Obesity and Adiposity-Related CKD Subgroups and Metabolites

Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study


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Study Background & Aim

- Chronic kidney disease (CKD) patients are a heterogeneous population.
- Obesity and excessive adiposity increases the risks of adverse outcomes of CKD.
- “Obesity-paradox” and CKD survival is not fully understood.

- Aim: we propose to identify distinct “adiposity-obesity-related” (AOR) CKD subgroups and to perform analysis on high-dimensional metabolomics data with CKD subgroups and clinical endpoints.

Methods

Study population: 1,529 of 3,939 participants from Chronic Renal Insufficiency Cohort (CRIC) Study, an NIDDK-funded, multi-center, longitudinal cohort of well-characterized adults with CKD in the U.S.

- 1,529 subjects with metabolomic measurements at CRIC year 1 visit
- 20 adiposity-obesity parameters from BL (No outcome)
- AI algorithm Consensus Clustering
- Examine potential number of clusters: 2, 3, …, 8 (K-mean)
- Metabolomics analysis: Uni/multivariable regression model
  - Bonferroni cut-off: \( p < 0.05/634 = 7.9 \times 10^{-5} \)
- Survival analysis: Cox regression model
  - 6 endpoints: CKD progression (×2), CVD (×3) and death
- Model adjustment: age, gender, race, eGFR, Log(UACR), smoking and CVD history
Arise from the adiposity-obesity data pattern of 20 variables, we identified three distinct CKD adiposity-obesity related (AOR) subgroups in a CKD population.

- **Low DM/Ob risk group** has relatively low prevalence of diabetes, preferable diabetic markers and obesity profiles, and uses less medications; the kidney function is the most optimal among all three groups.

- **High Ob risk group** has low HDL, relatively high prevalence of diabetes and high insulin resistance level and non-preferable obesity profiles.

- **High DM risk group** has average obesity risks but relatively high prevalence of diabetes WITHOUT adequate glycemic control and uses more diabetes medications; has more proteinuria.
Compared to CKD patients with low DM and obesity risks (ref) with confounder adjustment,

- High DM risk is associated with 87% increased hazard for eGFR halving and ESRD and 85% increased hazard for ESRD.
- High obesity risks is associated with 2.5 times increased hazard for CHF, and 2.1 times increased hazard for composite CVD outcome of CHF, MI, stroke and PAD.

### Metabolites significantly associated (adjusted) with AOR subgroups (p<7.9×10⁻⁵)

<table>
<thead>
<tr>
<th>Metabolite pathway</th>
<th>N</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td>146</td>
<td>81.56</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>12</td>
<td>6.7</td>
</tr>
<tr>
<td>Organic acids and derivatives</td>
<td>6</td>
<td>3.35</td>
</tr>
<tr>
<td>Cofactors and Vitamins</td>
<td>4</td>
<td>2.23</td>
</tr>
<tr>
<td>Nucleotide</td>
<td>4</td>
<td>2.23</td>
</tr>
<tr>
<td>Organic oxygen compounds</td>
<td>3</td>
<td>1.68</td>
</tr>
<tr>
<td>Organoheterocyclic compounds</td>
<td>2</td>
<td>1.12</td>
</tr>
<tr>
<td>Xenobiotics</td>
<td>2</td>
<td>1.12</td>
</tr>
<tr>
<td>(missing)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>179</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Among 634 known metabolites, 179 metabolites are significantly associated with AOR subgroup.

- 82% lipids metabolites
- 7% amino acid metabolites

### Kaplan-Meier curves

- **p < 0.0001**
  - Cluster 2: 1.873 (1.541, 2.278)
  - Cluster 3: 1.283 (1.038, 1.585)

- **p < 0.0001**
  - Cluster 2: 1.616 (1.213, 2.153)
  - Cluster 3: 2.451 (1.835, 3.274)

- **p < 0.0001**
  - Cluster 2: 1.514 (1.206, 1.900)
  - Cluster 3: 2.055 (1.626, 2.598)
Conclusions

• With consensus clustering and metabolomics analysis, we discovered three distinct AOR subgroups of CKD patients that were associated with numerous metabolites and different risks of clinical endpoints.

• Novel biomarkers that co-segregate with different patient subgroups could shine a light on the obesity related biology of CKD.