A Reduced Serum Level of Total Osteocalcin in Men Predicts Development of Diabetes in a Long-term Follow-up Cohort

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Background

Crosstalk between bone and energy metabolism

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Background

- Osteocalcin (OC), an osteoblast specific protein
- recently been demonstrated to affect glucose and energy metabolism
Osteocalcin

- 49-residual polypeptide
- Vitamin K-dependent for carboxylation
- 3 Gla residual can be carboxylated $\Rightarrow$ producing carboxylated osteocalcin of different status
- Mostly deposited in extracellular bone matrix
Osteocalcin

- Serum OC represent fraction of total OC
- Undercarboxylated osteocalcin (ucOC) is the active circulating fraction
- Effects adipocytes and pancreatic beta-cells
Ocn -/- mice

- When compare to wild type
  - ↑ fat mass and abnormal glucose metabolism
  - Higher basal glucose
  - Lower insulin level
    - ↓ insulin secretion
    - ↓ beta cell mass and proliferation

Osteocalcin

- Model of OC gain of function
  - Protected from obesity
  - Normal glucose tolerance and insulin sensitivity

- Recombinant ucOC
  - in wide type mice
    - Trigger expression of Insulin, beta cell proliferation marker
    - Increase in serum insulin level

Osteocalcin

- Studies in humans – cross-sectional
  - Plasma total OC has been shown to inversely related to
    - fat mass, BMI
    - plasma glucose
    - Fasting insulin
    - Insulin sensitivity
  - Relative role of total OC vs. ucOC unclear
Objective

- Examine serum osteocalcin and its posttranslational forms as potential biomarkers for future development of type 2 diabetes.
Methods

- A nested case-control study using data from the Electricity Generating Authority of Thailand (EGAT) Study
- Thai cohort
  - 2,677 individuals,
  - 35–55 years,
  - 10 years follow-up (1998-2008)
- In the exploratory cohort, we identified
  - 63 men without diabetes at baseline who developed type 2 diabetes (DM) during the follow-up period
  - 63 men age and BMI-matched for non-diabetes control (non-DM).
Methods

- Baseline blood samples
  - Serum N-mid OC and UCOC were measured.

- Logistic regression models
  - to explore and identify baseline factors, including OC, ucOC, and ucOC/OC ratio that predicted incident diabetes.

- Data were presented as mean ± SEM
### Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-DM</th>
<th>DM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>47.2 ± 0.5</td>
<td>47.8 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 0.5</td>
<td>25.9 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circ. (cm)</td>
<td>87.4 ± 1.9</td>
<td>90.5 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>29(46.0%)</td>
<td>20(31.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.92 ± 0.04</td>
<td>5.28 ± 0.07</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>88.6 ± 0.8</td>
<td>95.0 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>OC (ng/mL)</td>
<td>15.16 ± 0.49</td>
<td>13.04 ± 0.48</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ucOC (ng/mL)</td>
<td>1.51 ± 0.14</td>
<td>1.10 ± 0.11</td>
<td>NS</td>
</tr>
<tr>
<td>ucOC to OC ratio</td>
<td>0.10 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>
Relation between ucOC and OC

$R = 0.4, P < 0.001$
Relation between OC, log ucOC, ucOC/OC ratio and baseline FPG

OC was negatively related to baseline FPG \( (r = -0.27, P < 0.001) \)

\[ OC, R = -0.27, P < 0.01 \]
Relation between OC, log ucOC, ucOC/OC ratio and baseline FPG

No correlation between log ucOC (r = -0.07, NS) or ucOC/OC ratio to FPG (r = 0.04, NS) was found.
Multiple logistic regression analysis: Incident diabetes per one unit change in OC, ucOC or ucOC to OC ratio (Odds ratio and 95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Baseline FPG (mmol/L)</td>
<td>1.09 (1.04-1.15)</td>
<td>&lt; 0.01</td>
<td>1.10 (1.04-1.16)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.99 (0.91-1.07)</td>
<td>NS</td>
<td>0.99 (0.91-1.07)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.01 (0.91-1.13)</td>
<td>NS</td>
<td>1.03 (0.92-1.15)</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>0.46 (0.20-1.04)</td>
<td>NS</td>
<td>0.46 (0.21-1.04)</td>
</tr>
<tr>
<td>OC (ng/mL)</td>
<td>0.90 (0.81-0.99)</td>
<td>&lt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>ucOC (ng/mL)</td>
<td>-</td>
<td>-</td>
<td>0.71 (0.47-1.06)</td>
</tr>
<tr>
<td>ucOC to OC ratio</td>
<td>-</td>
<td>-</td>
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adjusted for baseline FPG, age and BMI
- **Model 1** OC adjusted for baseline FPG, age, BMI and exercise.
- **Model 2** ucOC adjusted for baseline FPG, age, BMI and exercise.
- **Model 3** ucOC to OC ratio adjusted for baseline FPG, age, BMI and exercise.
Results: Multiple logistic regression

- The analysis revealed independent risk factors for development of diabetes in this long term cohort
  - N-mid OC
  - Glucose
Conclusion

- Circulating total OC is associated with incident diabetes in males.
- Further studies to evaluate the potential utility of OC as a biomarker to predict the development of type 2 diabetes are warranted.