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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).

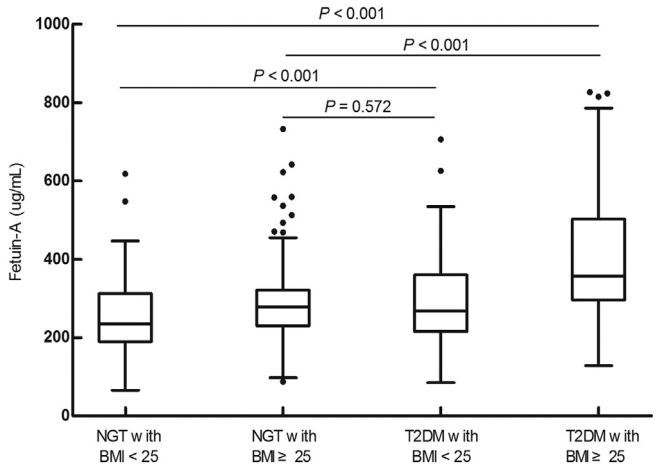

Fig. 1. Comparison of serum fetuin-A levels between subjects with normal glucose tolerance (NGT) and type 2 diabetes mellitus (T2DM), with body mass index (BMI) < 25 and ≥ 25, respectively.

3. Results

3.1. Clinical characteristics of the study subjects

The clinical characteristics of NGT subjects and T2DM patients classified by BMI were presented in Table 1. There were significant differences in BMI, WHR, systolic blood pressure (SBP), diastolic blood pressure (DBP), FFA, HOMA-IR, CRP and adiponectin between obese and non-obese NGT subgroups, and between the 2 subgroups of T2DM ($p < 0.05$ or $p < 0.001$). Significant differences also were observed in TG, HDL cholesterol and LDL cholesterol between obese and non-obese T2DM subgroups ($p < 0.05$ or $p < 0.001$).

In the comparison of serum fetuin-A levels among 4 subgroups (obese NGT, non-obese NGT, obese T2DM and non-obese T2DM subjects), the obese T2DM patients had significantly higher fetuin-A concentrations than those in other 3 subgroups ($p < 0.001$), and the obese NGT subjects had higher fetuin-A levels than those in non-obese NGT subjects ($p = 0.011$); significant differences also were observed between non-obese NGT and non-obese T2DM subgroup ($p < 0.001$), but no significant differences were found between obese NGT and non-obese T2DM subgroup ($p = 0.572$) (Fig. 1 and Table 1).

3.2. The correlations of fetuin-A with other clinical variables

The correlations between fetuin-A and other clinical variables among the 4 subgroups were presented in Table 2. Fetuin-A was correlated positively with BMI, WHR, FPG, HbA1c, TC, TG, LDL cholesterol, FFA, HOMA-IR and CRP, and correlated negatively with adiponectin in obese NGT and T2DM subgroups, and FFA and HOMA-IR were correlated positively with fetuin-A in non-obese NGT subgroups ($p < 0.05$ or $p < 0.001$). In non-obese T2DM subgroups, only FFA was observed to be correlated positively with fetuin-A ($p = 0.022$).

3.3. Multivariate linear regression analysis with fetuin-A as a dependent variable

In the multivariate regression model, after adjustment for age, gender, BMI, WHR, SBP, HbA1c, TG, HDL cholesterol, LDL cholesterol, FFA, HOMA-IR, CRP and adiponectin, the independent associations were found between fetuin-A and HOMA-IR in non-obese NGT subgroups, and FFA, HOMA-IR, CRP and adiponectin in obese NGT subgroups, and HbA1c, FFA, HOMA-IR, CRP and adiponectin in obese T2DM subgroups (Table 3), but no independent associations were found between fetuin-A and any variables in non-obese T2DM subgroups.

3.4. The correlations of quartiles of fetuin-a with obesity

The associations between quartiles of fetuin-A and obesity were presented in Table 4. The ORs for obesity were increased with increasing quartile of fetuin-A in both T2DM and NGT subjects (p for trend < 0.001), but which was more significant in T2DM patients. Moreover, this trend remained significant after adjustment for age, gender, BMI, WHR, and SBP (Model II), and further HbA1c, TG, HDL cholesterol, LDL cholesterol, FFA, HOMA-IR, CRP and adiponectin (Model III).

4. Discussion

To the best of our knowledge, this is the first study to examine serum fetuin-A levels in obese and non-obese subjects with and without T2DM. We found the obese T2DM patients had higher fetuin-A levels compared with non-obese patients and obese NGT subjects, and fetuin-A was significantly associated with related metabolic parameters in obese NGT and T2DM subjects, but not non-obese subjects. Moreover, the adjusted odds ratios for obesity were more significantly increased with increasing quartile of fetuin-A in T2DM patients than those in NGT subjects. These results indicate that the increased expression of fetuin-A may be as a bridge that connects obesity to obesity-related T2DM.

Adipocytes with more than the normal number and size in obese individuals secrete increased amounts of inflammatory cytokines and other factors that are involved in the development of insulin resistance and other metabolic disorders, which was considered to be the primary mechanisms linking obesity to T2DM in most of the previous reports [16–18]. But there are in fact many obese individuals complicated with insulin resistance who do not develop T2DM. So some research pointed out that pancreatic islet β-Cell failure is central to the development and progression of T2DM, and obese people with insulin resistance develop T2DM only when the damaged β-cells cannot compensate fully for decreased insulin sensitivity [19,20]. Fetuin-A is a multifunctional glycoprotein secreted from liver in human and then secreted into circulation in high concentrations [6]. In addition to increasing insulin resistance, elevated fetuin-A expression has also been shown to repress adiponectin production and stimulate secretion of inflammatory agents such as TNF-α, IL-6 in adipose tissue [9]. Adiponectin is an insulin-sensitizing hormone secreted by adipocytes that was shown to be decreased in individuals with obesity and T2DM [21], which was in line with our study; and inflammation was seen as an underlying cause or contributor to T2DM and as a link between obesity and T2DM [22]. In this study, fetuin-A was negatively related to adiponectin but positively related to CRP in obese subjects with NGT and T2DM, but not in non-obese individuals; and in the multivariate linear regression model, the correlations remained significant after adjustment for other confounders. Thus, lower expression of adiponectin and higher expression of inflammatory cytokines in obese individuals may be caused by increased fetuin-A levels. The independent associations between fetuin-A and FFA were also observed in obese subjects with NGT and T2DM, suggesting that increased expression of FFA is closely linked with fetuin-A. Research has indicated that Toll-like receptor 4 (TLR4) regulates obesity-associated inflammation and insulin resistance [23] and fetuin-A acts as an endogenous ligand of TLR4 through which lipids induce insulin resistance [24]. Further research carried out by Stefan et al. [25] revealed that there is a direct interaction between FFA and fetuin-A to induce insulin resistance in humans. Therefore, fetuin-A may regulate the inflammatory process, lipids metabolism and insulin resistance by several different ways. Recently, an in vitro investigation found that fetuin-A can stimulate vascular endothelial cells growth and produce angiogenic proteins by human perivascular fat cells [26]. In our earlier study, we also found that fetuin-A was positively correlated with VEGF [27]. VEGF affects both vascularization and innervation of the pancreatic islet [28], and which is necessary for maintaining normal structure and function of the pancreatic islet when normally expressed,

Table 2
Spearman's correlation analysis between fetuin-A and clinical variables.

	NGT with BMI < 25 (n = 204)		NGT with BMI ≥ 25 (n = 96)		T2DM with BMI < 25 (n = 211)		T2DM with BMI ≥ 25 (n = 134)	
	r	p value	r	p value	r	p value	r	p value
Age (years)	− 0.168	**0.016**	− 0.175	0.088	− 0.118	0.086	− 0.179	**0.039**
Body mass index (kg/m^2)	0.073	0.298	0.208	**0.042**	0.076	0.274	0.184	**0.034**
Waist - hip ratio	0.106	0.133	0.225	**0.027**	0.110	0.111	0.188	**0.030**
Systolic blood pressure (mmHg)	0.065	0.359	0.161	0.117	0.048	0.484	0.090	0.299
Diastolic blood pressure (mmHg)	0.074	0.294	0.135	0.191	0.062	0.371	0.112	0.198
Fasting plasma glucose (mmol/l)	0.124	0.078	0.225	**0.027**	0.129	0.062	0.254	**0.003**
2-h plasma glucose (mmol/l)	0.115	0.102	0.197	0.054	0.094	0.173	0.216	**0.012**
Hemoglobin A1c (%)	0.107	0.127	0.233	**0.022**	0.099	0.152	0.312	< **0.001**
Total cholesterol (mmol/l)	0.090	0.201	0.206	**0.045**	0.082	0.238	0.208	**0.016**
Triglyceride (mmol/l)	0.128	0.067	0.276	**0.007**	0.091	0.190	0.288	**0.001**
HDL cholesterol (mmol/l)	− 0.064	0.365	− 0.165	0.109	− 0.041	0.558	− 0.164	0.059
LDL cholesterol (mmol/l)	0.106	0.133	0.247	**0.015**	0.126	0.069	0.206	0.083
Free fatty acids (umol/l)	0.159	**0.023**	0.267	**0.008**	0.158	**0.022**	0.306	< **0.001**
HOMA-IR	0.182	**0.009**	0.338	**0.001**	0.089	0.196	0.326	< **0.001**
C-reactive protein (mg/l)	0.206	0.099	0.259	**0.011**	0.104	0.134	0.343	< **0.001**
Adiponectin (mg/l)	− 0.121	0.085	− 0.238	**0.020**	− 0.087	0.211	0.317	< **0.001**

NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance.

Table 3
Multivariate linear regression analysis with fetuin-A as a dependent variable.

	Beta coefficient	p value	95% confidence interval
NGT with BMI < 25			
HOMA-IR	0.141	0.047	0.291–27.718
NGT with BMI ≥ 25			
Free fatty acids	0.186	0.049	0.024–9.727
HOMA-IR	0.203	0.026	2.023–20.239
C-reactive protein	0.202	0.048	0.143–31.730
Adiponectin	0.205	0.028	− 18.026 – − 1.039
T2DM with BMI ≥ 25			
Hemoglobin A1c	0.239	0.005	15.294–85.101
Free fatty acids	0.175	0.029	1.218–21.246
HOMA-IR	0.236	0.004	4.701–24.918
C-reactive protein	0.248	0.001	6.183–25.030
Adiponectin	0.251	0.003	− 28.009 – − 6.060

NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus; BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance.
The variables of fetuin-A, free fatty acids, HOMA-IR, C-reactive protein and adiponectin were log-transformed before analysis.

but its overexpression is responsible for β-cell injury and consequential diabetes [29]. For this reason, the increased expression of fetuin-A is correlated with pancreatic islet β-Cell failure. In this study, we also found the correlations between fetuin-A and some variables such as FFA, HOMA-IR, CRP and adiponectin were more significant in obese T2DM patients than that in obese NGT subjects, suggesting that continuously elevated fetuin-A levels in individuals with obesity may further aggravate metabolic disorder and eventually develop into T2DM.

In the present study, no significant correlations were found between fetuin-A and other variables including HOMA-IR other than FFA in non-obese T2DM patients, but the independent associations between fetuin-A and HOMA-IR were observed in other all subgroups, which suggests fetuin-A may be not involved in the pathogenesis of non-obese T2DM. Previous studies have shown that obese and non-obese individuals with T2DM have different clinical features such as the former with higher HOMA-IR and CRP concentrations, but lower adiponectin levels [4,30], which were consistent with our study. Dullaart et al. [31] reported that lower adiponectin levels were associated with increased intima-media thickness in T2DM patients in whom obesity and non-obesity were not distinguished, but no significant associations were found between them in non-obese T2DM patients by Saif et al. [32]. A recent research observed that BMI and urinary albumin were independent risk factors for

Table 4
The associations between quartiles of fetuin-A and obesity.

Fetuin-A quartiles	NGT			T2DM		
	Model I	Model II	Model III	Model I	Model II	Model III
1st quartile	1	1	1	1	1	1
2nd quartile	1.489 (0.745–2.975)	1.486 (0.739–2.987)	1.399 (0.696–2.814)	1.656 (0.815–3.363)	1.705 (0.832–3.493)	1.635 (0.805–3.318)
3rd quartile	2.038 (1.022–4.061)	1.931 (0.962–3.875)	1.851 (0.922–3.716)	2.581 (1.295–5.143)	2.510 (1.192–5.285)	2.370 (1.164–4.826)
4th quartile	2.804 (1.407–5.587)	2.511 (1.210–5.213)	2.242 (1.092–4.602)	3.608 (1.794–7.255)	3.296 (1.545–7.030)	3.032 (1.491–6.162)
p for trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Data are given as adjusted odds ratios (ORs) and 95% confidence interval (CI).
NGT: normal glucose tolerance; T2DM: type 2 diabetes mellitus.
Model I: unadjusted.
Model II: adjusted for age, gender, body mass index, Waist - hip ratio, and systolic blood pressure.
Model III: adjusted for Hemoglobin A1c, triglyceride, HDL cholesterol, LDL cholesterol, free fatty acids, homoeostasis model assessment of insulin resistance, C-reactive protein and adiponectin, based on model 2.
The variables of fetuin-A, free fatty acids, HOMA-IR, C-reactive protein and adiponectin were log-transformed when they were introduced in the regression model.

high-sensitivity C-reactive protein (hs-CRP) levels in T2DM patients with obesity, whereas triglyceride and statin were independent risk factors in non-obese patients [33]. Therefore, in addition to causing an increase or decrease in the levels of certain cytokines, obesity influences the effect of them on the target organ and their regulation factors.

Some limitations of these findings must be considered. First, our study was a cross-sectional design, it could not allow a causal infer. Second, because the number of subjects in this study was relatively small, the findings probably were due to chance. Finally, as this study was executed in a single centre and the study cohort was confined to one ethnic group, the data may not be representative of the population as a whole. Even so, the present study might provide an important information that fetuin-A may be involved in the pathogenesis of obesity-related T2DM rather than non-obese T2DM.

In conclusion, this study showed the obese T2DM patients had higher fetuin-A levels compared with non-obese patients and obese NGT subjects, and the associations between fetuin-A and obesity were more significant in T2DM patients than those in NGT subjects.

this study showed higher fetuin-A levels were correlated with obesity and obesity-related T2DM, but not non-obese T2DM. Further large-scale prospective studies are needed to clarify that fetuin-A serve as a potential target in treatment of obesity-related T2DM.

Conflict of interest

None declared.

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