The impact of diet and supplements on endometriosis

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Endometriosis is a life-long disease

✓ Life-long management

✓ Body-friendly treatment

✓ Non hormonal treatment
Diet and Supplements for Endometriosis
Metabolic factors in endometriosis
Leptin, Adiponectin, Fatty Acids

- Energy Expenditure, Hormone Secretion
- Glomerular Filtration
- Insulin & Glucagon Secretion
- Lipid & Glucose Metabolism, Insulin Sensitivity
- Angiogenesis

Systemic Nutrient and Energy Homeostasis
Leptin and endometriosis

• Leptin in PF

• Leptin in serum

• Leptin promotes human endometriotic cell migration and invasion
  – Ahn JH et al. Mol Hum Reprod 2015
Adiponectin and endometriosis

Serum adiponectin concentrations are decreased in women with endometriosis.

Peritoneal fluid adiponectin concentrations are decreased in women with III/IV endometriosis.

Table 1. Characteristics of the subjects stratified by endometriosis stages and menstrual phases.

<table>
<thead>
<tr>
<th>Menstrual Phase</th>
<th>n</th>
<th>BMI mean ± S.D. (kg/m²)</th>
<th>Adiponectin in PF median (IQR) (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-endometriosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative Stages I/II</td>
<td>32</td>
<td>20.8 ± 4.3</td>
<td>2.10 (2.03–2.85)</td>
</tr>
<tr>
<td>Secretory Stages I/II</td>
<td>21</td>
<td>20.8 ± 3.1</td>
<td>2.20 (2.03–2.78)</td>
</tr>
<tr>
<td>Endometriosis Stages III/IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferative Stages III/IV</td>
<td>16</td>
<td>20.8 ± 3.3</td>
<td>1.79 (1.68–2.17)</td>
</tr>
<tr>
<td>Secretory Stages III/IV</td>
<td>16</td>
<td>20.8 ± 3.1</td>
<td>1.79 (1.68–2.17)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
Adiponectin suppressed the production of IL-6, IL-8, and MCP-1 induced by IL-1β in endometrial stromal cells.

Metformin suppresses aromatase activation, IL-8 production, and proliferation of endometriotic stromal cells

Metformin is effective in the treatment of endometriosis as measured by a decrease in the size of endometriotic implants in a rat model.
Regulators of metabolism affect endometriosis
Fatty acids
## Association between endometriosis and fat intake/sources

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>$P_{\text{trend}}$</td>
<td>$P_{\text{trend}}$</td>
<td>$OR$ (95% CI)</td>
<td>$P_{\text{trend}}$</td>
<td>$P_{\text{trend}}$</td>
<td>$P$</td>
</tr>
<tr>
<td>Total fat</td>
<td>0.05↑</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Animal fat</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Vegetable fat</td>
<td>0.001↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>0.05↑</td>
<td>–</td>
<td>–</td>
<td>NS$^{\text{a}}$</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>0.001↑</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Trans-fat</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>0.001↑</td>
<td>–</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>0.03↓</td>
<td>0.045↓</td>
</tr>
<tr>
<td>Omega-6 fatty acids</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>0.006↓</td>
</tr>
</tbody>
</table>

Conversion of Essential Fatty Acids

Omega-6 fatty acids:
- Linoleic acid (LA)
  - γ-Linolenic acid (GLA)
    - Dihomo-γ-linolenic acid (DGLA)
      - Arachidonic acid (AA)

Omega-3 fatty acids:
- α-Linolenic acid (ALA)
  - Stearidonic acid (SDA)
  - Eicosatetraenoic acid (ETA)
    - Eicosapentaenoic acid (EPA)
      - Docosapentaenoic acid (DPA)
        - Docosahexaenoic acid (DHA)

Conversion:
- Vegetable oils: Safflower oil
- Green leafy vegetables: Flax and chia seeds
- Canola, walnut, and soybean oils
- Meat: Poultry, Eggs
- Oily fish: Algae oil, Krill oil
- Oily fish: Algae oil, Krill oil
omega-3 fatty acids and endometriosis

• Dietary supplementation with fish oil, containing EPA and DHA retard endometriotic implant growth in the rabbit model of endometriosis.

• Oral EPA supplementation suppressed the thickening of the interstitium of endometriotic tissue.

• Women with high serum EPA levels were 82% less likely to have endometriosis compared to women with low EPA levels.

• Omega-3 PUFA caused significant regression of endometriotic implants in a rat model.
fat-1 gene

✓ is a gene of *C. elegans*.
✓ encodes an $\omega$-3 fatty-acid desaturase that converts $\omega$-6 to $\omega$-3 fatty acids.
✓ is absent in most animals, including mammals.

\[ \begin{align*}
\omega-6 \text{ FA} : & & \text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH} = \text{CH} - \ldots - \text{COOH} \\
\omega-3 \text{ desaturase} & & \\
\omega-3 \text{ FA} : & & \text{CH}_3\text{-CH}_2\text{-CH} = \text{CH} - \text{CH}_2\text{-CH} = \text{CH} - \ldots - \text{COOH}
\end{align*} \]
fat-1 mouse

Humanized fat-1 (optimized codon usage)

Microinjection of the gene into fertilized egg

Fat-1

Wild Type

http://www.llmt.org/research_fat1_mouse_model.htm
mouse endometriosis model

(recipient)

OVX  Em injection  ♦

-2 -1 0 1 2 3 (weeks)

= estradiol

(donor)

OVX  hysterectomy

Development of endometriotic lesions in fat-1 and wild type mice.

![Graph showing number of lesions and weight per lesion for WT and fat-1 mice.](image-url)
IL-6 expression in peritoneal macrophages derived from fat-1 and wild type mice.

lipoxigenases may act as coactivators of peroxisome-proliferator activator receptor-g (PPAR-g). This
The number of endometriotic lesions between wild type and 12/15-LOX-KO mice with or without EPA administration.
• Omega-3 fatty acids may suppress the endometriosis-associated inflammation and the growth of endometriotic lesion.

• The effect may partially be exerted by the metabolites converted by 12/15-LOX.
Vitamins
Vitamin A, Retinoic acids

- Fruit and vegetable consumption and risk of endometriosis
  - Harris HR, et al. Hum Reprod 2018

- Retinoic acid has the potential to suppress endometriosis development

- Retinoic acid biosynthesis is impaired in human and murine endometriosis
  - Pierzchalski K et al. Biol Reprod 2014

- Retinoic acid suppresses growth of lesions, inhibits peritoneal cytokine secretion, and promotes macrophage differentiation in an immunocompetent mouse model of endometriosis

- Retinoic acid suppresses interleukin-6 production in human endometrial cells
Vitamin C, Vitamin E

• Vitamin C is effective for the prevention and regression of endometriotic implants in an experimentally induced rat model of endometriosis
• Effect of vitamin C on the growth of experimentally induced endometriotic cysts
• A prospective cohort study of Vitamins B, C, E, and multivitamin intake and endometriosis
• Antioxidant supplementation reduces endometriosis-related pelvic pain in humans
  – Santanam N et al. Transl Res 2013
Vitamin D
Production and metabolism of vitamin D

25(OH)VD₃
Calcidiol
Storage form
Half life 15d

1,25(OH)₂VD₃
Calcitriol
Active form
Half life 15h

Increase calcium and phosphorus absorption
Mobilize calcium stores
Maintain serum calcium and phosphorus
Serum 25(OH) vitamin D concentrations and season-specific correlates in Japanese adults.

Figure. Distribution of serum 25-hydroxyvitamin D concentrations by survey season and sex
Prospective cohort study: 1385 endometriosis cases/ 69171 controls.

Women in the highest quintile of predicted vitamin D level had a 24% lower risk of endometriosis than those in the lowest quintile.

Vitamin D ↓ in endometriosis

In vivo experiments may be true, but mechanism?
The serum levels of $25$(OH)$D_3$

(October to March)
The effect of VD on IL-1α- and TNF-β-induced IL-8 expression in endometriotic stromal cells (ECSs)

The effect of VD on IL-1β-induced PGE2 secretion and mRNA expression of PGE2 synthesis and degradative enzyme by ESCs
The effect of VD on ESC number, DNA synthesis in ESCs

![Viability and BrdU incorporation graphs showing the effect of Vitamin D on ESCs.]

The effect of VD MMP-2 and MMP-9 mRNA expression in ESCs

![MMP-2 and MMP-9 mRNA level graphs showing the effect of Vitamin D on ESCs.]

Summary 3

• Vitamin D may suppress the development of endometriosis by inhibiting inflammation, proliferation and invasion of endometriotic stromal cells.

• Low Vitamin D levels may be a risk factor of endometriosis.
Conclusion

- Diet and supplements are suitable for the life-long management of endometriosis.
- Metabolic factors such as leptin, adiponectin, fatty acids may be important substances to develop dietary treatment of endometriosis.
- Vitamins including vitamin D may also be important to treat endometriosis.
- Further studies to develop ideal diet and supplements to prevent/ manage endometriosis are required.