Untargeted metabolomics indicates impaired reverse transport of cholesterol in young lean PCOS patients

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 6–10% of reproductive-aged women. PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries in its complete phenotype. PCOS carries an elevated prevalence of impaired glucose tolerance, T2D and metabolic syndrome. Symptoms of PCOS often manifest during adolescence making this an important time for the study of early biomarkers, recognition and intervention to prevent adverse metabolic outcomes.

2. GOALS

The aim of this study is to apply our metabolomic approach to discover new biomarkers of PCOS. Serum samples of young PCOS patients and healthy controls using LC-QTOF MS and NMR were analyzed.

3. MATERIALS AND METHODS

NMR lipoprotein profile
NMR metabolic profile
Untargeted metabolomics

Data Processing

# mZRT=51908
(i) analytical variability
# mZRT=38377
(ii) features intensity
# mZRT=4704
(iii) hypothesis testing + fold change
# mZRT=250
(iv) Hits into databases
# mZRT=80

Validation using LC-QQQ

11 metabolites identified

Fragmentation experiments (QTOF)

4. RESULTS

Untargeted metabolomics

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>p-value</th>
<th>% variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>0.047-05</td>
<td>-544</td>
</tr>
<tr>
<td>Methionine Sulfoxide</td>
<td>1.77F-03</td>
<td>40</td>
</tr>
<tr>
<td>S-oxoproline</td>
<td>4.98E-03</td>
<td>30</td>
</tr>
<tr>
<td>Tau-Ne</td>
<td>1.53F-02</td>
<td>28</td>
</tr>
<tr>
<td>Glu-Cys</td>
<td>1.50F-04</td>
<td>37</td>
</tr>
<tr>
<td>Glu-Glu</td>
<td>2.70E-02</td>
<td>55</td>
</tr>
<tr>
<td>Glutamate</td>
<td>6.04E-03</td>
<td>33</td>
</tr>
<tr>
<td>GSH</td>
<td>3.68E-02</td>
<td>34</td>
</tr>
<tr>
<td>GSH/GSSG</td>
<td>2.30F-02</td>
<td>23</td>
</tr>
<tr>
<td>Glu-Taurine**</td>
<td>3.03F-07</td>
<td>73</td>
</tr>
<tr>
<td>Glu-Cys</td>
<td>3.10F-02</td>
<td>-18</td>
</tr>
</tbody>
</table>

Lipoprotein profile

Methionine oxidation impairs reverse cholesterol transport by apoprotein AI
Met-148 residue in apo-AI changes the 3D structure of the protein impairing the LCAT activity in HDL lipoproteins

HYPOTHESIS: PCOS patients present greater oxidation of methionine residues in apo-AI relative to healthy women, and the increased levels of free methionine sulfoxide in PCOS may result from the turnover and degradation of these apo-AI protein

PCOS women shows increased levels of MetOx/Met-148 ratio in apo-AI

Levels of methionine sulfoxide in serum are positively correlated with oxidation levels of apo-AI

5. CONCLUSIONS

Untargeted metabolomic approach has revealed that γ-glutamyl cycle and oxidative stress is involved in PCOS disease.

Elevated levels of methionine sulfoxide in serum, oxidized methionine-148 in apo-AI, and the lipoprotein profile might constitute earlier biomarkers of metabolic syndrome.