Estrogen and Cardiovascular Health: Nutritional Implications for Peri- and Post-Menopausal Women*

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†Dr. Gersh has been retained as a medical consultant in advising Pure Encapsulations.
*These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
Speaker Disclosure

Felice Gersh, M.D.

I am a paid medical advisor for Pure Encapsulations. I have no other conflicts of interest to disclose.

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These therapies are not substitutions for standard medical care. Practitioners are solely responsible for the care and treatment provided to their own patients.
Learning Objectives

1. Understand the biochemical role of estrogen in maintaining vascular function.

2. Recognize the impact of menopause on cardiovascular health.

3. Learn which tests, diets, lifestyle changes and supplements can support the cardiovascular system in peri- and post-menopausal women.*

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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

Center for Disease Control and Prevention.
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

The Role of Estrogen

Estrogen:
- Influences gene expression
- Also activates non-genomic pathway
- Modifies the physiology, electrophysiology and pathophysiology of the heart
Estrogen-Regulated Cardiovascular-related Genes

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

Lipid Metabolism
- Lipoprotein lipase
- Apolipoproteins
- Leptin

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

Coagulation
- Fibrinogen
- Coagulation factors
- Protein S

Angiogenesis
- Matrix metalloproteinase
- Vascular endothelial growth factor

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

Vasodilation: Endothelial Nitric Oxide Synthase (eNOS)

Estrogen upregulates the expression of eNOS, which synthesizes NO.

In the endothelium, NO:
- Is essential for vasodilation
- Decreases leukocyte recruitment
- Functions as an antioxidant

Nitric oxide levels are associated with:
- Endothelial function
- Vascular health

Chakrabarti S, Lekontseva O, Davidge S. *IUBMB Life.* June 2008; 606(6): 376-382
The Impact of Menopause: Vasodilation

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

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

Menopause: Antioxidant Activity

- Estrogen maintains superoxide dismutase (SOD) expression in vascular tissue
- Estrogens are direct antioxidants
- The Impact of Menopause: The loss of estrogen results in a decline in these protective benefits

Menopause: Lipid Metabolism

Cholesterol Levels after Menopause:
- LDL levels rise (generally exceeding those of men) as well as oxidized LDL
- HDL levels decline

Triglyceride levels after Menopause:
- Male triglyceride levels typically decline after mid age
- Female triglyceride levels tend to increase until the age of 70

In the Framingham Study, every 10 mg/dL increase in HDL-C reduced the risk of CAD by 40-50% in women

Saltiki, K and Alevizaki M. Hormones. 2007; 6(1): 9-24
Lead exposure is associated with cardiovascular risk

The Impact of Menopause

- Loss of bone density
- 90% of lead accumulates in bone
- Lead stored in bone is released into circulation

Women in their second year of amenorrhea had blood lead levels 50% higher than pre- and peri-menopausal women

Circadian Rhythms

~24 hour oscillations in physiology and metabolism that allow organisms to predict the availability of food and light.
Circadian rhythms: Clinical relevance

- The suprachiasmatic nucleus (SCN) detects light
- “Peripheral clocks” respond to it, and also respond to meal timing
- The peripheral clocks regulate insulin response, lipid metabolism, appetite, microbiome, cortisol, blood pressure, many other processes
Menopause Overview

A decline in estrogen, as in menopause, is associated with changes in:
1. Vascular health
2. Lipid metabolism
3. Levels of oxidative stress
4. Circadian rhythm

Earlier menopause $\Rightarrow$ Increased risk of cardiovascular complications

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

Clinical trials on HRT and cardiovascular health are inconsistent.

The WHI used conjugated estrogens from horse urine and a progestin, since shown to cause harm.

Few human trials with bio-identical hormone

Saltiki, K and Alevizaki M. Hormones. 2007; 6(1): 9-24
What can you do?

Non-modifiable Risk Factors
- Age
- Gender
- Race
- Menopause
- Family history: Parental history of CAD increases a woman’s risk by 70%

Modifiable Risk Factors
- Tobacco and drug use
- Diet
- Sleep and circadian rhythm
- Stress management
- Cholesterol and lipid metabolism
- Physical inactivity
- Increased BMI and/or waist circumference
- Glucose metabolism

Where to Start?

1. Lab Testing and Imaging

2. Exercise

3. Diet

4. Supplementation*

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Testing

Imaging: Carotid Artery Ultrasound with CIMT, Echocardiogram

Lab Studies:

- Inflammatory markers
- Advanced and routine lipids
- Oxidized LDL
- Apo E
- MTHFR

- ADMA
- Micronutrients
- Microalbumin
- Heavy metals
- Gut health status
Asymmetric Dimethylarginine (ADMA)

- *eNOS inhibitor*
- Occurs naturally in plasma
- Levels are affected by blood lipids, homocysteine, glucose, thyroid hormones
- Citrulline supports higher Arginine:ADMA ratio
Detecting Endothelial Function with ADMA

**Normal conditions**

L-Arginine → ADMA → DDAH → L-citrulline + dimethylamine → eNOS → Nitric Oxide + L-Citrulline

**Increased oxLDL, inflammatory cytokines**

L-Arginine → ADMA → DDAH → L-citrulline + dimethylamine → eNOS → Nitric Oxide + L-Citrulline

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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

Maas R. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham heart study offspring cohort.
Exercise

Lack of exercise is as much of a risk factor as smoking!

Research has shown that women who regularly exercise have:

- Lower blood pressure
- Healthy Blood glucose levels
- Improved lipid profiles
- Reduced weight

Diet

Initially, if any abnormalities, start with a modified vegan diet

As health improves, progress to a modified Mediterranean diet

- Clinical studies have found that a Mediterranean diet improves lipid levels (raise HDL and lower TG) in postmenopausal women

## Diet: Feed Your Microbiome!

<table>
<thead>
<tr>
<th>INCLUDE</th>
<th>LIMIT</th>
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</table>
| • 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 | • Protein (approximately 12%) |

<table>
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<tr>
<th>AVOID</th>
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| • Initially, protein from dairy and eggs  
• Sugar and refined carbohydrates  
• Alcohol  
• Food intolerances |
Diet: Meal Timing to support circadian rhythms

Typical American Meal Pattern

Healthier (Circadian-aligned) Meal Patterns

A: 16 hour Overnight Fast
8 hour Daytime Eating Period

B: 12 hour Overnight Fast
12 hour Daytime Eating Period

C: 16 hour Daytime Eating Period
8 hour Overnight Fast
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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Berberine supports cardiometabolic health*

Over a 3 month period, berberine significantly reduced waist circumference (in women), moderated triglycerides and supported insulin sensitivity.*


After 3 months, berberine administration significantly decreased body weight, BMI while supporting healthy lipid profiles compared to placebo.*


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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


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Polyphenols

Micronutrients with antioxidant activity*
Key role in insulin sensitivity, cellular health, cognition, and cardiovascular health*
Play an important role as a prebiotic, increasing ratio of beneficial bacteria in gut*
• Pomegranate
• Resveratrol
• Quercetin
• Olives
• Green tea

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Phytosterols

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%.*


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


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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*


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Supporting Nitric Oxide: Why Citrulline?

**Arginase** degrades orally administered L-arginine
- Restricts arginine absorption by 38% - 70%

**Citrulline** not degraded by arginase

L-citrulline increased AUC and $C_{\text{max}}$ of plasma L-arginine more effectively than L-arginine*


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Citrulline

- Better absorbed
- Up to 80% of the ingested dose used to make NO
- Augments plasma arginine
- L-citrulline increased L-arginine/ADMA ratio, urinary nitrate and cGMP

### Additional Options

<table>
<thead>
<tr>
<th>Key Ingredients</th>
<th>Details</th>
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<tbody>
<tr>
<td>• Berberine</td>
<td>Supports healthy insulin function and glucose homeostasis*</td>
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<tr>
<td>• Resveratrol</td>
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</tr>
<tr>
<td>• EPA &amp; DHA rich fish oils</td>
<td>Supports healthy TGs and lipid metabolism, maintains healthy blood flow, supports healthy platelet function*</td>
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<tr>
<td>• GABA</td>
<td>Promotes the onset of sleep as well as sleep quality*</td>
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<td>• Valerian root extract</td>
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<tr>
<td>• Lignans</td>
<td>Moderates occasional hot flashes and supports menopausal health, comfort and emotional well-being*</td>
</tr>
<tr>
<td>• <em>L. acidophilus</em></td>
<td>A dairy-free blend of key probiotic bacteria to support immune and gastrointestinal health*</td>
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<tr>
<td>• <em>B. lactis</em></td>
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Summary

**Menopause**

- Estrogen

**Cardiovascular Health**

- Nitric Oxide
- Antioxidant Status
- Lipids & Glucose
- Metabolism
- Circadian Rhythm

Supported by [Diet, Lifestyle and Supplements](#)*

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Thank you for your kind attention!

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