Elevated Serum Levels of Adropin in Patients with Type 2 Diabetes Mellitus and its Association with Insulin Resistance

Mehrnoosh Shanaki, Ph.D.
Assistant Professor of Clinical Biochemistry
Shahid Beheshti University of Medical Sciences
Outline

• **Introduction:**
  - Type 2 Diabetes Mellitus
  - Metabolic Homeostasis
  - Adropin

• **Methods**

• **Results**

• **Discussion & conclusion**
Introduction
Pathogenesis of T2DM
Metabolic homeostasis

- Peptides secreted from peripheral organs regulate metabolism in key insulin-target tissues and are important for energy homeostasis and maintaining insulin sensitivity.
Metabolic homeostasis in pathogenesis of T2DM

- Role of molecules involved in regulation of metabolic homeostasis and complicated interactions between its components in pathogenesis of T2DM.
Adropin

A metabolic homeostasis-related protein (novel secreted peptide)

liver / brain

Peripheral tissues

Energy Homeostasis
Associated gene (Enho)
Adropin

Regulation of:
Carbohydrate and lipid metabolisms

To prevent:
- Insulin resistance
- Dyslipidemia
- Impaired glucose tolerance
Methods
Study Population

Blood Sampling

Serum Separation

ELISA
Patient selection

40 (men) / 40-65 years

T2DM, based on ADA criteria

✓ FBG $\geq 126$ mg/dL or
✓ OGTT $\geq 200$ mg/dL or
✓ Random blood glucose $\geq 200$ mg/dL or
✓ HbA1c $> 6.5$

Healthy subjects

40 Men with 40-65 years

Exclusion criteria

✓ Chronic liver and renal disease
✓ History of inflammatory
✓ Infectious
✓ Malignant diseases
Laboratory & anthropometric data recorded

- Age
- Height
- Weight
- BMI
- Consumed drugs
- FBS
- Lipid profile (TG, TC, LDL-c, HDL-c)
- HbA1c
- HOMA-IR
- Adropin Elisa
Results
Demographic and Clinical Characteristics of T2DM patients and controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Controls</th>
<th>T2DM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.88 ± 7.31</td>
<td>61.25 ± 6.94</td>
<td>0.140</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.21 ± 0.58</td>
<td>25.62 ± 3.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²</td>
<td>0 (0%)</td>
<td>16 (40%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>85.12 ± 2.43</td>
<td>89.23 ± 3.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HC (cm)</td>
<td>93.41 ± 1.05</td>
<td>92.69 ± 0.94</td>
<td>0.002</td>
</tr>
<tr>
<td>WHR</td>
<td>0.91 ± 0.03</td>
<td>0.96 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFA (%)</td>
<td>27 (67.5%)</td>
<td>38 (95%)</td>
<td>0.002</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>80 (72-87)</td>
<td>108 (87-132)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>9.35 (7.7-14)</td>
<td>14.75 (12-22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.81 (1.41-2.63)</td>
<td>4.57 (3.53-7.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.88 ± 0.85</td>
<td>8.17 ± 1.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>44 (38-49)</td>
<td>31 (25-36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>102 (88-112)</td>
<td>70 (49-98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>144 (101-175)</td>
<td>150 (105-188)</td>
<td>0.567</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>135 (114-151)</td>
<td>136 (105-160)</td>
<td>0.725</td>
</tr>
</tbody>
</table>

Continuous variables are described as mean ± SD for normally distributed data, but non-parametric variables are presented as median (interquartile range: P25-P75). Categorical variables are described as frequencies. Differences between cases and controls are obtained based on Student's t-test or Mann-Whitney U test, where indicated for continuous variables. Chi-square test was performed for categorical variables.

BMI, Body Mass Index; WC, Waist Circumference; HC, Hip Circumference; WHR, waist to hip ratio; CFA (central fat accumulation) was defined as WHR ratio ≥ 0.9
FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin;
LDL-c, Low Density Lipoprotein Cholesterol; HDL-c, High Density Lipoprotein Cholesterol;
TG, Triglyceride; TC, Total Cholesterol; T2DM, Type 2 Diabetes Mellitus
HOMA-IR, Homeostatic Model Assessment of Insulin Resistance
Adropin Levels

Mann-Whitney U test  p-value=0.004
Receiver operating characteristic (ROC) curve

2.25 ng/ml

Sensitivity=57.5%
Specificity=82.5%
Correlations

• Adropin levels were inversely correlated with FBG (Spearman's rho= -0.335; p=0.017).

• Adropin levels were inversely correlated with HOMA-IR (Spearman's rho= -0.391, p=0.024).
Discussion
Animal & human studies….

Adropin

Metabolic homeostasis

Insulin sensitivity

Improve glucose tolerance

Prevention of dyslipidemia

Glut4
Akt phosphorylation
Regulation of FA oxidation
Animal & human studies....

- Adropin deficient mice have increased body weight due exclusively to increased fat mass (Kumar et al, 2012).

- Reversal of obesity and metabolic syndrome after Roux-en-Y gastric bypass leads to increased adropin levels (Butler et al, 2012)

T2DM patients with normal weights produce more adropin
Conclusion

• These data show that T2DM patients have higher adropin levels, which seem to be a feedback response to high glucose levels.

• To assess adropin therapeutic roles in T2DM patients
Thank you for your attention
## Logistic Regression

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>( p )-value</th>
<th>OR</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate Model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adropin ( \geq 2.25 ) ng/ml</td>
<td>1.853</td>
<td>0.525</td>
<td>12.463</td>
<td>(&lt;0.001)</td>
<td>6.378</td>
<td>2.280 - 17.842</td>
</tr>
<tr>
<td><strong>Adjustment for FBG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adropin ( \geq 2.25 ) ng/ml</td>
<td>1.867</td>
<td>0.628</td>
<td>8.824</td>
<td>0.003</td>
<td>6.467</td>
<td>1.887 - 22.164</td>
</tr>
<tr>
<td>FBG</td>
<td>0.073</td>
<td>0.021</td>
<td>11.805</td>
<td>(&lt;0.001)</td>
<td>1.076</td>
<td>1.032 - 1.122</td>
</tr>
<tr>
<td><strong>Adjustment for LDL-c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adropin ( \geq 2.25 ) ng/ml</td>
<td>1.658</td>
<td>0.615</td>
<td>7.265</td>
<td>0.007</td>
<td>5.248</td>
<td>1.572 - 17.519</td>
</tr>
<tr>
<td>LDL-c</td>
<td>-0.056</td>
<td>0.014</td>
<td>15.091</td>
<td>(&lt;0.001)</td>
<td>0.946</td>
<td>0.919 - 0.973</td>
</tr>
<tr>
<td><strong>Adjustment for HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adropin ( \geq 2.25 ) ng/ml</td>
<td>2.247</td>
<td>0.986</td>
<td>5.192</td>
<td>0.023</td>
<td>9.462</td>
<td>1.369 - 65.382</td>
</tr>
<tr>
<td>HbA1c</td>
<td>2.493</td>
<td>0.734</td>
<td>11.537</td>
<td>(&lt;0.001)</td>
<td>12.097</td>
<td>2.870 - 50.980</td>
</tr>
<tr>
<td><strong>Adjustment for HOMA-IR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adropin ( \geq 2.25 ) ng/ml</td>
<td>2.961</td>
<td>1.231</td>
<td>5.787</td>
<td>0.016</td>
<td>19.311</td>
<td>1.731 - 215.494</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.940</td>
<td>0.646</td>
<td>9.019</td>
<td>0.003</td>
<td>6.961</td>
<td>1.962 - 24.698</td>
</tr>
</tbody>
</table>

FBG, Fasting Blood Glucose; LDL-c, Low Density Lipoprotein Cholesterol; HbA1c, Glycated Hemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance
Discussion

• Serum and urine adropin levels are significantly higher in diabetic patients compared to healthy controls (Ugur et al).

• Administration of recombinant adropin has been demonstrated to reverse insulin resistance and dyslipidemia in mice (Kumar et al).

• Adropin treatment of diet-induced diabetic mice enhances glucose tolerance, improves insulin resistance (Gao et al).
System Integration and Homeostasis

• Metabolic homeostasis are the integration of metabolism at the cellular and the organ tissue levels

• These processes of integration are essential for the survival of the entire organism which receives its direction from body system
The term “adropin” was coined by merging the first three letters of two Latin words: adura, which means “to set fire to”, and pinquis, which means “fats or oils”. Adropin is coded by the Energy Homeostasis Associated genes, and is symbolized as “enko” [74]. This abbreviation will be used throughout this review to refer to the Energy Homeostasis Associated gene. Adropin contains 76 amino acids and has a molecular weight of 4499.9 Da. Human, mouse, and rat adropin amino acid sequences are 100% identical. Fig. 1 presents the amino acid sequencing of adropin. The half-life of adropin has not been identified yet. However, it is assumed that the half-life of this peptide hormone is as short as several minutes, because the half-lives of peptide hormones range between 3 and 30 min. The normal adropin concentration in the blood varies between 3.1 ± 1.3 ng/mL [32], 3.4–4.5 ng/mL [28] and around 10 ng/mL [11]. The normal adropin concentration in human milk varies from approximately 9–14.5 ng/mL [11]. Urine adropin levels were found to be approximately 4 times higher than that of corresponding serum adropin concentrations.