Bioenergetic and Metabolic Consequences of the Menopause Transition

SCOR on Sex Differences
P50 HD073063

SCORE on Sex Differences
U54 AG062319

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Outline

1. Potential consequences of the loss of gonadal function – working model

2. Bioenergetic and metabolic consequences of the loss of ovarian function – preclinical

3. Bioenergetic and metabolic consequences of the loss of ovarian function – clinical

4. New SCORE directions
Loss of Gonadal Function

Women: 51 y

Impact on Other Systems

Men: 70+ y

Increased Disease Risk
Loss of Gonadal Function

- Bone Loss
  - Other Tissues
    - Dementia
    - Sarcopenia
  - Fat Gain
    - CVD
    - T2D

Spontaneous Physical Activity

Distribution Composition

Osteoporosis
Outline

1. Potential consequences of the loss of gonadal function – working model

2. Bioenergetic and metabolic consequences of the loss of ovarian function – preclinical
Body Weight in Mice and Rats
OVX vs Sham

Adapted from: Witte MM et al. General Compar Endocrinol 166:520, 2010
Locomotor Activity in Mice and Rats
OVX vs Sham

Adapted from: Witte MM et al. General Compar Endocrinol 166:520, 2010
Wheel-running Distance in Sham and OVX Mice

Effects of OVX and E₂ Add-back in Mice

Effects of Programmed Exercise on Adiposity and Insulin Action

Adapted from: Pighon A et al. Climacteric 13:238, 2010
Effects of OVX:

- decreased physical activity
- decreased resting metabolic rate
- increased energy intake (some species)
- increased abdominal fat gain
- metabolic dysfunction

Prevented by $E_2$ treatment and by exercise
Outline

1. Potential consequences of the loss of gonadal function – working model

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**Ovarian Hormone Suppression (GnRH\textsubscript{AG}; 5 months) With Placebo or E\textsubscript{2}**

<table>
<thead>
<tr>
<th>2-group model</th>
<th>GnRH\textsubscript{AG}+PL (n=35)</th>
<th>GnRH\textsubscript{AG}+E\textsubscript{2} (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36 ± 2</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>74 ± 3</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>28 ± 2</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>FM, kg</td>
<td>28 ± 2</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>46 ± 1</td>
<td>48 ± 1</td>
</tr>
</tbody>
</table>

**Ovarian Hormone Suppression (GnRH\textsubscript{AG}; 5 months) + Placebo or E\textsubscript{2}, ± Resistance Exercise**

<table>
<thead>
<tr>
<th>4-group model</th>
<th>GnRH\textsubscript{AG}+PL n=35</th>
<th>GnRH\textsubscript{AG}+E\textsubscript{2} n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-Ex n=23</td>
<td>+Ex n=12</td>
</tr>
<tr>
<td>Age, y</td>
<td>36 ± 2</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>74 ± 4</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td>28 ± 1</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>FM, kg</td>
<td>27 ± 3</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>47 ± 1</td>
<td>47 ± 2</td>
</tr>
</tbody>
</table>

GnRH\textsubscript{AG} + PL vs GnRH\textsubscript{AG} + E_2
5-mo Changes in FFM and Muscle CSA

Shea K et al. Menopause 22:1045, 2015
GnRH$_{AG}$, +/- $E_2$, +/- Exercise Training
5-mo Changes in FFM and Muscle CSA

Shea K et al. Menopause 22:1045, 2015
GnRH_{AG}^{+}PL vs GnRH_{AG}^{+}E_{2}

5-mo Changes in Fat Mass and Abd Fat Areas

Shea K et al. Menopause 22:1045, 2015
GnRH$_{AG}$+PL vs GnRH$_{AG}$+E$_2$

5-mo Changes in Fat Mass and Abd Fat Areas

GnRH$_{AG}+$PL vs GnRH$_{AG}+$E$_2$

Changes in Moderate-Vigorous Physical Activity

5-mo Changes in Energy Expenditure

GnRH$_{AG}$+PL vs GnRH$_{AG}$+E$_2$ vs GnRH$_{AG}$+PL+Ex

**REE**
-250 to +50 kcal/d

**TEE**
-250 to +100 kcal/d

GnRH$_{AG}$+PL vs GnRH$_{AG}$+E$_2$ vs GnRH$_{AG}$+PL+Ex

Change in Fat-free Mass
-1.6 to +0.8 kg

Figure 4. Changes in fat mass and fat-free mass in response to 12 to 24 weeks of gonadotropin releasing hormone therapy.
### 6 Months of Placebo vs GnRH Agonist Therapy + Endurance Exercise

<table>
<thead>
<tr>
<th>6-month intervention</th>
<th>Placebo</th>
<th>GnRH&lt;sub&gt;AG&lt;/sub&gt; + Exercise</th>
<th>GnRH&lt;sub&gt;AG&lt;/sub&gt;</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Age, y</td>
<td>46 ± 2</td>
<td>45 ± 3</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>72 ± 13</td>
<td>70 ± 13</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>FM, kg</td>
<td>26 ± 12</td>
<td>23 ± 7</td>
<td>27 ± 7</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>46 ± 5</td>
<td>47 ± 5</td>
<td>47 ± 5</td>
</tr>
</tbody>
</table>

Gavin KM et al *preliminary data*
Ovarian Suppression and Endurance Exercise
Change in Fat-free Mass

![Graph showing change in fat-free mass withPlacebo group at 12 and 24 weeks.](image-url)
Ovarian Suppression and Endurance Exercise Change in Fat Mass

- 12 weeks
- 24 weeks

DXA ∆Fat Mass, Kg

Placebo
Ovarian Suppression and Endurance Exercise
Change in Trunk Fat Mass

ΔTrunk Fat Mass, kg

-0.2  0.0  0.2  0.4  0.6  0.8  1.0

-0.2  0.0  0.2

Placebo

12 weeks
24 weeks
E₂ Regulation of Adipose Cellular Composition

**BMDA production is regulated by sex/ovarian hormone status:**

- *p < 0.05 and #p = 0.0001 vs WT

**BMDA vs Convention Adipocyte Gene Expression Signature:**
- Highly inflammatory
- Lower mitochondrial enzymes
- Lower leptin

Gavin KM et al *Front Endocrinol* 2018
Majka SM, Barak Y, Klemm DJ *Stem Cells* 2011
### E$_2$ Regulation of BAT Thermogenesis

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Activity</th>
<th>Parameter</th>
<th>Measurement</th>
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</thead>
<tbody>
<tr>
<td>-60</td>
<td>$^{13}$C-acetate (185 MBq)</td>
<td>Cold exposure</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>$^{18}$F-FDG (185 MBq)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>Study time (T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>Clock time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>Skin temp, core temp, EMG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>PET/CT</td>
<td></td>
<td>A, B, C</td>
</tr>
<tr>
<td>240</td>
<td>Indirect Calorimetry</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Image of person wearing a black suit and helmet](image1)

![Image of a person lying on a table with medical equipment](image2)
$^{18}$FDG Tissue Uptake
Pre- vs Postmenopausal Women

Melanson et al preliminary data
Cold-induced Thermogenesis in Pre- vs Postmenopausal Women

Melanson et al preliminary data
Preclinical (OVX) and clinical studies (GnRH\textsubscript{AG}) provide consistent evidence for the role of estrogens in the regulation of energy balance.

The loss of estrogens (OVX, GnRH\textsubscript{AG}) may promote fat gain through multiple system-level mechanisms:

- Decreased resting metabolic rate
- Decreased physical activity
- Increased energy intake (some species)
- Decreased BAT thermogenesis
In animals, exercise prevents the effects of OVX to increase abdominal adiposity and metabolic dysfunction.

Preliminary studies of women suggest resistance exercise may attenuate the loss of lean mass in response to ovarian aging, but not the increase in abdominal adiposity or decrease in resting metabolic rate. Endurance exercise may attenuate fat gain, but not central body fat.
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3. Bioenergetic and metabolic consequences of the loss of ovarian function – SCOR results

4. New SCORE directions
Colorado SCORE - Scientific Focus

Loss of Gonadal Function

↓ Estradiol

↑ FSH

Altered cellular composition
- ↑ Bone marrow progenitor-derived adipocytes
- ↑ Inflammatory signature

Altered peripheral glucocorticoid metabolism
- ↑ Adipose tissue HSD1 activity
- ↑ Total body HSD1 activity

↑ Abdominal Adiposity

Increased Disease Risk
- type 2 diabetes
- heart disease
- hypertension
- cancer
- osteoarthritis
Blocking FSH induces thermogenic adipose tissue and reduces body fat

Peng Liu1*, Yaoting Ji1,2*, Tony Yuen1, Elizabeth Rendina-Ruedy3, Victoria E. DeMambro1, Samarth Dhawan1, Wahid Abu-Amer1, Sudeh Izadmehr1, Bin Zhou4, Andrew C. Shin1, Rauf Latif1, Priyanthan Thangeswaran1, Animesh Gupta1, Jianhua Li1, Valeria Shnayder1, Samuel T. Robinson4, Yue Eric Yu4, Xingjian Zhang4, Feiran Yang4, Ping Lu1, Yu Zhou1, Ling-Ling Zhu1, Douglas J. Oberlin1, Terry F. Davies1, Michaela R. Reagan3, Aaron Brown3, T. Rajendra Kumar3, Solomon Epstein1, Jameel Iqbal6, Narayan G. Avadhani7, Maria I. New1, Henrik Molina8, Jan B. van Klinken9, Edward X. Guo4, Christoph Buettner1, Shozeb Haider10, Zhuan Bian3, Li Sun1§, Clifford J. Rosen1§ & Mone Zaidi1§

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