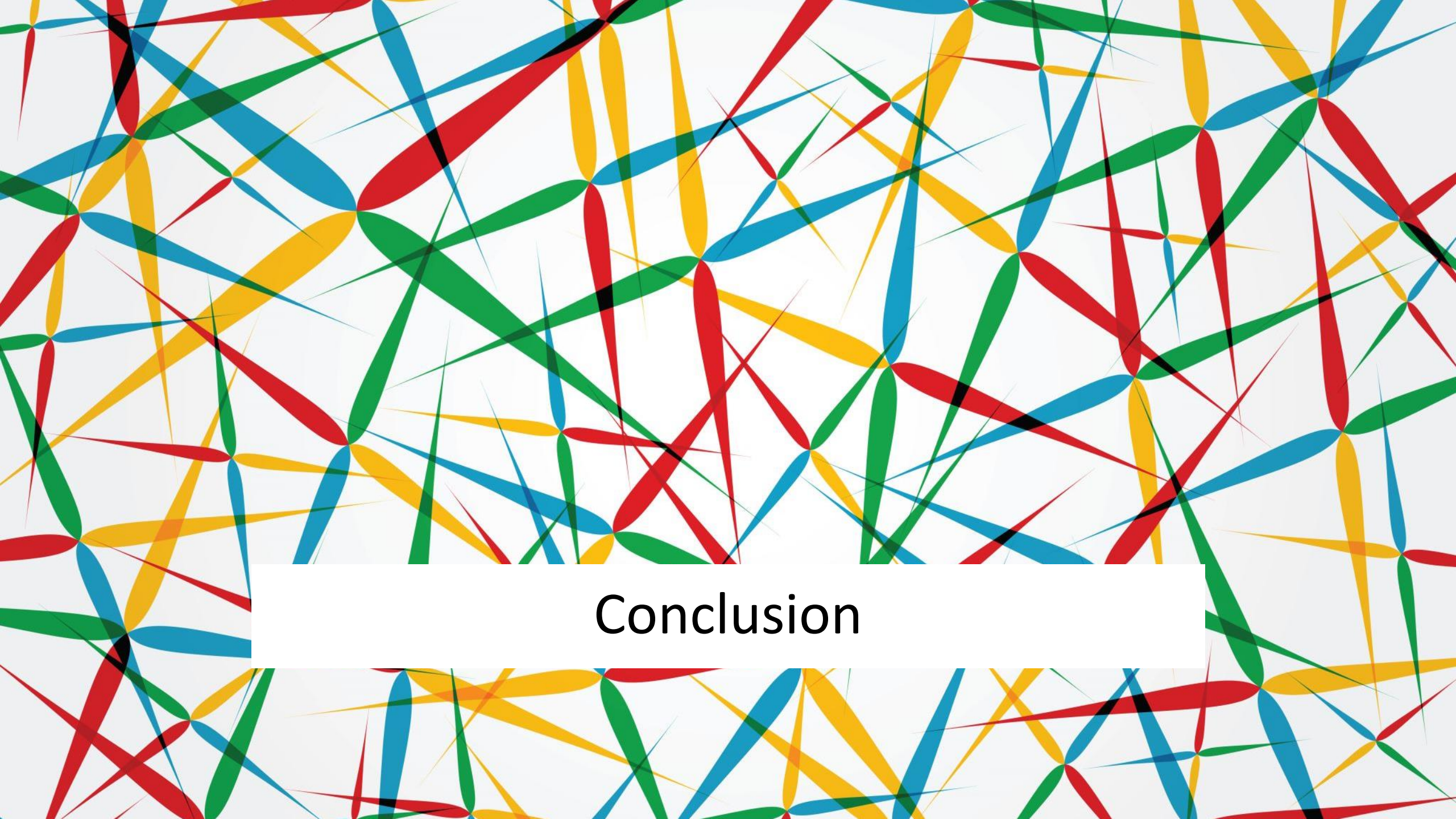
- Shin, M., et al., “Modulation of collagen metabolism by the topical application of dehydroepiandrosterone to human skin,” Jour Invest Dermatol 2005; 124(2);315-23.

Cortisol and the Skin

- Long-term chronic stress can also lead to premature skin aging. The central role in cellular skin reactivity to various stressors may be attributed to dermal mast cells. Many other cells also actively take part in skin response to stress.
- Moreover, psychological stress has been linked to the stimulation of the autonomic nervous system, renin-angiotensin system, and hypothalamus-pituitary-adrenal system, contributing to inflammation, oxidative stress, and DNA damage, which influence all tissues, including the skin.
    - Sandoval, M., Ayres, E., Skin Aging and Stress. In: França, K., Jafferany, M., (Eds.) Stress and Skin Disorders. Springer, Cham, 2017.

References

- Altemus, M., et al., “Stress-induced changes in skin barrier function in healthy women,” Jour Invest Dermatol 2001; 117(2):309-17.
- Reich, A., et al., “Stress and the skin,” G Ital Dermatol Venereol 2010; 145(2):213-19.
- Dunn, J., et al., “Psychological Stress and skin aging: a review of possible mechanisms and potential therapies,” Dermatol Online Jour 2013; 19(6):18561.
- Chen, Y., Maidof, R., Lyga, J., Brain-Skin Connection: Impact of Psychological Stress on Skin. In: Farage, M., Miller, K., Maibach, H., (Eds.) Textbook of Aging Skin. Springer, Berlin, Heidelberg, 2017.



Conclusion

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- As you have seen, natural hormone replacement therapy helps the patient relieve symptoms of menopause.
- However, it is so much more. It helps the patient prevent major diseases and improves skin-aging.

Thank You!

Questions?