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Clinical implication of changes in serum adiponectin in patients with hepatogenic diabetes

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Adiponectin is a protein hormone that modulates glucose metabolism and fatty acid oxidation. We explored the clinical implication of serum adiponectin in hepatogenic diabetes. Serum adiponectin levels were determined using enzyme–linked immunochemistry assay in 78 individuals including 19 hepatogenic diabetes, 20 type 2 diabetes (T2D), 20 chronic liver disease and 19 healthy controls. Cases and controls were matched by gender and body mass index (BMI). There is no difference in serum adiponectin levels among hepatogenic diabetic, T2D and healthy control groups. The levels of adiponectin are highest in chronic liver disease and lowest in T2D. Insulin levels are highest in hepatic diabetics and lowest in T2D. Hepatic diabetics have the lowest insulin sensitivity index (ISI). Serum adiponectin levels were negatively correlated with triglycerides and total cholesterol in T2D. Serum adiponectin is significantly increased in chronic liver disease, but lacks association with hepatogenic diabetes.

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Results
The differences in age, waist, body mass index (BMI), serum adiponectin, fasting glucose, fasting insulin, total cholesterol, triglycerides, and insulin sensitivity index (ISI) were compared among the four groups (Table 1).

Plasma adiponectin levels. A significant difference in plasma adiponectin levels was observed among the four groups (P < 0.01). Patients with chronic liver disease had the highest, followed by the healthy control and hepatogenous diabetic group, T2D had the lowest level of adiponectin.

Fasting glucose. There was a significant difference in fasting glucose levels among the four groups (P < 0.01). Compared to healthy controls or patients with chronic liver disease, T2D and hepatogenous diabetics had increased fasting glucose levels (P < 0.05).
Triglycerides clinical application. Thus amendments have been proposed to insulin clamp technique; however, the high expense has limited its concentrations of the adiponectin are decreased in parallel with therapeutic target of hepatogenic diabetes. Insulin resistance has been role of adiponectin in hepatic diabetes is unclear. We are interested in insulin resistance and enhance peripheral tissue sensitivity to insulin, Recent studies suggest that adiponectin can significantly improve Discussion Fasting insulin. We found a significant difference in fasting insulin levels among four groups were (P < 0.01). Higher levels of fasting insulin were detected in T2D and hepatogenous diabetics than in healthy controls or chronic liver disease (P < 0.01). T2D patients had even higher insulin levels than hepatogenic diabetics (P < 0.01).

Triglycerides. T2D had higher triglycerides than other subjects (P < 0.05).

Total cholesterol. T2D showed increased total cholesterol levels than other subjects (P < 0.01).

Insulin sensitivity Index (ISI). Patients with hepatogenous diabetes presented significantly decreased ISI compared with other subjects (P < 0.01).

Correlation of serum adiponectin with other clinical indicators. Serum adiponectin levels negatively correlated with triglycerides and total cholesterol levels in all subjects as demonstrated in Table 2. Compared with healthy control, serum adiponectin levels in T2D negatively correlated with triglycerides and total cholesterol levels, but positively correlated with ISI (P < 0.01) as illustrated in Table 3.

Table 1 | Clinical indicator (mean ± SD) in study population

| Groups                      | Healthy control (n = 19) | Hepatogenic diabetes (n = 19) | Type II diabetes (n = 20) | Chronic liver disease (n = 20) |
|-----------------------------|-------------------------|-----------------------------|--------------------------|-------------------------------|
| Age                         | 48.9 ± 4.5              | 53 ± 8.6                    | 57 ± 6.2                 | 51 ± 4.1                      |
| Waist (WC)                  | 21.7 ± 3.3              | 22.7 ± 2.6                  | 23.3 ± 1.8               | 22.0 ± 1.9                    |
| Adiponectin [μg/mL]         | 7.16 ± 3.45             | 5.56 ± 3.04                 | 2.84 ± 0.85              | 10.24 ± 6.23*                 |
| Glucose (mg/dL)             | 3.3 ± 2.5               | 8.8 ± 2.4                   | 9.6 ± 4.0                | 4.1 ± 2.0*                    |
| Insulin [μU/mL]             | 9.8 ± 3.1               | 15.5 ± 4.1                  | 8.2 ± 3.1*               | 10.6 ± 4.4*                   |
| Triglycerides (mmol/L)      | 1.22 ± 0.29             | 1.06 ± 0.64                 | 2.04 ± 0.51*             | 1.13 ± 0.30                   |
| Total cholesterol (mmol/L)  | 3.61 ± 0.46             | 3.32 ± 0.85                 | 5.53 ± 1.03*             | 3.28 ± 0.88                   |
| Insulin sensitivity index   | -1.66 ± 0.14*           | -2.04 ± 0.17                | -1.83 ± 0.24*            | -1.68 ± 0.21*                 |

*P < 0.05, comparison between hepatogenic diabetes and chronic liver disease.
*P < 0.05, comparison between hepatogenic diabetes and healthy control.
*P < 0.05, comparison between hepatogenic diabetes and type 2 diabetes.

Adiponectin levels were gradually reduced with the development of insulin resistance. In our study, patients with T2D had relatively low levels of baseline insulin compared to healthy controls. We suggest that some patients had low levels of insulin due to dysfunction in secretion or delayed peak at diagnosis.

Hepatogenous diabetes develops in chronic liver disease; especially liver cirrhosis and sex hormone metabolism disorders, where estrogen levels are elevated but androgen are relatively low, resulting in elevated levels of adiponectin. Interestingly, serum adiponectin levels in mice presented gender dimorphism, where the females had higher adiponectin than the males11. Adiponectin receptor 1 (AdipoR1) and 2 (AdipoR2) have been implicated in adiponectin hoist caused by hepatic diabetes12. Human AdipoR1 was expressed in skeletal muscle and AdipoR2 mainly in the liver. Hepatogenic diabetics may have reduced expression of AdipoRs and thus elevated serum adiponectin due to the destruction and dysfunction of liver cells5,13.

Adiponectin can be produced by human hepatoma HepG2 cells after treatment with IL-6 or damaged hepatocytes in response to CCl₄-induced injury in mice14. Adiponectin levels were elevated during the progression from chronic hepatitis B to liver fibrosis, which declined in response to antiviral therapy15. Serum adiponectin levels were significantly increased in liver cirrhosis, associated with the reaction of active inflammation in chronic liver disease16.

Adiponectin negatively regulates fatty acid oxidation. We found that the level of triglyceride and total cholesterol were lower in chronic liver disease and hepatogenic diseases, but higher in T2D. We observed increased insulin levels but decreased insulin sensitivity index in hepatogenic diabetes, which are consistent with a previous study16. Another study found no association between adiponectin levels and insulin resistance of varying degrees of liver cirrhosis16.

In our study, serum adiponectin in healthy controls and T2D negatively correlated with BMI, triglycerides and cholesterol, but positively correlated with ISI (P < 0.01) as illustrated in Table 3.

Table 2 | Correlation of serum adiponectin with clinical indicators

| R values | P values | R values | P values |
|----------|----------|----------|----------|
| Triglycerides | -0.279 | 0.013 | -0.485 | 0.001 |
| Total cholesterol | -1.6 | 0.043 | -7.11 | <0.001 |
| Insulin sensitivity index | 0.032 | 0.78 | 0.391 | 0.01 |

Table 3 | Correlation of serum adiponectin with other indicators in healthy controls and type II diabetics
by high-fat and high-sugar diet can lose weight and present reduced glucose, fatty acids, triglycerides and insulin resistance when treated with the globular domain of adiponectin\(^7\). Additionally, adiponectin could reduce glucose levels of murine type 1 diabetes by reducing hepatic glucose output\(^8\). In our study, adiponectin levels were lower in hepatic diabetics than healthy controls and chronic liver disease. Hepatogenous diabetes may benefit from exogenous adiponectin. The limitations of this study include a small sample size and the absence of other clinical indicators such as tumor necrosis factor. Our findings need to be expanded in a large patient population. The metabolic characteristics and mechanisms of serum adiponectin in hepatic diabetes need further investigation.

**Methods**

**Patient population.** A total of 78 male subjects were recruited at Beijing Shijitan Hospital including 19 cases of hepatogenic diabetes, 20 cases of T2D, 20 cases of chronic liver disease and 19 healthy controls. Among hepatic diabetics (mean age 53 ± 8.6 years, range 42–71 years), 17 cases were hepatitis B virus-related and 2 cases were hepatitis C virus-related. T2D patients were newly diagnosed (mean age 57 ± 6.2 years, range 37–76 years). Among the 20 patients with chronic liver disease (mean age 51 ± 4.1 years, range 42–67 years), 17 cases were hepatitis B virus-related and 3 cases were hepatitis C virus-related. The healthy control group consisted of 19 individuals (mean age 48 ± 4.5 years, range 37–52 years) with normal blood pressure, blood lipids, blood glucose levels and no previous history of chronic hepatitis. Each subject had a body mass index (BMI) of less than 25 according to the Obesity Guidelines for Asia-Pacific Region. Non-participative patients were excluded from the study. Informed consent was obtained from all subjects. This study was approved by the institutional review board of Beijing Shijitan Hospital Affiliated to Capital Medical University (The 9th affiliated hospital of Peking University) and was carried out in accordance with established national and institutional ethical guidelines regarding the involvement of human subjects and the use of human tissues for research.

**Diagnostic, inclusion and exclusion criteria.** The diagnosis of T2D is based on the Diagnosis and Classification of Diabetes Mellitus of American Diabetes Association\(^9\). Diagnosis of chronic viral hepatitis and liver cirrhosis was based on American Association for the Study of Liver Diseases (AASLD) Practice Guideline in 2004\(^10\). The diagnostic criteria for hepatogenic diabetes include: 1) Chronic liver disease occurred before the diabetes; 2) The patient’s liver function was abnormal; 3) Elevated glucose was consistent with the deterioration of liver function; 4) Symptoms of diabetes were mild or absent and without the complications of diabetes; 5) Fasting plasma glucose ≥7.0 mmol/L or normal, but the 2-hour postprandial blood glucose ≥11.1 mmol/L; oral glucose tolerance test (OGTT) or fasting blood glucose was normal or mildly elevated but postprandial glucose ≥11.1 mmol/L; 6) Insulin release test showed high levels of fasting plasma insulin and postprandial insulin response delay; C-peptide/insulin ratio was decreased; 7) Patients had no family history of diabetes. Patients with secondary hyperglycemia caused by the pituitary, adrenal, pancreas, and thyroid disease were excluded. Patients with glucose metabolism disorder caused by drugs such as diuretics, corticosteroids, antihypertensive drugs, and contraceptives were excluded.

**Acquisition and processing of specimens.** All subjects were fasted for 12–14 hours, and fasting venous blood 5 ml were collected in the next morning. Specimens were centrifuged at 3500 rpm for 10 minutes; serum was separated and kept at −80°C.

**Determination of adiponectin.** Adiponectin was demined using Enzyme–linked immunosorbent assay (ELISA) according to the manufacturer’s instruction. The ELISA kit was purchased from Jingmei Biotech Co Ltd. The data was analyzed using the MRX-automatic production fluorescence microplate reader (Dynex Technologies, USA).

**Measurement of Glucose, triglycerides, and total cholesterol.** Concentrations of blood glucose, triglycerides, and total cholesterol applied Hitachi 7170 automatic biochemical analyzer.

**Determination of fasting insulin.** Fasting insulin was measured using chemiluminescence detection.

**ISI (insulin sensitive index).** ISI was calculated as the natural logarithm of the reciprocal of product fasting blood glucose and fasting insulin.

**Statistical analysis.** Statistical analysis was performed using SPSS software (version 11.5). The measurement data were expressed as mean ± standard deviation (SD). For the data with normal distribution, the differences between groups were examined by pairwise comparisons; otherwise, data with skewed distribution were first transformed to log-normal distribution. Association between different indicators was evaluated by Pearson correlation. A P < 0.05 was considered as statistically significant.

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**Author contributions**

Z.Y.B. was responsible for experimental design and supervised the study. Z.Y.B., X.D.Y. and Duan, S.H. wrote the manuscript. X.Q.D. performed statistical analysis and prepared the figures and tables. Z.Y.B., X.D.Y., S.H.D. and X.Q.D. wrote, revised, and reviewed the manuscript.

**Additional information**

Competing financial interests: The authors declare no competing financial interests.

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