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Serum fetuin-A levels in obese and non-obese subjects with and without type 2 diabetes mellitus

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ABSTRACT

Background: Higher fetuin-A expression is linked to both obesity and type 2 diabetes mellitus (T2DM), However, studies in non-obese patients with T2DM are scarce.
Methods: 345 newly diagnosed T2DM patients and 300 subjects with normal glucose tolerance (NGT) were divided into obese and non-obese subgroups, respectively. Serum fetuin-A and adiponectin levels and related parameters were measured.
Results: T2DM patients with obesity had higher fetuin-A levels compared with non-obese patients and obese NGT subjects ($p < 0.001$). Significant correlations were observed between fetuin-A and most metabolic parameters in obese NGT and T2DM subjects, but which was not in non-obese patients with T2DM. The independent associations were found between fetuin-A and free fatty acids, HOMA-IR, C-reactive protein and adiponectin only in obese NGT and T2DM subjects (all $p < 0.05$). The adjusted odds ratios for obesity were increased with increasing quartile of fetuin-A in both T2DM and NGT subjects in logistic regression models (p for trend < 0.001), but which was more significant in T2DM patients.
Conclusion: Higher serum fetuin-A levels in obese T2DM patients compared with non-obese patients and obese NGT subjects supports the hypothesis that fetuin-A may be as a bridge connecting obesity and obesity-related T2DM.

1. Introduction

Obesity has now become an epidemic involving in public health issue around the world [1] and been considered to be one of the major risk factors for type 2 diabetes mellitus (T2DM) [2,3]. With the increasing number of obese people, obesity-related T2DM has presented a prevalent tendency. Data from a voluntary health checkup program contained 34,297 people between 1998 and 2006 conducted in Japan showed that obese men and women (body mass index [BMI] ≥ 25) were 39.2% and 38.0%, respectively, in all the T2DM patients [4]. A recent study conducted from 2010 to 2011 in 104 hospitals across almost all major geographic area in China reported that 43.0% of T2DM patients were overweight (24 ≤ BMI ≤ 27.9) and 16.7% were obese (BMI ≥ 28) [5]. Given the high prevalence of overweight and obesity nowadays and the close relationship of which with T2DM, it is vital important to find the linking mechanism between obesity and T2DM.

Fetuin-A is an endogenous inhibitor of insulin receptor tyrosine kinase in the liver and muscles [6]. Previous animal experiments indicated that the fetuin-A gene mRNA expression levels were significantly higher in rats fed by high-fat diet than those in low-fat diet [7], but on the contrary, fetuin-A knockout mice showed significantly decreased body fat and resistant to weight gain when fed a high-fat diet compared with wild-type controls [8]. In humans, higher fetuin-A levels have turned out to be an independent risk factor of T2DM [9] and closely associated with insulin resistance and fat accumulation in the liver [10]. Reinehr et al. [11] reported that obese adolescents with T2DM showed significantly higher serum fetuin-A levels compared with obese controls without T2DM. In a randomized controlled trial, Choi et al. [12] examined the effect of caloric restriction on fetuin-A expression and found that fetuin-A levels were significantly reduced both in hepatocyte and the circulating blood in corpulent rats and T2DM patients after 12 weeks of caloric restriction.

Increased fetuin-A levels are linked to both obesity and T2DM, and obesity is one of the most important risk factors for T2DM. However, it

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Table 1
Clinical characteristics of subjects classified by body mass index (BMI).

Parameters	NGT			T2DM		
	BMI < 25 (n = 204)	BMI ≥ 25 (n = 96)	p value	BMI < 25 (n = 211)	BMI ≥ 25 (n = 134)	p value
Age (years)	50.62 ± 10.18	51.33 ± 9.59	0.413	52.23 ± 9.22	50.84 ± 9.76	0.296
Male/female	109/95	45/51	0.289	95/116	73/61	0.087
Body mass index (kg/m2)	21.97 ± 1.51	27.84 ± 1.89	< **0.001**	22.24 ± 1.46	28.13 ± 2.05	< **0.001**
Waist-hip ratio	0.85 ± 0.07	0.93 ± 0.05	< **0.001**	0.84 ± 0.06	0.92 ± 0.06	< **0.001**
Systolic blood pressure (mm Hg)	121.34 ± 15.22	131.86 ± 16.18	< **0.001**	129.63 ± 16.96	141.27 ± 18.35	< **0.001**
Diastolic blood pressure (mm Hg)	76.81 ± 10.13	81.47 ± 10.82	< **0.001**	80.25 ± 11.16	86.64 ± 12.03	< **0.001**
Fasting plasma glucose (mmol/l)	4.89 ± 0.51	5.03 ± 0.55	0.226	8.25 ± 1.97	8.41 ± 2.16	0.272
2-h plasma glucose (mmol/l)	5.34 ± 0.91	5.82 ± 1.05	0.147	13.68 ± 3.86	14.74 ± 4.22	0.183
Hemoglobin A1c (%)	4.92 ± 0.36	5.11 ± 0.42	0.203	8.53 ± 1.29	8.86 ± 1.48	0.195
Total cholesterol (mmol/l)	4.42 ± 0.82	4.60 ± 0.78	0.316	4.49 ± 0.88	4.74 ± 0.86	0.345
Triglyceride (mmol/l)	1.54 ± 0.43	1.68 ± 0.49	0.371	1.65 ± 0.72	2.31 ± 0.89	< **0.001**
HDL cholesterol (mmol/l)	1.40 ± 0.26	1.33 ± 0.25	0.283	1.18 ± 0.27	1.03 ± 0.28	**0.023**
LDL cholesterol (mmol/l)	2.53 ± 0.58	2.79 ± 0.62	0.237	2.68 ± 0.74	3.35 ± 0.95	**0.008**
Free fatty acids (umol/l)	475.2 (226.7)	588.4 (265.8)	< **0.001**	553.6 (259.5)	732.5 (316.2)	< **0.001**
HOMA-IR	1.91 (0.77)	2.55 (2.25)	< **0.001**	3.09 (1.64)	4.80 (3.12)	< **0.001**
C-reactive protein (mg/l)	1.99 (0.96)	2.98 (1.64)	< **0.001**	2.90 (2.02)	4.56 (2.67)	< **0.001**
Adiponectin (mg/l)	10.54 (2.57)	8.75 (2.26)	< **0.001**	8.83 (2.47)	6.35 (2.94)	< **0.001**
Fetuin-A (mg/L)	234.7 (122.8)	277.9 (91.0)	**0.011**	268.8 (145.5)	356.4 (206.7)	< **0.001**

Data are expressed as mean ± SD or median (interquartile ranges).
NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance.
Bold type indicates statistically significant (p-values < 0.05)

was not yet clear if higher fetuin-A expression is only associated with obesity-related T2DM, but not non-obese patients with T2DM. In this present study, we examined serum fetuin-A levels in obese and non-obese subjects with and without T2DM and explored the linking mechanism between obesity and T2DM.

2. Methods

2.1. Study population

This cross-sectional study was conducted in the Affiliated Yancheng Hospital of Southeast University Medical College from December 2013 to November 2014. A total of 345 T2DM outpatients who were newly diagnosed based on the 1999 WHO criteria [13] were recruited in this study. Healthy volunteers were recruited from individuals who had been admitted for a routine health check-up at the hospital. All the volunteers received an oral glucose tolerance test (OGTT), and 300 individuals with normal glucose tolerance (NGT) were selected as controls. Subjects were asked to sign a consent form before enrolment in the study, and informed consent was obtained from all subjects involved in this project. The protocol was approved by the Ethics Committee of the hospital. For this study, obesity was defined as BMI ≥ 25 kg/m^2 based on the characteristics of Asian populations [14]. On the basis of this concept, NGT subjects and T2DM patients were divided into 2 subgroups, respectively, according to BMI: NGT with BMI < 25 and NGT with BMI ≥ 25; T2DM with BMI < 25 and T2DM with BMI ≥ 25. Exclusion criteria included: diabetes combined with acute complications such as ketoacidosis and hyperosmolar coma, acute or chronic inflammation, severe hepatic and renal dysfunction, malignant tumour and other endocrine and metabolic disorders.

2.2. Laboratory measurements

Subject's height, weight, and waist and hip circumference were measured in order to calculate BMI and waist-to-hip ratio (WHR). Resting blood pressures were taken by trained staff using a standard mercury sphygmomanometer after a minimum 10-min rest.

Blood samples were obtained in the morning after all participants underwent OGTT. Fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG), total cholesterol (TC), triglyceride(TG), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and free fatty acids (FFA) were analyzed enzymatically on Roche P800 automatic biochemical analyzer using commercial reagents. Hemoglobin A1c (HbA1c) was determined by high performance liquid chromatography. Serum C-reactive protein (CRP) and insulin concentrations were measured by rate nephelometry assay and electrochemiluminescence method, respectively. Insulin resistance was calculated by modified homoeostasis model assessment of insulin resistance (HOMA-IR): [fasting insulin (uU/mL) × FPG (mmol/L)/22.5] [15]. The fasting serum fetuin-A and adiponectin levels were determined by an ELISA kit (Biovendor, Modrice, Brno, Czech Republic).

2.3. Statistical analysis

The statistical package SPSS 20.0 was used for statistical analysis. Data are presented as mean ± SD for normally distributed variables or median (interquartile ranges) for skewed parameters. One-way ANOVA was conducted for comparison of serum fetuin-A levels across groups and post hoc analysis (Bonferroni correction) was taken to compare between groups. Unpaired t-tests and Mann-Whitney U tests were applied to compare other variables. A Chi-squared test was used for categorical variables. The correlations between fetuin-A and other continuous variables were analyzed by Spearman's correlation test. Multivariate linear regression analysis with fetuin-A as a dependent variable was conducted to determine the independent predictors for fetuin-A in all the subgroups. Multivariable logistic regression analysis with obesity (BMI < 25 and BMI ≥ 25) as the dichotomous dependent variable was conducted to determine the association between fetuin-A and obesity in NGT subjects and T2DM patients, and the resulting odds ratios (ORs) and 95% confidence interval (CI) are reported. When the variables were in non-normal distributions in one-way ANOVA or regression analysis, the logarithmic transformation was performed in them. A p-value < 0.05 was considered statistically significant (two-tailed).