CKD and gut microbiome

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2018.3.14. OECD & HUGO iin Yokohama
Eleveated uremic toxins are CVD and CKD risk

Gut
- Tryptophan
- Tyrosine
- Phosphatidylcholine

micobiota
- Indole
- p-Cresol
- Trimethylamine

Liver
- Indoxyl sulfate
- p-Cresylsulfate
- TMAO

Survival (%)
- Overall Cumulative Survival
  - Time (days)
    - 0 200 400 600 800
    - 1.0 0.8 0.6 0.4 0.2 0.0
  - p=0.001

Concentration
- Low
- High

Barreto FC. CJASN 4: 1551, 2009
Wu WI NDT 26: 938, 2011
“Gut-cardio-renal axis”

- Heart disease
- Gut-derived metabolites
- Renal disease
- Dysbiosis
- Constipation
- Dietary intake
- Hypertension
- Fibrosis
- Heart failure
- Atherosclerosis

Malignant cycle

- Inflammation
- Fibrosis
- Renal failure

Heart disease
Metabolites in Germ-free mice

**Gut-derived**

In plasma

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>SPF-C</th>
<th>SPF-KD</th>
<th>GF-C</th>
<th>GF-KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoxyl sulfate</td>
<td></td>
<td>25</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Cholate</td>
<td>0</td>
<td>15</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Hippurate</td>
<td>0</td>
<td>15</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>p-CS</td>
<td></td>
<td>1500</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Phenyl sulfate</td>
<td></td>
<td>15</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

**Gut and Diet-derived**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>SPF-C</th>
<th>SPF-KD</th>
<th>GF-C</th>
<th>GF-KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMAO</td>
<td></td>
<td>22</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Phenaceturate</td>
<td></td>
<td>6</td>
<td>N.D.</td>
<td>N.D.</td>
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</tbody>
</table>

microbiota-derived

Diet-derived

**Host-derived**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>SPF-C</th>
<th>SPF-KD</th>
<th>GF-C</th>
<th>GF-KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMG</td>
<td></td>
<td>30</td>
<td>N.D.</td>
<td>N.D.</td>
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<tr>
<td>γ-GB</td>
<td></td>
<td>30</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>Glutarate</td>
<td></td>
<td>30</td>
<td>N.D.</td>
<td>N.D.</td>
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<tr>
<td>2-Hydroxy pentanoate</td>
<td>80</td>
<td>60</td>
<td>N.D.</td>
<td>N.D.</td>
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</tbody>
</table>

*Mishima E. Kidney Int. 92:634, 2017*
Diet-induced TMAO level in healthy volunteers

Concentration after meal

Concentration among protein diet

Gut microbiota diversity

Adaptations to hydrostatic pressure by TMAO

<table>
<thead>
<tr>
<th>Common name</th>
<th>Habitant</th>
<th>TMAO (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantic jack mackerel</td>
<td>Marine</td>
<td>2000</td>
</tr>
<tr>
<td>Hairtail</td>
<td>Marine</td>
<td>1300</td>
</tr>
<tr>
<td>Red snapper</td>
<td>diadromous</td>
<td>2600</td>
</tr>
<tr>
<td>Atlantic salmon</td>
<td>diadromous</td>
<td>380</td>
</tr>
<tr>
<td>Japanese sillago</td>
<td>Marine</td>
<td>340</td>
</tr>
<tr>
<td>Sea bass</td>
<td>Marine</td>
<td>290</td>
</tr>
<tr>
<td>Striped bonito</td>
<td>Marine</td>
<td>180</td>
</tr>
<tr>
<td>Japanese eel</td>
<td>diadromous</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Yancey PH. Comp Biochem Physiol A Mol Integr Physiol. 133: 667, 2002
Chung SW. Food Addit Contam Part B 2: 44, 2009
Heart disease

Gut-derived metabolites

Malignant cycle

Renal disease

Diet control
Intervention

Dysbiosis
Constipation
Dietary intake

Hypertension
Fibrosis
Heart failure

Heart disease

Atherosclerosis

inflammation
Fibrosis
Renal failure

"Gut-cardio-renal axis"
Constipation and renal failure

Chronic Kidney disease (CKD)

End-stage renal failure (CKD)

Sumida K. *JASN*, 28: 1248, 2017
Lubiprostone ameliorates the progression of CKD

Lubiprostone (Lub.)

Drug for constipation
CIC-2 chloride channel activator

Adenine-induced renal failure mouse

![Lub. mouse illustration]

Uremic toxin

Indoxyl sulfate

\[
\text{μM} \quad \text{cont} \quad \text{RF} \quad \text{RF+Lub.}
\]

\[0 \quad 50 \quad 100 \quad 200\]

*p*

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Uremic toxins are from gut microbiota

Diet control

Gut

tryptophan
choline
carnitine

Microbiota

TMAO (Trimethylamine-N-Oxide)

Intervention

TMA
TMAO

Heat failure

Renal failure

Further Retention in circulation

TMAO

Indoxyl sulfate (IS)

Indoxyl

Atherosclerosis

Liver

Diet

Intervention