Metabolic changes in menopausal transition

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Steroid hormones

- Progesterone
- Testosterone
- Estrogens
Steroid hormones and their mechanisms of action

- Produced from cholesterol
- Lipid soluble
  - Diffuse to cell
- Mainly act through nuclear receptors
- Their action depends on the presence of nuclear receptors
Steroid hormones and their metabolic effects

• Several clinical implications
  • Menopause
  • POI
  • PCOS
  • Contraceptives
  • HRT

• Manifestations
  • Lipids
  • Glucose metabolism
  • Inflammation
Menopausal transition and metabolism
Metabolic effects of estrogens

Modified from Foryst-Ludwig and Kintscher, 2010
Menopausal transition in women: $E_2$ and FSH

Lovejoy et al., 2008
Oophorectomy in mice

Rogers et al. Endocrinology, 2009
Oophorectomy in mice

Rogers et al. Endocrinology, 2009
Oophorectomy in mice

Increased inflammation in OVX mice

Fat accumulation in the liver

Rogers et al. Endocrinology, 2009
Oophorectomy in mice

Rogers et al. Endocrinology, 2009
Menopausal transition in women

• Lovejoy et al., 2008
  • 156 women
  • 43 years or older
  • had at least five menstrual periods in the 6 months prior to screening
  • serum FSH <30 mIU/ml

→ Were followed for 4 years
Menopausal transition in women: Activity and total caloric intake

Lovejoy et al., 2008
Menopausal transition in women: Weight and body fat

Lovejoy et al., 2008
Menopausal transition in women: Visceral and subcutaneous fat during

Lovejoy et al., 2008
Menopausal transition: Metabolite expression

- The differences in metabolite expression between women and men diminish after menopause

Auro et al., Nature Communications 2014
Inflammation and menopausal transition

• Increased inflammation
  • Related to increased abdominal fat (Lee et al., JCEM 2009)

• No significant change after adjusting for BMI
  (Matthews et al., JCEM 2006, Puurunen JCEM 2011)
Adiposity decreases glucose tolerance

1. Hormonal changes
2. Fat redistribution
3. FFA overload due to ageing
4. Inhibition if insulin signaling pathway
5. Insulin resistance

Pararasa et al., 2015, Biogerontology
Menopausal transition: Glucose tolerance

N Pre= 43 (mean age 47yrs)
N Post = 40 (mean age 51 yrs)

Toth et al., Diab Care 2000
Menopausal transition: Glucose tolerance

N Pre = 11 (mean age 47 yrs)
N Post = 18 (mean age 56 yrs)

Puurunen et al., JCEM 2011
## Risk for DMT2 and menopause

### Menopausal Women

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age</th>
<th>Age, BMI</th>
<th>Age, BMI, risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45 years</td>
<td>1.89 (1.21–2.96)</td>
<td>1.73 (1.10–2.73)</td>
<td>1.49 (0.94–2.35)</td>
</tr>
<tr>
<td>45-49 years</td>
<td>1.29 (0.87–1.91)</td>
<td>1.24 (0.84–1.85)</td>
<td>1.09 (0.73–1.62)</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>1.39 (1.01–1.92)</td>
<td>1.32 (0.95–1.82)</td>
<td>1.14 (0.82–1.57)</td>
</tr>
</tbody>
</table>

### Men

<table>
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<tbody>
<tr>
<td></td>
<td>4.02 (3.15–5.14)</td>
<td>2.86 (2.23–3.68)</td>
<td>2.34 (1.82–3.02)</td>
</tr>
</tbody>
</table>

N (premenopausal women) = 6,308  
N (postmenopausal women) = 4,570  
N (men) = 29,189

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Heianza et al., Diabetes care 2013
Androgens
Androgen secretion during ageing

17-OHP
Androstenedione
Testosterone
Estradiol

Piltonen et al., JCEM 2003
Spencer et al., JCEM 2007
Menopausal transition: Chol, LDL, Trigly

- Endogenous estrogens have positive effects on metabolic profile in women

- Lipid profile resembles that of men in postmenopause

Anagnostis et al., Maturitas 2015
Hyperandrogenism in mice and women

- Promoting postnatal hyperandrogenism (DHT)
  - Adverse metabolic (lipid) profile
  - Increased adiposity
  - Mild changes in glucose tolerance

- Postmenopausal hyperandrogenism in women
  - Several having luteinized ovaries (ovarian hypertechosis) or small androgen secreting tumors (n=30, mean age 57.5 yrs)
  - Women were obese (53.3%), dmt2 (70%), HTA (70%), dyslipidemia (56.6%)
  - Ovariectomy and normalizing androgen levels did not have beneficial metabolic effects

Caldwell et al., Endocrinology 2014
Crespo et al., Abstract, ENDO 2017
Hyperandrogenism in mice and women

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  • Women were obese (53.3%), DMT22 (70%), HTA (70%), dyslipidemia (56.6%)
  • Ovariectomy and normalizing androgen levels did not have beneficial metabolic effects up till 2 yrs after surgery

  Crespo et al., Abstract, ENDO 2017
PCOS

Androgen Excess

Hyperinsulinemia

Glucose intolerance

Obesity
HA in women with PCOS <30 years

Modified from Piltonen et al. JCEM 2004
Ovarian and adrenal androgen secretion is still pronounced after menopause

Modified from Puurunen et al. JCEM 2009 and 2011
Hyperandrogenism and metabolic factors in PCOS

• HA – no strong effect
  • Ranasinha et al., 2015
  • Forrester-Dumont et al., 2012

• HA – effect
  • O’Reilly et al., JCEM, 2014
  • Corbould et al., 2008

• Data is conflicting
  • Using FAI causes problems
    • (T/SHBG x100)
    • Obesity increases SHBG
Obesity in women with or without PCOS symptoms at age 46

PCOS ja BMI

Ollila et al. JCEM 2016
Hyperandrogenism and lipid profile in PCOS
BMI-adjusted data

- No difference in glucose tolerance

Pinola et al., Fesr and Ster 2017
PCOS and risk for DMT2 according to BMI

Ollila et al. Hum Reprod 2017
FAI as a risk factor for metabolic markers in PCOS, POI and menopause

Daan et al., HR, 2015
FAI as a risk factor for metabolic markers in PCOS, POI and menopause

Daan et al., HR, 2015
Life style factors and SES and healthy menopausal transition

- Lower educations levels 1.7X
- Unhealthy lifestyle 1.6X
  risk for metabolic disturbances in MP transition

Kim et al. Menopause 2016
Conclusions

• Steroid hormones have metabolic effects

• Menopausal transition (hypoestrogenism) increases adiposity, alters lipid profile and promotes chronic inflammation

• Menopausal transition does not immediately alter glucose metabolism to same extend as adiposity
  • Long-term changes in glucose metabolism
  • BMI-driven
  • Risk for DMT2 remains higher in men
Conclusions

• PCOS women are more hyperandrogenic also after menopause

• Hyperandrogenisms seems to relate with more severe metabolic phenotype in PCOS
  • Often coincides with insulin resistance and obesity
  • Long footprint of hyperandrogenism in PCOS
    → increases the metabolic risks
    → un-reversable?
    → DMT2 risk associates strongly with high BMI

• Long-term follow-up data and more specific data on menopausal transition are lacking
Thank you.