Women, Hearts, and Hormones:

New understandings of the foundations of female cardiovascular health and the impact of menopause

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Disclosures

- Speaker – Cleveland HeartLab/Quest, Pure Encapsulations, L-Nutra
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 estrogen and the Circadian Rhythm are linked and of the major role played by estrogen and the maintenance of the Master Clock
4. 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
The significance of cardiovascular health

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

More than all forms of cancer, diabetes, Alzheimer’s & pneumonia

Center for Disease Control and Prevention
The Major Overlooked Factor in Women’s Cardiovascular Health
Consequences of menopause ARE the consequences of estrogen deficiency

- Obesity
- Disturbed Sleep
- Mood Disorders
- Metabolic Syndrome and Diabetes
- Osteoporosis
- Cardiovascular Health and Atherosclerosis
- Alzheimer’s Disease and Neuro-inflammatory
- Breast Cancer
- Fatty Liver
- GI Disorders: Colon Cancer, GERD, Malabsorption

Adapted from Exp Rev Endocrinol Metab ® 2011 Expert Reviews Ltd
Menopause & cardiovascular health overview

1. Impact on insulin resistance
2. Impact on dyslipidemia (↑LDL, oxidized LDL, ↓HDL)
3. Impact on arteries - decreased nitric oxide (↑BP) and other effects
4. Impact on the myocardium
5. Impact on gut microbiome (Estrobolome) & oral cavity - impaired gut barrier function - reduced Nitric Oxide production
6. Impact on estrogen metabolites – role of 2 MethoxyEstradiol
7. Impact on Circadian Rhythm
8. Impact on adipose tissue
9. Impact on mitochondrial function – oxidative stress

Saltiki, K and Alevizaki M. Hormones. 2007; 6(1): 9-24
Vieira et al. Front Microbiol. 2017;8:1884
Estrogen basics

- **ER alpha →** Regulates genes
  - 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
  - Primarily expressed in *non-gonadal* tissues: GI tract, colon, bone marrow, vascular endothelium, lung, bladder, B cells, and much of brain

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

Dahlman-Wright et al. *Aspet Pharmacological Reviews.* 2006: 58 (4); 773-781
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
Estrogen deficiency: impact on cardio-metabolic health

### Some products of genes regulated by estrogen

<table>
<thead>
<tr>
<th>Vasodilation and vasoconstriction</th>
<th>Immune activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial NO synthase</td>
<td>Vascular-cell adhesion molecule</td>
</tr>
<tr>
<td>Prostacyclin cyclooxygenase</td>
<td>Cytokines (IL1, IL6, TNFα)</td>
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<tr>
<td>Prostacyclin synthase</td>
<td>Cytokine receptors</td>
</tr>
<tr>
<td>Renin and angiotensin</td>
<td>Superoxide Dismutase</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Coagulation</td>
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<tr>
<td></td>
<td>Fibrinogen</td>
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<td></td>
<td>Coagulation factors</td>
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<td>Protein S</td>
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#### Lipid Metabolism
- Lipoprotein lipase
- Apolipoproteins
- Leptin
- PON 1
- LDL receptors
- HMG-CoAR activity

#### Coagulation
- Matrix metalloproteinase
- Vascular endothelial growth factor

#### Angiogenesis

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

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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

Role of Estrogen Metabolites – 2 MethoxyEstradiol

Impact on cardiovascular health not 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 neointima formation and smooth muscles cell growth

Barchiesi et al. Circ Res. 2006; 99(3): 266-74
**Estrogen alleviates diastolic dysfunction**

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

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.

Estrogen and the heart summary
There is a growing understanding of the role which E2 plays in metabolism via its regulation of mitochondrial function.
Estrogen and mitochondrial function

Additional cardiovascular benefits of estradiol (E2)

1. Insulin sensitivity & glucose metabolism
2. Lipid profile
3. Endothelial function
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
Estrogen - lipids and paraoxonase (PON 1)

- Estrogen increases PON 1 activity & reduces oxLDL
- 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 supports insulin sensitivity

- Supports glucose transporter (GLUT3, GLUT4) function
- Enhances glucose-stimulated insulin biosynthesis
- Promotes β cell survival

Menopause and the development of Cardio-Renal-Vascular-Metabolic Syndrome

Estrogen – master of metabolic homeostasis

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

The impact of menopause: vascular health

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

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

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, PGI Synthase, and PGI expression

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

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 coagulation

Mensah GA. *Vascul Pharmacol* 2007;46 (5):310-4
Lam et al. *Am J Physiol Heart Circ Physiol* 2006;290:786-93
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
  - Reduced platelet aggregation
  - Endothelial function
  - Myocardial function

Nitric oxide maintains endothelial health and is cardio-protective

- Improve dilation of blood vessels
- Reduce blood clotting
- Reduce inflammation in artery wall
- Reduce free radical formation
- Reduce LDL oxidation
- Reduce artery wall thickening

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
Progression with age: a NO perspective

Adapted from:
Egashira K et al. Circulation. 1993; 88 (1):77-81
Overview: estrogen and arterial health

Iorga A et al. *Biol Sex Differ*. 2017; 8: 33
Estrogen supports nitric oxide synthesis

Estrogen supports the expression and activation of eNOS
Estrogen moderates the formation of uncoupled eNOS

SOD, Superoxide dismutase
Zhao Z et al.. Am J Physiol Heart Circ Physiol. 2013; 306:
Estrogen supports nitric oxide in the presence of inflammation

- ADMA competes with Arginine for eNOS receptor and prevents the synthesis of NO
- Estrogen can overcome the effects of ADMA to increase NO production

Estrogen: Antioxidant Activity

Circadian Rhythms

• ~24h oscillations in physiology and metabolism that allow organisms to predict the availability of food and light.

• Estrogen is the master hormone regulating the Circadian Rhythm

Estrogen, reproduction, metabolism: interconnected with the circadian rhythm

The rhythm of insulin sensitivity

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**
Circadian rhythm & reduced estrogen

INFLAMMATION

• Atherosclerosis and cardiovascular disease
• Metabolic alterations and altered appetite – weight gain
• Impaired cognition
• Immune system alterations
• Reduced energy
• Significant reduction in neurotransmitter production – melatonin and serotonin - poor sleep quality, oxidative stress, mood alterations

Circadian rhythm and intestinal rhythms

**Chrono-nutrition**
1. Clock regulation
   - ex. High-fat diet (HFD), Caffeine
2. Meal-time effects
   - ex. Skipping breakfast (SB)
   - Nocturnal eating (NE)

**Regular/Time-restricted Feeding**
- Synchronization
- Amplified rhythms
  - Healthy

**Irregular/Unusual Feeding**
- Desynchronization
- Attenuated rhythms
  - Metabolic disorders

Your patient is menopausal …
NOW WHAT DO YOU DO??

## Deal with what is modifiable

<table>
<thead>
<tr>
<th>Non-modifiable Risk Factors</th>
<th>Modifiable Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗ Age</td>
<td>✓ Diet choices and meal timing</td>
</tr>
<tr>
<td>✗ Gender</td>
<td>✓ Sleep time and quantity</td>
</tr>
<tr>
<td>✗ Race</td>
<td>✓ Circadian rhythm influencers</td>
</tr>
<tr>
<td>✗ Menopausal status</td>
<td>✓ Stress management</td>
</tr>
<tr>
<td>✗ Family history: Parental history of CAD increases a women’s risk by 70%</td>
<td>✓ Physical activity level</td>
</tr>
<tr>
<td></td>
<td>✓ Hormone use</td>
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<tr>
<td></td>
<td>✓ Tobacco and drug use</td>
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<tr>
<td></td>
<td>✓ Supplements</td>
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</tbody>
</table>

Where to begin?

1. Laboratory Testing
2. Exercise
3. Diet
4. Supplements
Key cardiovascular testing options

- Inflammatory markers
- Advanced lipid profile
- Insulin and HbA1c
- Oxidized LDL
- Ferritin
- ApoE and MTHFR
- B12 and Homocysteine
- 25 OH Vitamin D
- Omega Check
- Uric acid

- Heavy metals
- Thyroid: TSH, Free T3, Free T4, Anti-TPO, Thyroglobulin antibodies
- Testosterone, DHEAS, Pregnenolone
- Other micronutrients
Hormone therapy revisited

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

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

- Regular exercise contributes to:
- Lower blood pressure
- Lower blood glucose levels
- Improved lipid profiles
- Healthy body weight
- Improves microbiome diversity
- Resets the circadian clocks

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

Exercise reversed impaired microvascular NO function in sedentary adults!

Begin with a vegan diet -- 10–12 servings vegetables, 2 fruit

The Modified Mediterranean Diet (leave out all or most dairy and gluten) supports healthy lipid levels (raises HDL & lowers TG) in postmenopausal women - reduces risk of obesity, hyperglycemia & CVD

Eat foods that support the microbiome!
- Prebiotics and Probiotics
- Complex fiber-rich carbohydrates
- Polyphenol-rich foods

Fasting & Time Restricted Eating

Benefits of high-amylose starch

- Fiber intake is lower than recommended

- High-amylose starch
  - 40-60% fermentable carbohydrate
  - Amylose can be fermented

- Biological impact
  - Enhances gut microbiota profile and production of short-chain fatty acids
  - Improves gut barrier function
  - Mimics effects of caloric restriction

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

Systems & pathways involved

Supported by:
- Estrogen
- Exercise
- Caloric restriction
- Resveratrol
- Berberine
- Alpha lipoic acid

Mitochondria
AMPK
Insulin signaling
Microbiome
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
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.

- Resveratrol
- Alpha lipoic acid
- Berberine
- Exercise

**AMPK**
- Insulin function
- Fat utilization
- Fatty acid synthesis
- Triglyceride synthesis
Supplements: key areas of support to address the needs of your menopausal patients

- Insulin sensitivity & glucose metabolism
- Lipid Profile
- Antioxidant status
- Blood flow
- Endothelial function and arterial wall integrity

Berberine
Phytosterols, Bergamot
Citrulline
Vitamin C
Taurine
Magnesium
Polyphenols
Phytosterols support a healthy lipid profile

- Compete with cholesterol for absorption into the body
- 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 a healthy lipid profile.

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

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

L-citrulline is more Effective at Increasing Plasma L-Arginine than L-Arginine

- Double-blind, randomized, placebo-controlled crossover study of 20 healthy volunteers

- L-citrulline increased AUC and Cmax of plasma L-arginine more effectively than L-arginine

- L-citrulline increased L-arginine/ADMA ratio, urinary nitrate and cGMP

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
Magnesium

- Essential roles in vasomotor function:
  - Regulation of calcium channels
  - Production of nitric oxide
  - Prostacyclin formation
- Preferred form – magnesium glycinate; well tolerated, highly bioavailable
Case study: Katherine M.

Background
• 50 years old year woman G3 P2 SAB1

Presenting Complaints
• Periods have been irregular over the past 3 years, varying from 1-4 months apart – now none for 9 months
• Had been healthy with no significant medical history
• Eats mostly home cooked foods, little processed food
• Difficulty sleeping over past 2 years
• 8 pound weight gain in past year, 5 over previous 2 years
• Binges on snack food late at night, feels best at night and gets very hungry, very fatigued in the morning
• Heartburn, fatigue, mood swings, hot flashes, low sex drive, foggy brain
Case study: Katherine M.

Lab Results
- Insulin resistance – Pre DM, elevated triglycerides, normal cholesterol, mild inflammation, borderline low thyroid
- Adrenal Stress Index: Low morning cortisol, high evening levels: Flipped circadian rhythm
- FSH, estradiol in menopausal ranges
- Testosterone – low end of reference range

Therapeutic Program Initiated
- **Detoxification**: DIM, probiotics, psyllium, chlorella, EPA/DHA, turmeric extract, broccoli extract, artichoke extract, L-glutamine, NAC, taurine, milk thistle, Calcium-D-glucarate
- **Symptom Management**: Hop extract, 7-hydroxymatairesinol, Ashwagandha, Maca extract, L-theanine, resveratrol, rhodiola rosea,
- **Lifestyle**: Time Restricted Eating, mild Exercise Program, sleep hygiene, stress control program (Guided Imagery, Tapping, Progressive Relaxation)
After Initial 4 weeks:

- Felt “enormously better”
- Cravings, snacking and night eating nearly completely resolved
- Lost 6 pounds
- Sleeping much better but still some hot flashes – but much reduced

More energy
Brighter outlook on life
Minimal heartburn
Decided to begin bioidentical hormone therapy

Therapeutic Program Continued – Next Phase

- Bio-identical hormones
- Continue initialization protocol
- Cardiometabolic: Berberine HCl, chromium, ALA, magnesium glycinate
- Stress/Mood/Sleep: L-theanine, magnesium glycinate
- Polyphenol blend for daily wellness and neurocognitive/cardiovascular support (resveratrol, pomegranate, cranberry, Acai, blueberry, green tea)
Case Study: Katherine M.

6 months later

- Lost 18 pounds total
- All metabolic tests were now in the normal range
- Sleep much better
- Hot flashes entirely resolved
- Exercising regularly
- Good sex drive
- Great energy
- Great focus

“I feel like my old self.”
Modifiable through diet, lifestyle, & supplementation

Menopause

Estrogen

Insulin sensitivity & glucose metabolism
Healthy lipid profile
Endothelial function

Supported by diet, lifestyle, and supplementation

Cardiovascular health
Living to the beat: maintain metabolic & cardiovascular health
Thank You

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