Cardiovascular Health in Menopausal Women: New Understandings New Solutions

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Learning Objectives:

1. Understand the surprising link between reproduction and cardiometabolic health, recognizing the profound and enduring role of estrogen
2. Recognize the impact of estrogen directly and indirectly on all cardiovascular structures, and the profound implications of menopause on female cardiovascular wellbeing
3. Learn how to implement effective strategies to help menopausal women maintain cardiovascular wellness and metabolic homeostasis, through the application of hormonal therapy, nutritional medicine, time restricted eating, stress reduction, sleep quality, and efficacious supplementation

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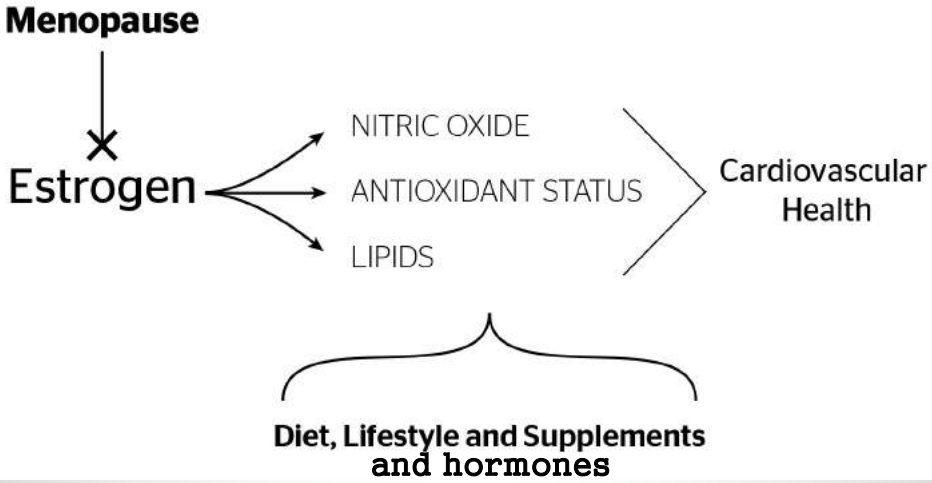
Begin at the end … Menopause is the end of an era and the beginning of a new one



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The Significance of Cardiovascular Health

Coronary artery disease (CAD) is the number one cause of death in women (and men) in the world

More than all forms of cancer, diabetes, Alzheimer's & pneumonia (and SARS-CoV-2)

Center for Disease Control and Prevention.

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Cardiovascular Health is often Overlooked in Women

- **Historically, women have been underrepresented in cardiovascular research.**
- **Most women believe CAD is a "man's disease"**
- **When women are diagnosed, outcomes are usually worse-- Women are typically treated more conservatively**
- **Women have the benefits of estrogen (but that doesn't make them invincible) and those benefits are substantially reduced with the onset of menopause**

Ramachandran H, Wu V, Kowitlawakul Y, Wang W. *Heart & Lung*. 2016; 45: 173-185

5

Women and the Incidence of Hypertension

- **In the world, 25% of adult women are hypertensive**
- **60% of women have uncontrolled BP (NHANES)**
- **In the US, more than 75% of women over 60 are hypertensive**
- **85% of all women in the US are hypertensive by the age of 75**

Mensah GA. Healthy endothelium: the scientific basis for cardiovascular health promotion and chronic disease prevention. Vascul Pharmacol 2007;46 (5):310-4

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ESTROGEN
Overlooked Factor in Women's Cardiovascular Health

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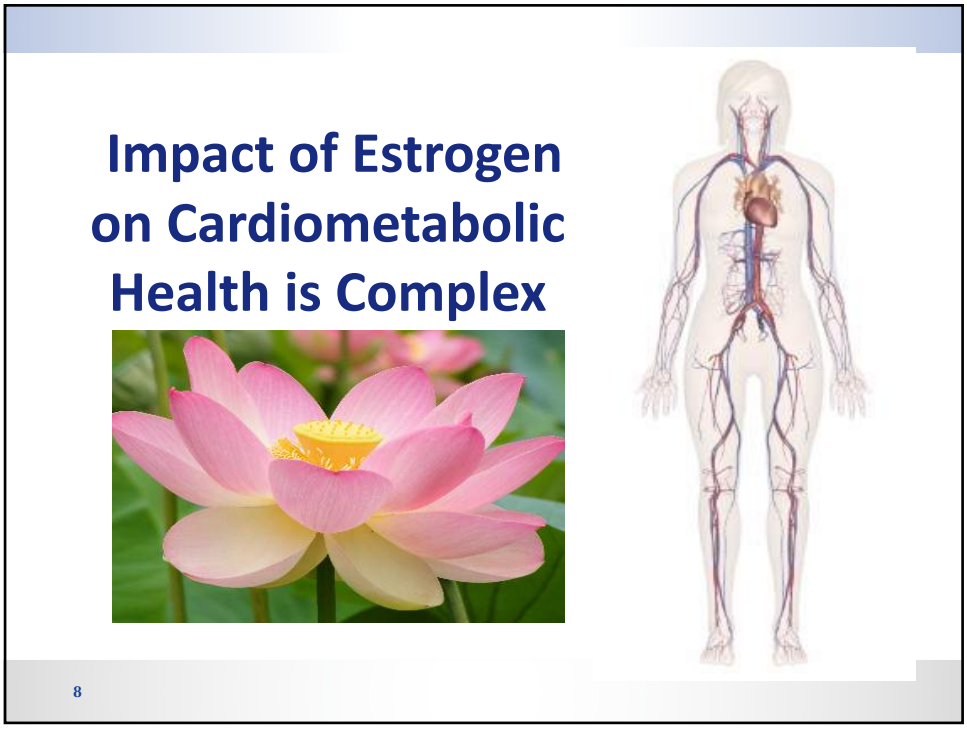
Impact of Estrogen on Cardiometabolic Health is Complex
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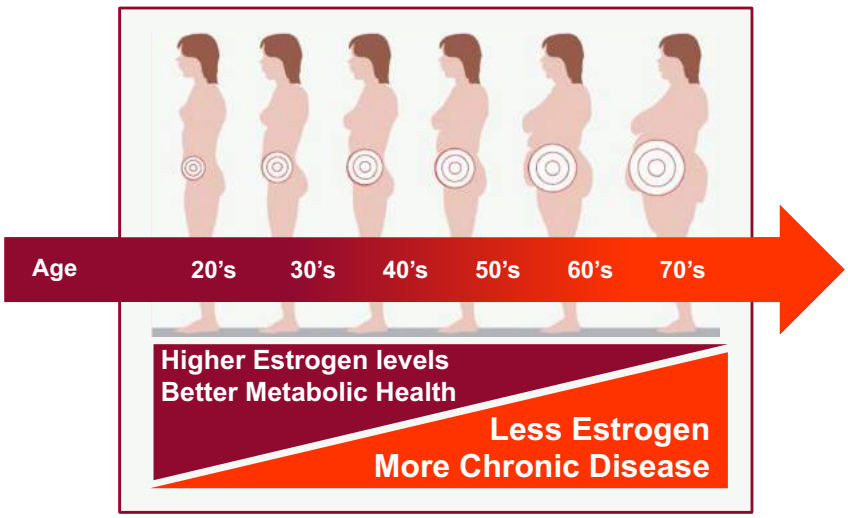
Age-Dependent Shift in Estrogen Levels



Adapted from *Exper Rev Endocrinol Metab* ®

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A Review of Estrogen Basics

ESTRADIOL

ESTRONE

ESTRIOL

Steroid hormones that bind to receptors throughout the body and regulate a multiplicity of functions

Physiologic and rhythmic levels of estrogens support:

1. **Metabolic Homeostasis**
2. **Cardiovascular Health**
3. **Immune Health**
4. **Cognition & Emotional health**

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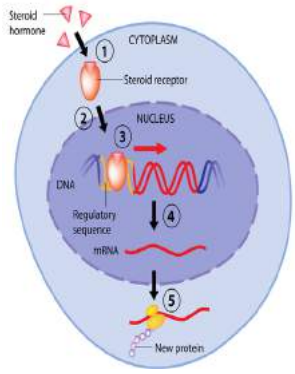
Estradiol Receptors (ER)



ER alpha → Regulates genes and membrane receptors

Primarily expressed in the gonadal organs: uterus, ovary, prostate, testes, and breast, and in the hypothalamus of the brain, mast cells

ER beta → Regulates genes and membrane receptors

Primarily expressed in *non-gonadal* tissues: GI tract, colon, bone marrow, vascular endothelium, lung, bladder, and brain

Membrane-associated ER →
no effect on genes, but rapid effects on cellular signaling

Mendelsohn ME, and Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med.* 1999: 340; 1801-1811
Dahlman-Wright et al. International Union of Pharmacology. LXIV. Estrogen Receptors. *Aspet Pharmacological Reviews.* 2006: 58 (4); 773-781

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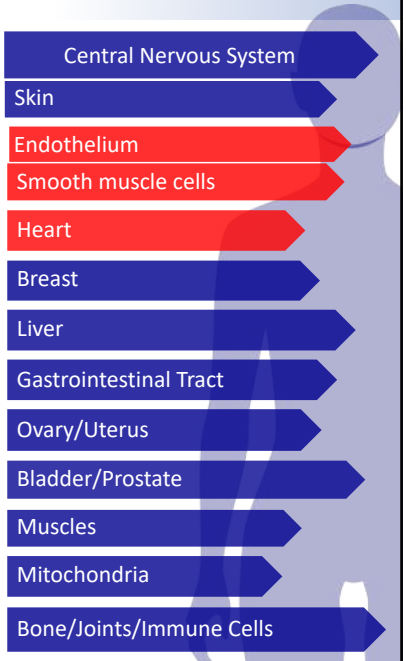
Estrogen is supportive of a wide variety of physiological functions

Estrogen receptors are everywhere!

Estrogen receptors

1. **Influence gene expression**
2. **Activate non-genomic pathways**



Am J Physiol Endocrinol Metab 2008;295:E904-912

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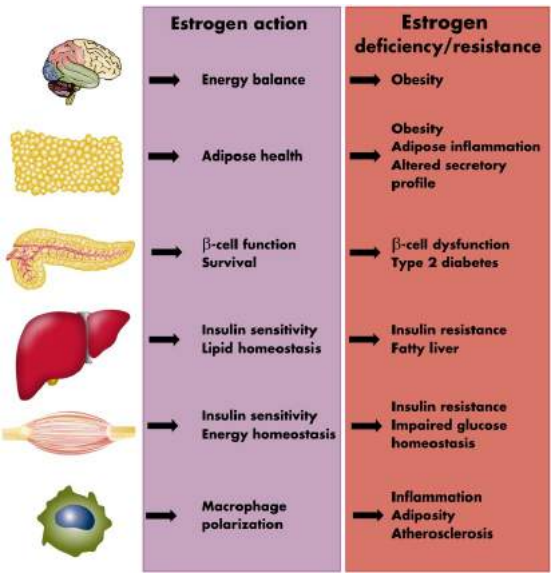

Estrogen Deficiency: Impact on Metabolism

Estrogen deficiency leads to an abrupt reduction in metabolic rate, shift to increased central adiposity, dyslipidemia and progression of metabolic syndrome –

Increases risk of nonalcoholic steatohepatitis, type 2 diabetes, and cardiovascular disease

Mol Cell Endocrinol. Evolution of steroid receptors from an estrogen-sensitive ancestral receptor 2011;334:31-38
Endocr Rev. The role of estrogens in control of energy balance and glucose homeostasis

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Consequences of Estrogen Deficiency

Obesity

Disturbed Sleep & Mood Disorders

Metabolic Syndrome and Diabetes

Osteoporosis

Cardiovascular Health and Atherosclerosis

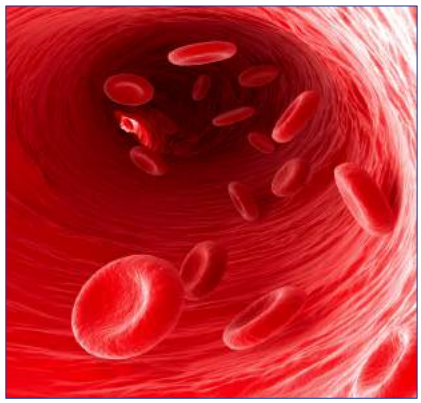
Alzheimer's Disease and Neuro-inflammatory Conditions

Breast Cancer

Fatty Liver

Colon Cancer

GERD



Adapted *from Exper Rev Endocrinol Metab* ® 2011 Expert Reviews Ltd

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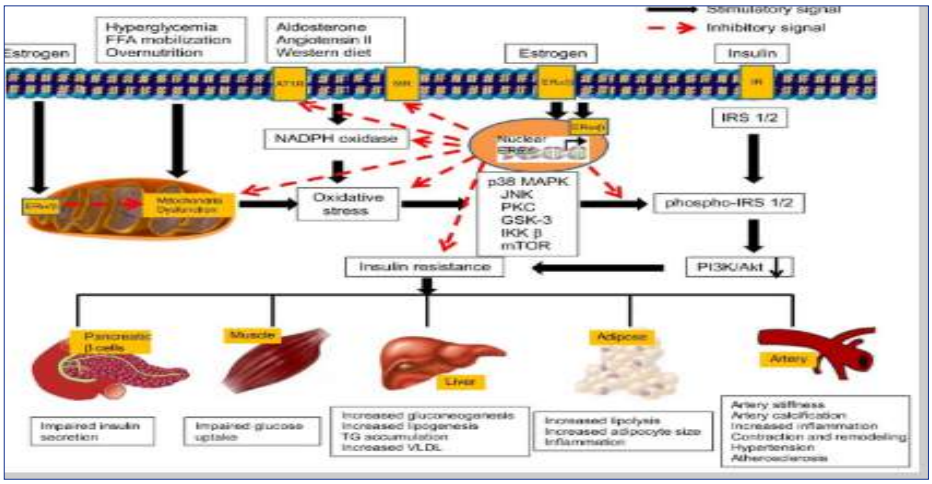
Estrogen – Master of Metabolic Homeostasis



Rettberg et al. Front Neuroendocrinol. 2014; 35(1):8-30

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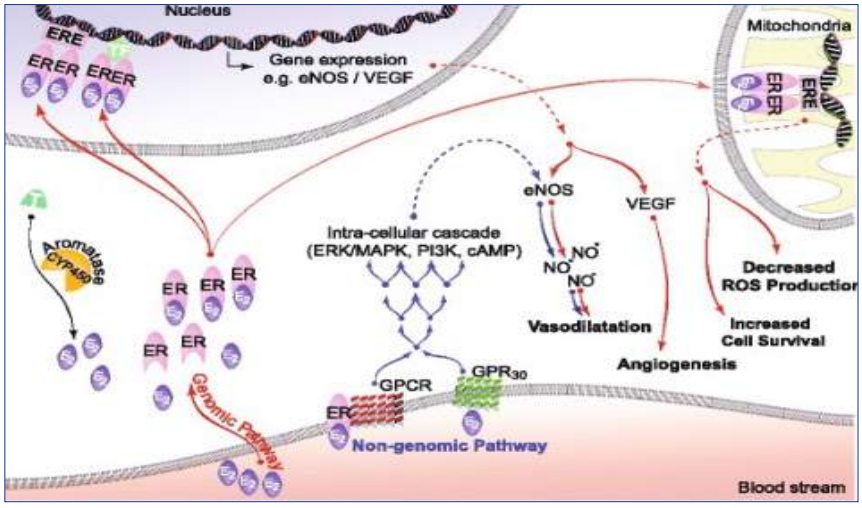
Overview: Estrogen and Arterial Health



Iorga et al. Biol Sex Differ. 2017; 8: 33.

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Some of the Genes and Enzymes Regulated by Estrogen

Vasodilation and vasoconstriction
- Endothelial NO synthase
- Prostacyclin cyclooxygenase
- Prostacyclin synthase
- Renin and angiotensin
- Endothelin-1

Lipid Metabolism
- Lipoprotein lipase
- Apolipoproteins
- Leptin
- PON 1
- LDL receptors
- HMG-CoAR activity

Immune activity
- Vascular-cell adhesion molecule
- Cytokines (IL1, IL6, TNFα)
- Cytokine receptors
- Superoxide Dismutase

Coagulation
- Fibrinogen
- Coagulation factors
- Protein S

Angiogenesis
- Matrix metalloproteinase
- Vascular endothelial growth factor

Non-Genomic Effects
- Fast-acting actions such as NO facilitated vasodilation

Saltiki, K and Alevizaki M.. *Hormones*. 2007; 6(1): 9-24

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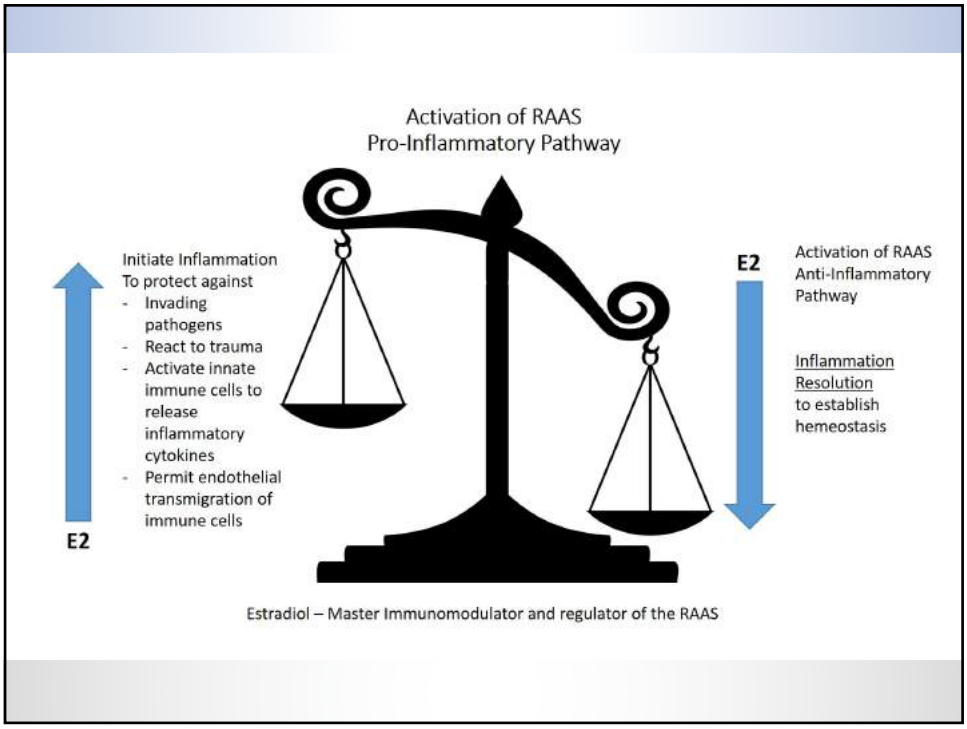

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Estrogen Related Receptor (ERR) Isoforms Expressed in Myocardium

Members of steroid hormone superfamily- regulate expression of genes for energy metabolism, mitochondrial biogenesis, fatty acid oxidation, oxidative phosphorylation

ERRα and γ – share target genes in myocardium

ERRβ – maintains proper oxygen consumption rates in myocardium

Cunningham et al. Estrogen-Related Receptor α (ERRα) is required for adaptive increases in PGC-1 isoform expression during electrically stimulated contraction of adult cardiomyocytes in sustained hypoxic conditions. *Am J Cardiovasc Dis.* 2016;6(2):46-54

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Role of Estrogen Metabolites – 2 MethoxyEstradiol

Impact on cardiovascular health – not always via estrogen receptors

- **Down regulates synthesis of Angiotensin Type 1 Receptor in liver epithelial cells**
- **Down regulates Endothelin 1 in coronary artery endothelial cells**
- **Inhibits cell growth in human aortic smooth muscle cells by decreasing ERK1/2 phosphorylation – inhibits neo-intima formation and smooth muscles cell growth**

Kigabti et al. Eur J Pharmacol. 2014. 723, 131-40
Dubey et al. Hypertension, 2001, 37:640-644
Barchiesi et al. Circ Res. 2006; 99(3): 266-74

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Estrogen Alleviates Diastolic Dysfunction

Table 2 Doppler echocardiographic diastolic indices of transmitral flow in the oestradiol and placebo groups at baseline, 90 minutes, and 12 weeks

Variable	Time point	Oestradiol	Placebo	p Value
Vel E (cm/s)	Baseline (T1)	66 (19)	63 (11)	NS
	90 minutes (T2)	68 (20)	61 (13)	NS
	12 weeks (T3)	74 (22)	61 (16)	NS
Vel A (cm/s)	Baseline (T1)	81 (21)	79 (14)	NS
	90 minutes (T2)	81 (21)	76 (11)	NS
	12 weeks (T3)	75 (23)*	73 (13)*	NS
E/A ratio	Baseline (T1)	0.8 (0.2)	0.8 (0.1)	NS
	90 minutes (T2)	0.9 (0.2)	0.8 (0.1)	NS
	12 weeks (T3)	1.0 (0.2)†	0.8 (0.2)	0.04
DTE (ms)	Baseline (T1)	260 (42)	254 (22)	NS
	90 minutes (T2)	248 (40)	245 (20)	NS
	12 weeks (T3)	238 (20)*	274 (42)*	0.01
IVRT (ms)	Baseline (T1)	127 (23)	121 (15)	NS
	90 minutes (T2)	121 (17)	120 (16)	NS
	12 weeks (T3)	106 (16)†	121 (16)	0.01

The values are expressed as mean (SD).
*p<0.05 (T1 *v* T3) in the same group.
†p<0.001 (T1 *v* T3) in the same group.
DTE, deceleration time of mitral E wave; E/A, the ratio between the peak velocity of mitral E and A wave; IVRT, isovolumic relaxation time; Vel A, peak velocity of mitral A wave; Vel E, peak velocity of mitral E wave.

Alecrin I et al. Acute and chronic effects of oestradiol on left ventricular diastolic function in hypertensive post menopausal women with left ventricular diastolic dysfunction. *Heart*. 2004;90:777-781.

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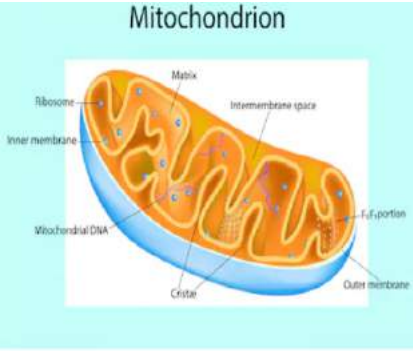
Estrogen Supports Mitochondrial Health

There is a growing understanding of the role which E2 plays in metabolism via its regulation of mitochondrial function



Duckles et al. Molecular Interventions, 2006;Vol 6, No1, pp26-35
Wang et al. J Neurochemistry, 2001; Vol 77, No.3; pp 804-11

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Focus on 3 Cardiovascular Benefits of Estradiol (E_2)

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Estrogen and Paraoxonase (PON 1)

- **Oxidized low-density lipoproteins (oxLDL) involved in initiation of atherosclerosis**
- **PON 1 located on HDL – protects against oxidation of HDL and LDL by hydrolysing lipid peroxides**
- **Oxidative status reduces PON 1 activity, increases oxLDL**

Estrogen increases PON 1 activity

Topcuoglu et al. The effect of hormone replacement therapy on oxidized low density lipoprotein levels and paraoxonase activity in postmenopausal women. *J Exp Med*. 2005;205(1): 79-86

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Estradiol Promotes Prostacyclin Expression

Prostacyclin (PGI2)

Produced by endothelial and vascular smooth muscle cells

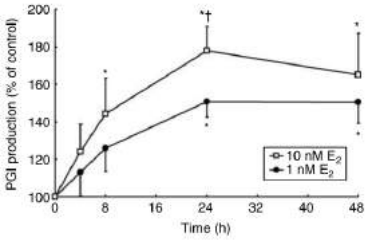
Major anti-atherogenic prostanoid

Counter effects thromboxane – important balance in cardiovascular homeostasis

Estradiol

E2 promotes vasodilation through release of prostanoids (and others)

Binds to ERα to up-regulate (Cyclooxygenases and (PGI Synthase) PGI expression



Endothelial cells treated with estrogen induces PGI production in a dose dependent manner

Sobrino et al. Estradiol selectively stimulates endothelial prostacyclin production through estrogen receptor α. *J Mol Endocrinol*. 2010;44(4

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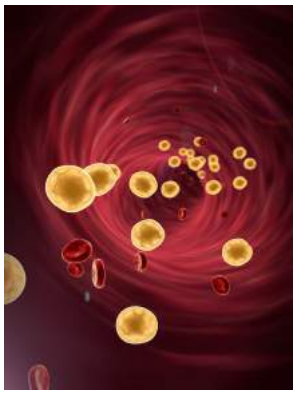
Estrogen Supports a Healthy Lipid Profile

- **Supports HDL levels by promoting apolipoprotein A-I and moderating hepatic lipase activity**

- **Moderates LDL levels by promoting levels of hepatic LDL receptors**



Knowlton A and Lee A. *Pharmacology & Therapeutics*. 2012; 135,(1): 54-70

Feingold K, Brinton E and Grunfeld C. EndoText.com , 2000.

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Lipid Metabolism: Cholesterol

Compared to men, during reproductive years, women have:

- **Lower LDL levels**
- **Higher HDL levels**
- **Lower total lipid levels**

Estrogen upregulates the expression of:

- **Apo-proteins**
- **LDL receptors – responsible for the uptake of lipoprotein**

Estrogen decreases:

- **Lipoprotein lipase**
- **HMG-CoA Reductase activity**

Saltiki, K and Alevizaki M. Coronary heart disease in postmenopausal women; the role of endogenous estrogens and their receptors. Hormones. 2007; 6(1): 9-24

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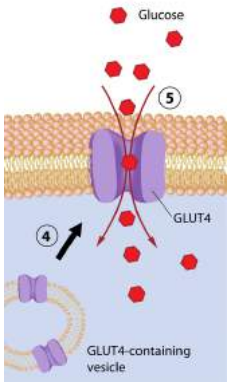
Estrogen Supports Insulin Sensitivity

1. **Supports glucose transporter (GLUT3, GLUT4) function**
2. **Enhances glucose-stimulated insulin biosynthesis**
3. **Promotes β cell survival**



Mauvais-Jarvis F, Clegg D, and Hevener A. *Endocr Rev*. 2013 Jun; 34(3): 309–338.
Gupte A , Pownall H, Hamilton D. *J Diabetes Res*. 2015; 2015: 916585.

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The Impact of Menopause: Insulin Resistance

Estrogen knock-out animals consistently present with:

- **Insulin resistance**
- **Hyperinsulinemia**
- **Abnormal glucose homeostasis**
- **Obesity**
- **Hyperleptinemia**

…which are resolved when estradiol or ERα are restored.

Assess insulin sensitivity in post-menopausal patients

Mauvais-Jarvis F, Clegg D, and Hevener A. *Endocr Rev*. 2013 Jun; 34(3): 309–338.

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The Impact of Menopause on Cardiovascular Health

1. **Insulin resistance**
2. **Dyslipidemia (↑LDL, oxidized LDL, ↓HDL)**
3. **Decreased nitric oxide (↑BP)**

As well as: Increased oxidative stress, Increased risk of atherosclerosis, Myocardial changes & Adipose tissue alterations

Chakrabarti S, et al. June 2008; 606(6): 376-382
Saltiki, K and Alevizaki M. *Hormones*. 2007; 6(1): 9-24

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The Impact of Menopause: Endothelial Function

85% of all women in the US are hypertensive by the age of 75

- Typically expressed as systolic hypertension
- Often develops around menopause
- Attributed to the decline in estrogen
- Risk factor for CAD and other cardiometabolic events

Lee V and Foody *J. Current Atherosclerosis Reports*. 2008; 10:295-302.

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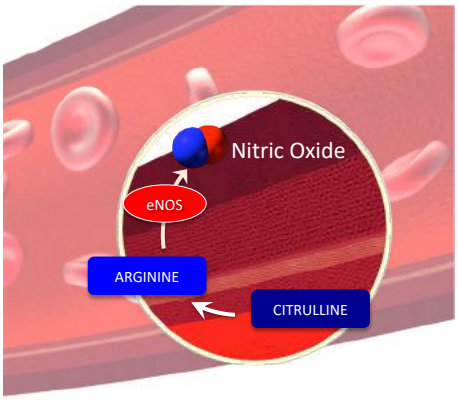
Estrogen Supports Blood Pressure & Endothelial Function

Estrogen supports Nitric Oxide (NO)

NO is a short-lived (3-5 sec half-life), lipid/water soluble gas

NO supports:

- Healthy blood pressure
- Platelet aggregation
- Endothelial function
- Myocardial function



Nevzati E, Shafighi M, Bakhtian KD, et al.. *Acta Neurochir Suppl*. 2015;120:141-5.
Simoncini T1, Genazzani AR.. *Eur J Endocrinol*. 2003 Mar;148(3):281-92.

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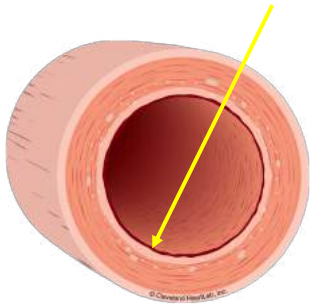
Introduction to the Endothelium

Simple squamous layer (one cell thick) that lines inner surface of all blood vessels – from the heart to the smallest capillary

Enough to cover the surface of 8 tennis courts

Interface: circulating blood and vascular wall

Classically thought of as an inert membrane, but is now known to play an integral role in metabolic, immunologic, and CV health



Healthy endothelium prevents:

Platelet aggregation and leukocyte adhesion

And Controls:

Vascular tone – BP, arterial stiffness, inflammation, permeability, growth, blood fluidity, and

Mensah GA. Healthy endothelium: the scientific basis for cardiovascular health promotion and chronic disease prevention. Vascul Pharmacol 2007;46 (5):310-4

Lam et al. Increased blood flow causes coordinated upregulation of arterial eNOS and biosynthesis of tetrahydrobiopterin. *Am J Physiol Heart Circ Physiol* 2006;290:786-93

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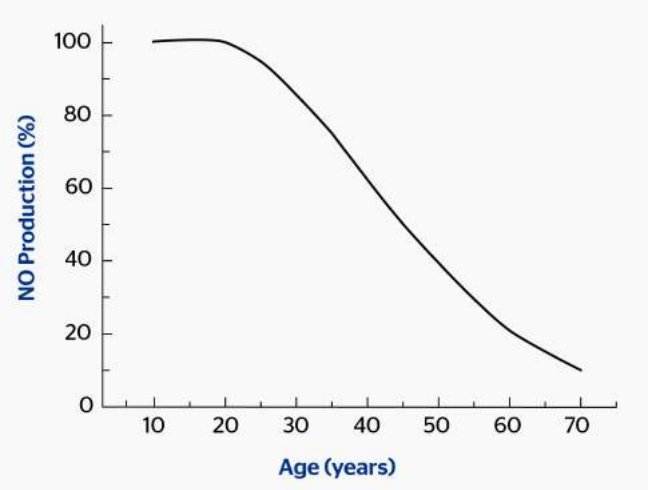
Nitric Oxide Levels Decline with Age



Torregrossa A, Aranke M, Bryan N. *Journal of Geriatric Cardiology*. 2011; 8:230-242

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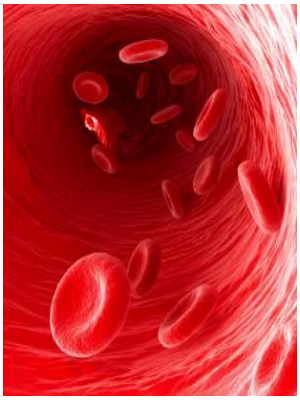
Consequences of Diminished Nitric Oxide

- Endothelial dysfunction
- Platelet aggregation
- Hypertension
- Vascular dysfunction
- Thrombosis
- Cognitive decline
- Immune Dysfunction
- Chronic Inflammation
- Sexual Dysfunction (male and female)



Napoli C and Ignarro LJ. *Arch Pharm Res.* 2009; 32 (8):1103-8

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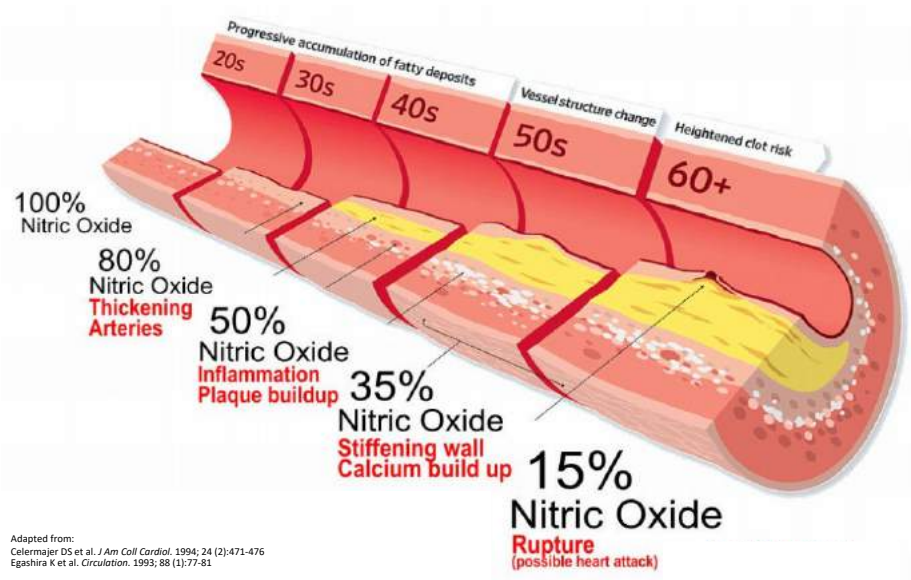
Progression with Age: from a Nitric Oxide Perspective



Adapted from:
Celermajer DS et al. *J Am Coll Cardiol.* 1994; 24 (2):471-476
Egashira K et al. *Circulation.* 1993; 88 (1):77-81

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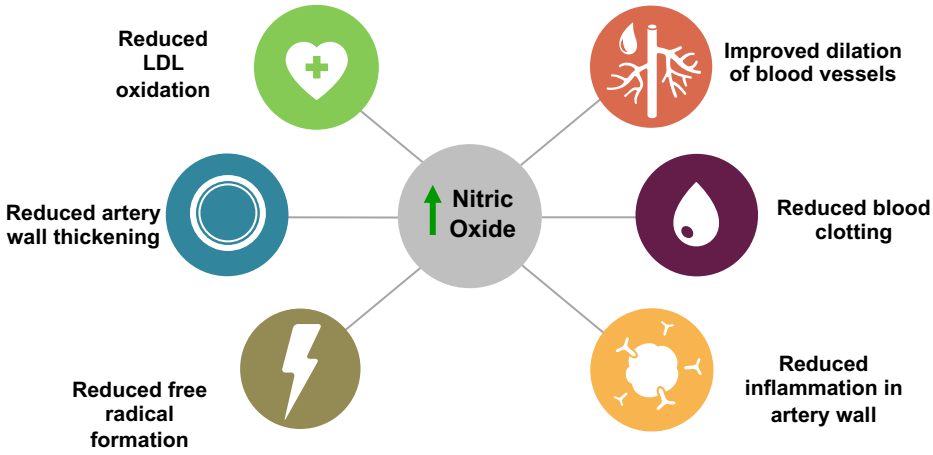
Nitric Oxide Maintains Endothelial Health and is Cardio-protective



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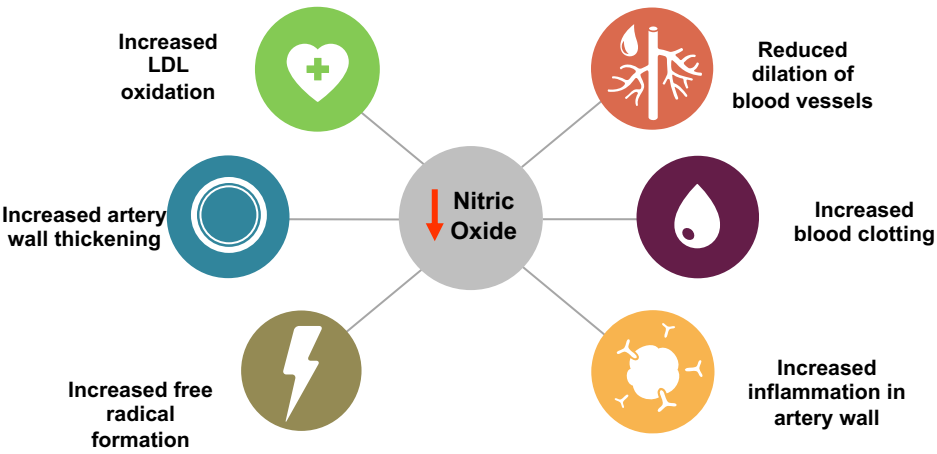
Nitric oxide Deficiency Causes Endothelial Damage and is Pro-Atherogenic



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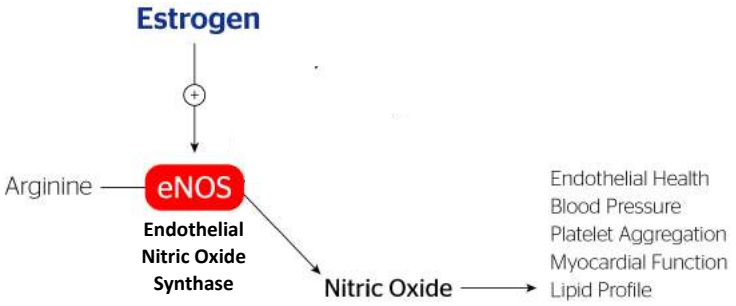
Estrogen Supports Nitric Oxide Synthesis

1. **Estrogen supports the expression and activation of**

2. **Estrogen moderates the formation of uncoupled eNOS**



Chakrabarti S, et al. *IUBMB Life*. June 2008; 606(6): 376-382
Nevzati E et al. *Acta Neurochir* Suppl. 2015;120:141-5.
Zhao Z et al.. *Am J Physiol Heart Circ Physiol*

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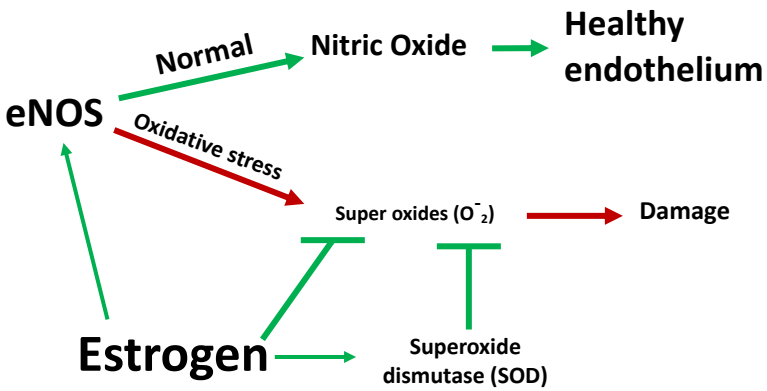
Estrogen: Antioxidant Activity



Chakrabarti S, et al. Estrogen is a modulator of vascular inflammation. IUBMB Life. June 2008; 606(6): 376-382

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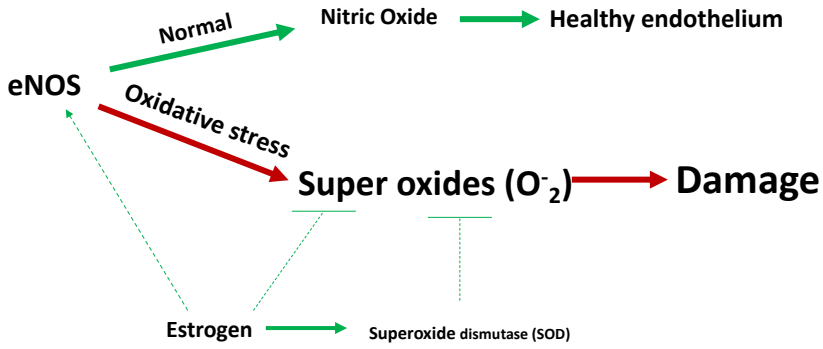
Menopause: Greater Burden of Oxidative Stress



Chakrabarti S, et al. Estrogen is a modulator of vascular inflammation. IUBMB Life. June 2008; 606(6): 376-382

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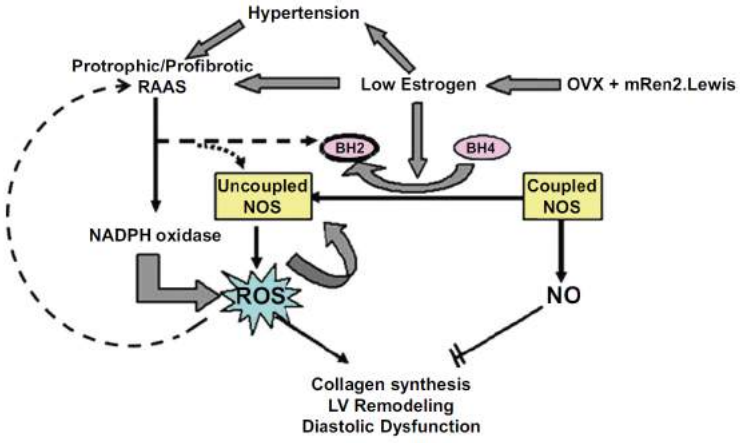
Menopause: Greater Burden of Oxidative Stress



Zhao Z et al. Role of estrogen in diastolic dysfunction. *Am J Physiol Heart Circ Physiol.* 2013; 306: H628-H640.

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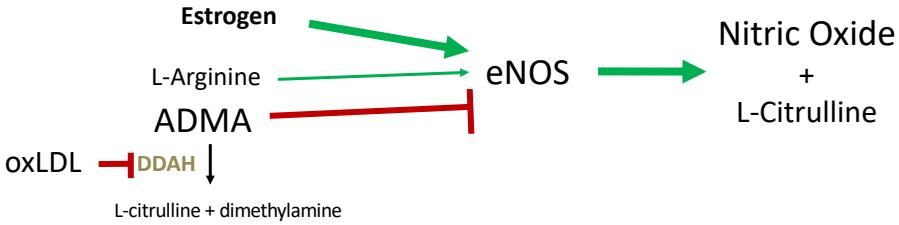
Estrogen Rescues NO deficiency

Estrogen can overcome the effects of oxLDL to increase NO production



Elevations in ADMA correlate with carotid thickness

Hormone therapy (long term >2 years) slows progression of CIMT in healthy post-menopausal women

Monsalve et al. Estradiol counteracts oxidized LDL-induced asymmetric dimethylarginine production by cultured human endothelial cells. *Cardiovascular Res*. 2007; (73): 66-72
Ito et al. Novel mechanism for endothelial dysfunction: dysregulation of dimethylarginine dimethylaminohyrolase. *Circulation. 1999;* 99: 3092-3095.
Maas R. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham heart study offspring cohort.
Tostes et al. Effects of estrogen on the vascular system. *Braz J Med Biol Res.* 2003;36:1143-5

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Estrogen Supports:

- **Insulin sensitivity**
- **Healthy lipid profile**
- **Vascular health**
- **Myocardial health**
- **Mitochondrial health**
- **Gut health**
- **Circadian rhythm**

But your patient is menopausal…

now what?

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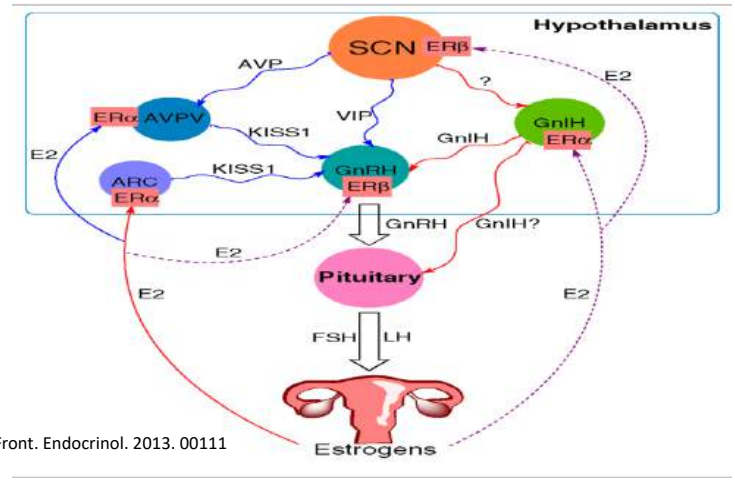
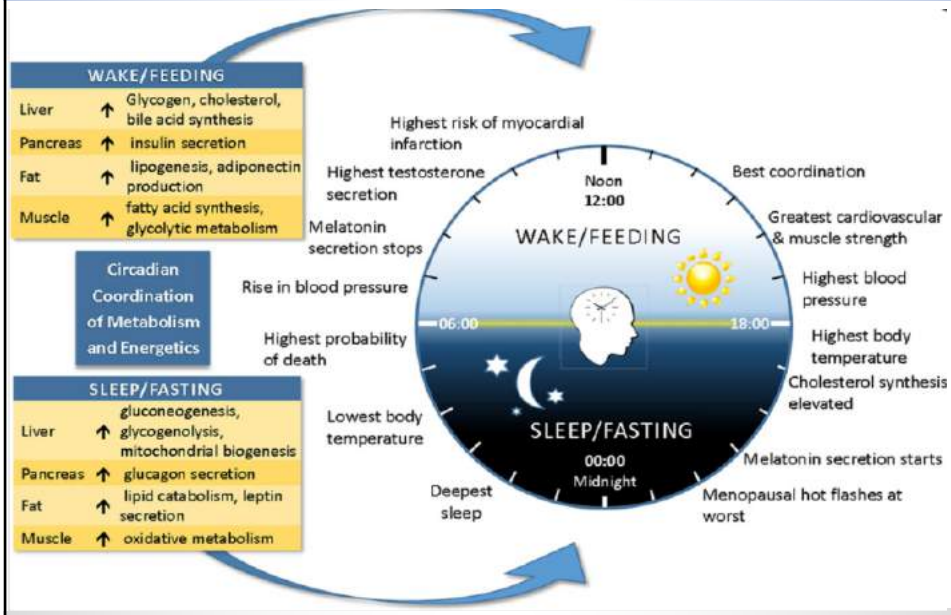
The Link Between Estrogen, Reproduction, Metabolism



Urlep et al. Front. Endocrinol. 2013. 00111

45



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Patterson et al. J Acad Nutr Diet. 2015;115(8):1203-1212

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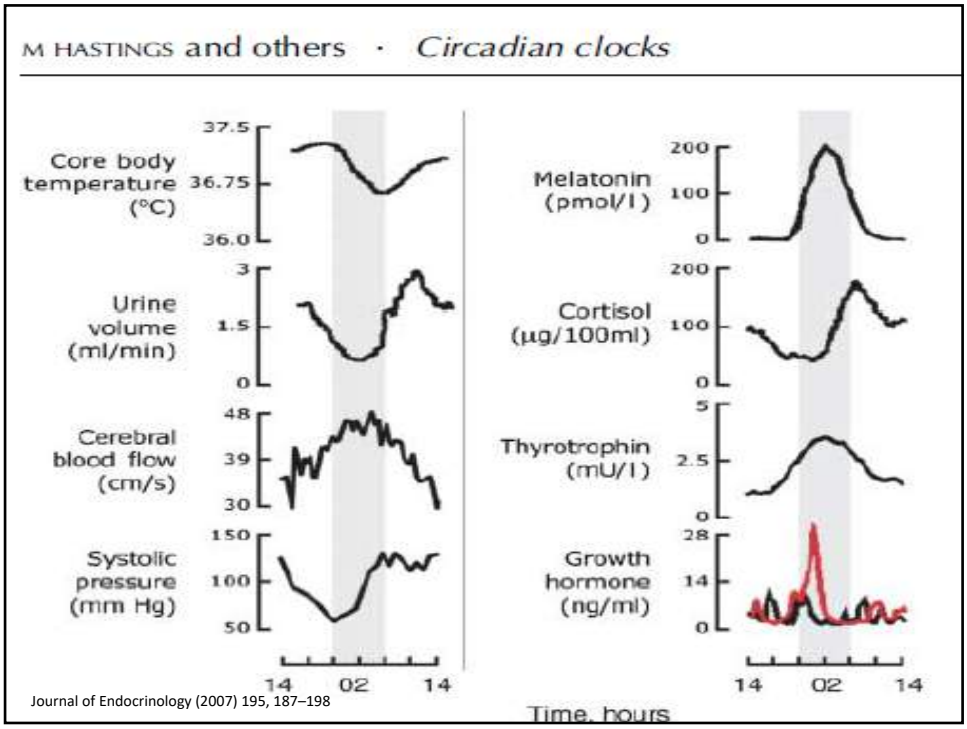

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Circadian Disruptors

- **Nocturnal light exposure**
- **Improper meal timing**
- **Poor or interrupted sleep**
- **Stress**
- **Traveling across time zones**
- **Social jet lag**
- **Shift work**
- **Endocrine Disruptors**

- ***Loss of estrogen in women***

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Perimenopause/Menopause and Sleep

33-51% of women report complaints of sleep quality

- Dramatic hormonal changes with increase FSH/decrease E2 - complaints of poor sleep quality
- Women have phase advanced endogenous temperature and melatonin rhythms
- Women are sleeping at a later Circadian time than men
- Post-menopausal women have an advanced melatonin onset, leading to early morning awakening
- Poor sleep linked to metabolic dysfunctions

Estrogen associated with improved subjective sleep quality in peri and postmenopausal women

Duffy et al. Proc Natl Acad Sci USA.2011;108: Supp 3:15602-8
Polo-Kantola et al. Maturitas.2011;68:224-32
Shaver et al.Sleep;1988;11:556-561

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What Can You Do?

Non-modifiable Risk Factors

- **Age**
- **Gender**
- **Race**
- **Menopausal status**
- **Family history: Parental history of CAD increases a women's risk by 70%**

Modifiable Risk Factors

- **Diet choices and meal timing**
- **Sleep time and quantity**
- **Circadian rhythm influencers**
- **Stress management**
- **Physical activity level**
- **Hormone use**
- **Tobacco and drug use**

Ramachandran H, Wu V, Kowitlawakul Y and Wang W.. Heart & Lung. 2016; 45: 173-185

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Where to Begin?

1. Test
2. Exercise
3. Diet
4. Supplements

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Key Cardiovascular Testing Options

- ADMA
- Advanced lipid profile, Oxidized LDL
- Insulin and HbA1c
- Inflammatory markers: hs CRP, MPO, F2isoprostane, LpPLA2
- ApoE, MTHFR
- Hormones
- Thyroid
- Ferritin
- CBC, CMP

- Micronutrients
- Microalbumin
- Heavy metals
- Gut microbiome testing

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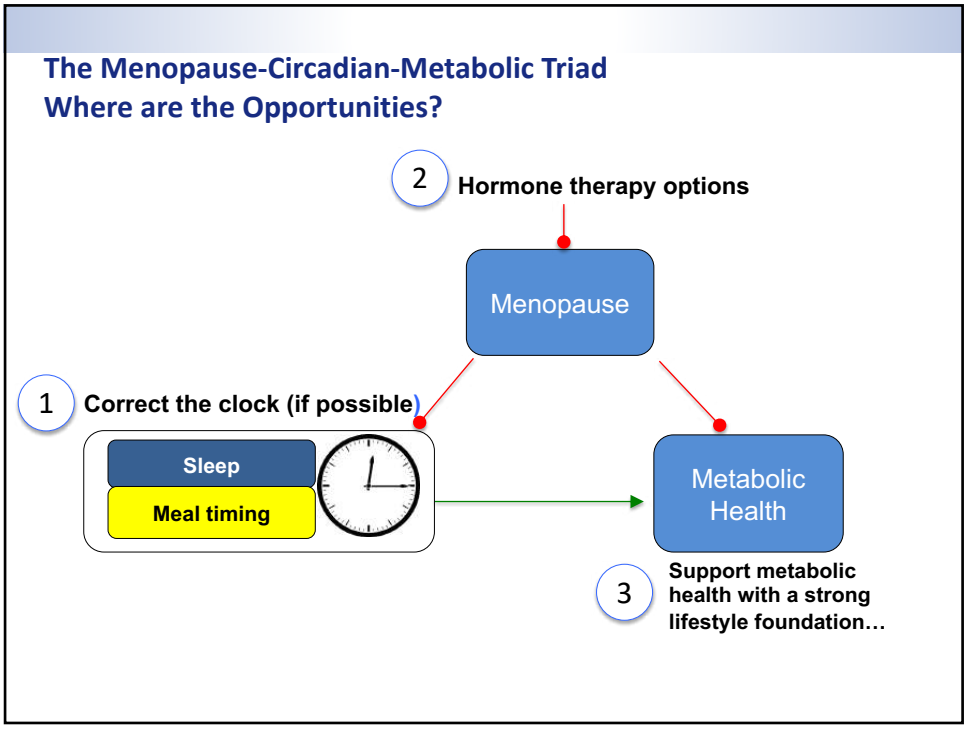
The Menopause-Circadian-Metabolic Triad
Where are the Opportunities?
2
Hormone therapy options
Menopause
1
Correct the clock (if possible)
Sleep
Meal timing
Metabolic Health
3
Support metabolic health with a strong lifestyle foundation…

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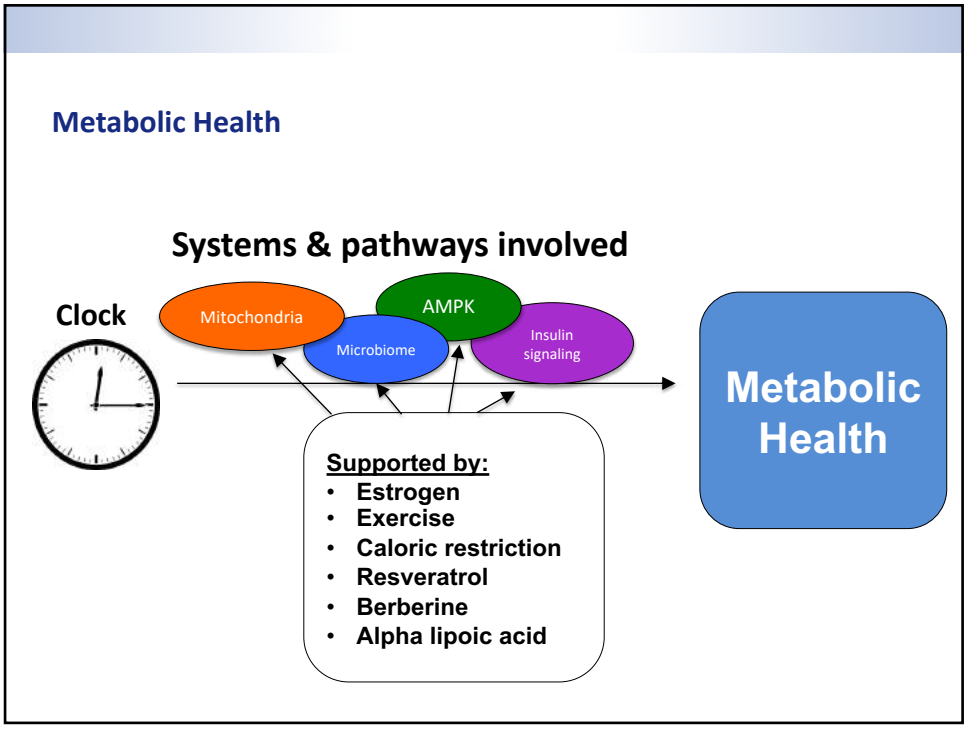
Metabolic Health
Systems & pathways involved
Clock
Mitochondria
AMPK
Microbiome
Insulin signaling
Metabolic Health
Supported by:
• Estrogen
• Exercise
• Caloric restriction
• Resveratrol
• Berberine
• Alpha lipoic acid

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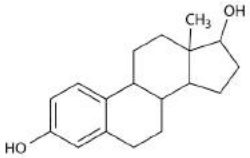
Hormone Therapy Revisited

Conventional HRT

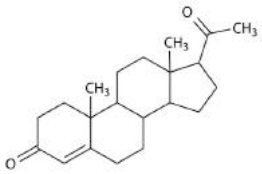
- Estradiol patch or gel
- Oral micronized progesterone (preferably cyclic)



Estradiol

Rhythmic HRT

- Estradiol and progesterone creams
- Applied twice daily with variable dosing to mimic a normal menstrual cycle



Progesterone

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Perimenopause/Menopause and Sleep And Must Manage Stress as Well

33-51% of women report complaints of sleep quality

- **Dramatic hormonal changes with increase FSH/decrease E2 - complaints of poor sleep quality**
- **Women have phase advanced endogenous temperature and melatonin rhythms**
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Shaver et al.Sleep:1988;11:556-561

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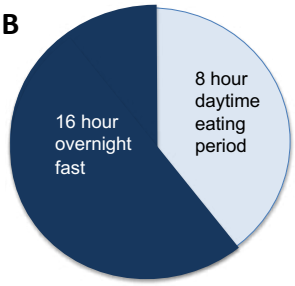
Correct the Clock: Meal Timing

Typical American Meal Pattern

Healthier (Circadian-Aligned) Meal Patterns:

A

B



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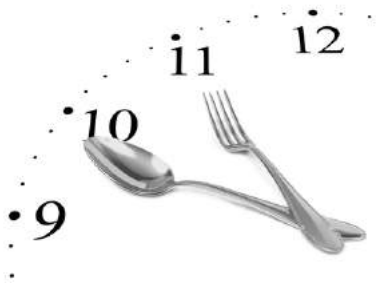
Correct the Clock: Meal Timing

- **Eat dinner early.**
- **Eat at approximately the same times each day.**
- **Limit snacking.**
- **Consider a daytime fast once or twice per week. Eat larger meals (breakfast and dinner) about 13 hours apart.**
- **Consider intermittent or periodic fasting or a fasting mimicking diet**



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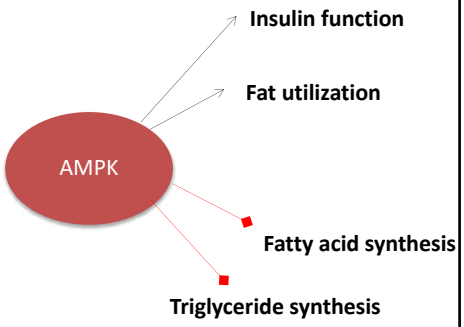
Correct the Clock: Meal Timing

The next best thing:

Fasting mimetics

Agents that partially emulate the metabolic benefits of fasting by supporting the AMPK pathway



Examples:

- **Resveratrol**
- **Alpha lipoic acid**
- **Berberine**
- **Exercise**

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Exercise

Regular exercise contributes to:

- **Lower blood pressure**
- **Lower blood glucose levels**
- **Improved lipid profiles**
- **Healthy body weight**
- **Normal gut microbiome**

Sedentary elderly adults had decreased NO-mediated vasodilator function, compared to age-matched active adults.

Exercise reversed impaired microvascular NO function in sedentary adults!

Black M, Green D, NT Cable. *J Physiol*. 2008 Jul 15;586(14):3511-24.
Lee V and Foody J. Current Atherosclerosis Reports. 2008; 10:295-302.

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Supplements: Key Areas of Support

1. Lipid and glucose metabolism
2. Antioxidant status
3. Endothelial function and arterial wall integrity
4. Blood flow

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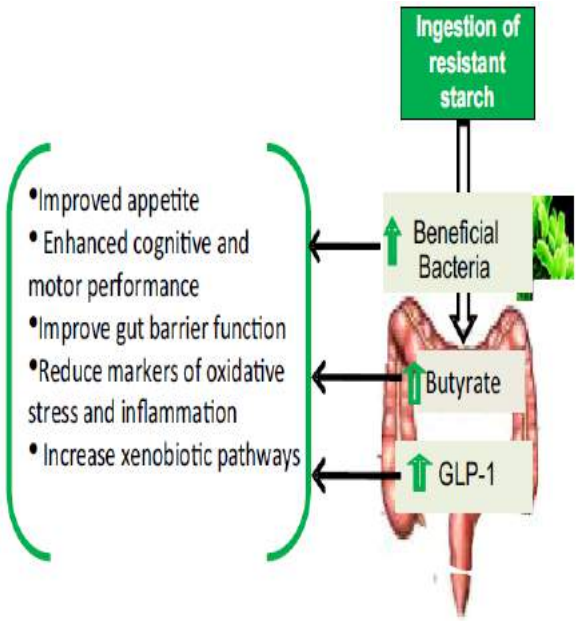
Fig. 1 Proposed mechanisms of HAS and Improved healthspan. Ingestion of high-amylose starches increases beneficial microbiota and stimulates the production of butyrate and increases GLP-1 release from the gut



Keenan, M., Marco, M., Ingram, D., Martin, R. AGE (2015) 37;98

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Diet: Feed & Nurture Your Microbiome

INCLUDE	• Complex carbohydrates (70%) whole-grains, all varieties of vegetables, beans, legumes, etc. • Healthy fats (omega's 3, 6 and 9) from nuts, seeds, olives and coconut • Natural fiber and prebiotic rich foods • Probiotic rich foods • Green leafy vegetables and root vegetables
LIMIT	• Protein (approximately 12%)
AVOID	• Initially, protein from dairy and eggs • Sugar and refined carbohydrates • Alcohol • Food intolerances

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Diet

Consider beginning with a vegan diet

The Mediterranean diet (and modifications thereof) has shown to support healthy lipid levels (raise HDL and lower TG) in postmenopausal women and reduce the risk of obesity, hyperglycemia and CVD

Eat foods that support your microbiome!

- **Prebiotics and Probiotics**
- **Complex carbohydrates**
- **Polyphenol-rich foods**

Bihuniak, J. D., Ramos, A., Huedo-Medina, T. et al.. J Acadam Nutri & Diet. 2016. 116(11), 1767-1775
de la Iglesia R, Loria-Kohen V, Angeles Zulet M et al. Int J Mol Sci. 2016 Nov; 17(11): 1877.

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Dietary Nitrates

Nitrates from food can be reduced to nitrite and nitric oxide by commensal bacteria in the mouth

NITRATE NO_3^- → NITRITE NO_2^- → NITRIC OXIDE NO^-

1. **Dietary nitrates contribute to systemic nitric oxide (*Use of anti-bacterial mouth wash has been associated with increased blood pressure!)***
2. **Salivary glands selectively absorb nitrate and may utilize nitrogenous compounds as innate immune molecules**

Bihuniak, J. D., Ramos, A., Huedo-Medina, T. et al.. *J Acadam Nutri & Diet*. 2016. 116(11), 1767-1775.

65

Opportunities for Supplementation: Overview

Insulin Sensitivity & Glucose Metabolism ← Berberine

Lipid Profile ← Phytosterols

Endothelial Function ← Citrulline, Vitamin C, Taurine, Magnesium, Polyphenols

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N-Acetyl-L-Cysteine

Derivative of the amino acid: l-cysteine

Precursor to glutathione

In animal models, NAC supported:

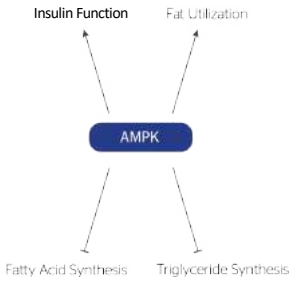
- **Healthy lipoprotein function**
- **Immune mediator activity in the arterial wall**
- **Glucose homeostasis**
- **Antioxidant status**
- **Glutathione status**

Meng XP, Yin CS, Li ZX, et al. Zhonghua yi xue za zhi. 2009; 89(26):1850-1853]
Souza GA, Ebaid GX, Seiva FR, et al. Evid Based Complement Alternat Med. 2011;2011:643269.

67

Berberine Supports Insulin Sensitivity

1. **Supports glycolysis and enhances GLUT4 translocation, via activation of AMPK**
2. **Supports the expression of the insulin receptor gene**
3. **Moderates intestinal absorption of glucose**



Over a 3-month period, berberine significantly reduced waist circumference, moderated triglycerides and supported insulin sensitivity.

Pérez-Rubio KG, González-Ortiz M, Martínez-Abundis E. *Metab Syndr Relat Disord*. 2013 Oct;11(5):366-9.

Caliceti C, Rizzo P, Cicero A. *Oxid Med Cell Longev*. 2015; 2015: 723093
Pang B, Zhao LH, Zhou Q, et al. *Int J Endocrinol*. 2015; 2015: 905749.

68

Phytosterols Support a Healthy Lipid Profile

1. **Compete with cholesterol for absorption into the body**
2. **Promote excretion of cholesterol via bile acids**

Plant sterol moderated LDL-cholesterol concentrations from baseline by between 15.1% and 26.8%

Lau VW, Journoud M, Jones PJ. *Am J Clin Nutr*. 2005 Jun;81(6):1351-8.

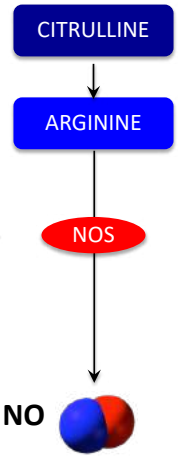
Meta-analyses of over 40 clinical trials suggest that phytosterols provide significant support for a healthy lipid profile.

Chen JT, Wesley R, Shamburek RD, et al. *Pharmacotherapy*. 2005 Feb;25(2):171-83.

69

Nitric Oxide Supports Endothelial Health

1. **Provide precursors**
   - **Citrulline**
2. **Support NOS production or activity**
   - **Vitamin C**
   - **Taurine**
   - **Magnesium**
   - **Polyphenols**
3. **Improve NO stability**
   - **Vitamin C**



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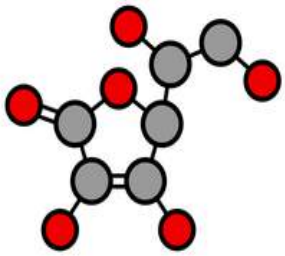
Vitamin C

1. **Vitamin C supports "NO bioavailability" by promoting eNOS expression and/or activit**
2. **Supports healthy levels of tetrahydrobiopterin, a critical cofactor for eNOS**
3. **Protects NO from degradation by ROS**



Mortensen and Lykkesfeldt, *Nitric Oxide 36:*2014

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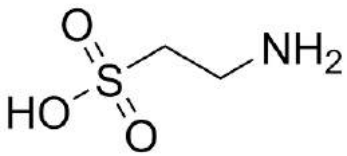
Taurine

Semi-essential amino acid with major roles in cardiovascular homeostasis

Supplementation in humans supports healthy vascular flexibility and function



Abebe and Mozaffari, 2011

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Magnesium

Essential roles in vasomotor function:

- **Regulation of calcium channels**
- **Production of nitric oxide**
- **Prostacyclin formation**

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Polyphenols

Key sources: Cranberries and Grape seeds

Cranberries and grapes are rich in proanthocyanidins (PACs) and other polyphenols.

PACs are antioxidants and support mechanisms that are associated with healthy endothelial function.

PACs protect eNOS and NO from reactive oxygen species

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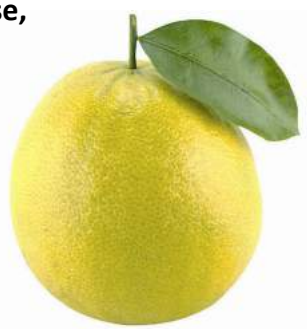
Bergamot Orange Extract

Bergamot - flavonoids that moderate hydroxymethylglutarate (HMG)-CoA reductase, which promotes lipid biosynthesis



In animal models, Bergamot maintained healthy lipid, triglyceride and plasma glucose levels in 30 days

Mollace V, Sacco I, Janda E, et al. *Fitoterapia*. 2011 Apr;82(3):309-16.
Leopoldini M, Malaj N, Toscano M, et al. *J Agric Food Chem*. 2010 Oct 13;58(19):10768-73.

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Summary

- **Menopause is a universal female experience**
- **Estrogen is critical for metabolic homeostasis**
- **Loss of ovarian estrogen production results in a myriad array of symptomatology, including metabolic and cognitive effects**
- **Treatment with hormonal therapy is a viable option, but not encouraged by medical societies for cardiovascular wellbeing, and it can never actually provide a perfect substitute for the natural production of hormones from the ovaries**
- **Herbal, mineral, and vitamin supplements, as well as lifestyle modifications, can greatly assist with all aspects of menopausal transition and the many years thereafter**

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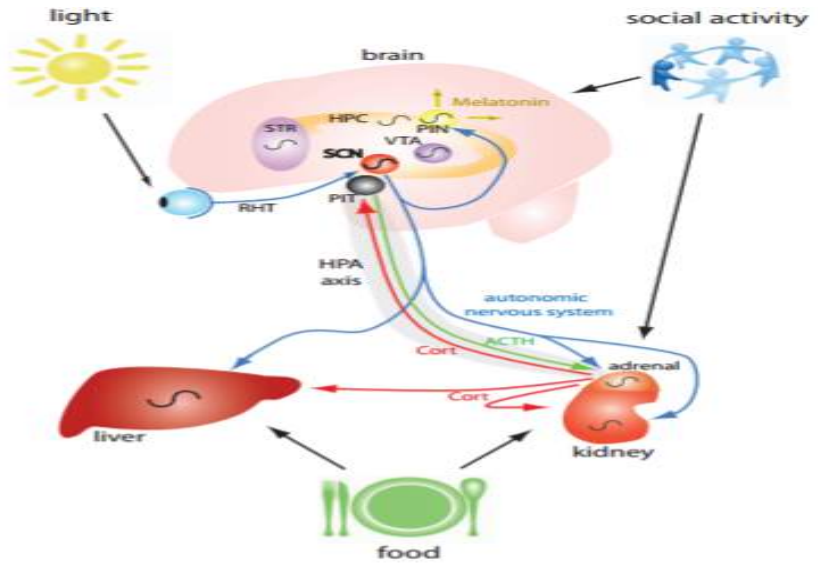
Metabolic and Cardiovascular Health During the Menopausal Years



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Thank you for your kind attention!

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Follow me on Instagram!
@dr.felicegersh

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