Decreased Plasma Levels of CTRP5 in Patients with Type 2 Diabetes and NAFLD in Comparison with Healthy Subjects

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Non-Alcoholic Fatty Liver Disease (NAFLD)

- non-alcoholic steatohepatitis (NASH)
- simple steatosis
- cirrhosis
- hepatocellular carcinoma
C1q/TNF-related protein (CTRP) family

proteins that share adiponectin's metabolic regulatory function and structure
Evidences for Roles of CTRPs in pathogenesis of metabolic disease

- Overexpression of CTRP1 is involved in improvement of insulin sensitivity in transgenic mice.

- Transgenic animal models overexpressing CTRP3 are resistance to diet-induced steatosis.

- Overexpression of CTRP9 in mice:
  - To reduce hepatic and skeletal muscle triglyceride levels
  - To improve hepatic steatosis in diet-induced obesity
Evidences for Roles of CTRPs in pathogenesis of metabolic disease

- High serum levels of CTRP1 in
  - diabetic patients
  - subjects with metabolic syndrome

- High CTRP3 levels in metabolic syndrome patients and its association with cardiometabolic parameters

- Our recent data showed that circulating levels of CTRP1 are significantly increased in patients with NAFLD and T2DM compared to healthy subjects
✓ To be initially recognized as a molecule involved in:
  - late-onset macular degeneration
  - long anterior lens zonules

✍ To be expressed in:
  ✓ adipocytes, (particularly in the stromal vascular cell fraction)
  ✓ spleen
  ✓ Liver
  ✓ testis
  ✓ brain
  ✓ retinal pigment
  ✓ myocytes
Why CTRP-5?

- To induce phosphorylation of AMP-activated protein kinase (AMPK):
  - To stimulate glucose uptake
  - To stimulate fatty acid oxidation

- Circulating CTRP5 is elevated in animal models of obesity-associated diabetes.

- CTRP5 might be a human adipokine with large quantities in serum.

- SNP in 3’-UTR of CTRP5 is associated with metabolic syndrome.
So...

- To investigate circulating levels of CTRP5 in patients with NAFLD, T2DM and NAFLD+T2DM compared with controls.
- To study the association between CTRP5 levels with some NAFLD and diabetes-related parameters.
Methods

To select patients and control

To collect venous blood in heparinized tubes and clot activator tube to separate plasma and serum

Liver stiffness assessment
Methods (cont.)

- **Anthropometric and clinical characterization**
- **Biochemical and laboratory measurements**
  - CTRP5 measurement
- **Data analysis**
# Subject inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Patients with NAFLD</th>
<th>Control group N=21</th>
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<tbody>
<tr>
<td>outpatient clinic of Shariati Hospital, Tehran, Iran</td>
<td>Subjects age and sex matched with patients</td>
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<tr>
<td>To diagnose according clinical and bright liver on ultrasound imaging and increased liver function tests</td>
<td>Normal liver on ultrasound imaging and normal liver function tests according questionnaire</td>
</tr>
<tr>
<td>NAFLD Patients without type 2 diabetes (NAFLD) N=22</td>
<td>NAFLD Patients with type 2 diabetes (NAFLD+T2DM) N=22</td>
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<td></td>
<td>Patients with T2DM (T2DM) N=22</td>
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**Exclusion Criteria:**
- viral or autoimmune hepatitis,
- Wilson’s disease,
- primary biliary cirrhosis,
- haemochromatosis,
- congenital cardiac disease,
- infectious disease,
- acute or chronic renal failure,
- malignancies,

  all patients were free from taking medication that could cause steatosis.
Discussion
Our findings of lower CTRP5 levels in patients with NAFLD and T2DM than in controls, are partly in line with:

- **Flehmig G et al. (2014)**: CTRP5 levels tended to be higher (albeit not significantly) in obese individuals without diabetes than those in obese subjects with diabetes.
- **Flehmig G et al. (2014)**: CTRP5, along with other adipokines, is related to several parameters of glucose metabolism, lipid metabolism, and fat mass.

Inconsistent with:

- **Park SY et al. (2009)**: CTRP5 levels were increased in animal models of diabetes.
- **Choi HY et al. (2013)**: No association between circulating CTRP5 levels with insulin resistance index or other cardiometabolic risk factors.
After adjustment for HOMA-IR and BMI:

- The association between low levels of CTRP5 with NAFLD, T2DM and NAFLD+T2DM was weakened, albeit it was remained significant.
Possible mechanisms

To treat myocytes recombinant CTRP5
  To activation AMPK
    To enhance GLUT4 translocation
      To enhance Glc uptake

To treat myocytes and liver cells with CTRP5
  To activation AMPK
    To increase fatty acid oxidation
      To decrease fatty acid synthesis
Low levels of CTRP5

Disturbances in fatty acid oxidation and subsequent excessive lipid storage
Impaired Glc uptake

NAFLD and T2DM
Limitations

• Relatively small sample size

• The study design is cross-sectional:
  – To precludes drawing inferences about causality

• Lack of measurements of other adipokines and inflammatory markers.
THANKS FOR YOUR ATTENTION