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*Original Article*

# Association of plasma Fetuin-A and clinical characteristics in patients with new-onset type 2 diabetes mellitus

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**Abstract:** Context: Fetuin-A is an abundant plasma protein known to inhibit insulin signaling and pathologic calcification, has emerged as a promising candidate biomarker for diabetes risk. Objective: The objective of this study was to investigate the relationships between plasma Fetuin-A level with clinical characteristics in patients with new-onset type 2 diabetes mellitus (nT2DM). Subjects and Methods: Plasma Fetuin-A levels, and clinical characteristics were assessed in 100 patients with nT2DM and 100 normal glucose tolerance (NGT). Results: nT2DM subjects had significantly higher Fetuin-A levels than NGT subjects (368.5 ± 15.6 vs 152.7 ± 7.1 mg/ml, $P < 0.01$). In the Pearson's correlation coefficients, Fetuin-A levels and clinical parameters. Fetuin-A was positively correlated with HOMA-insulin resistance index (HOMA-IR), carotid intima media thickness(CIMT), HbA1c, triglyceride (TG), Low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), systolic blood pressure (SBP), fasting plasma glucose (FBG) and 2 h post-glucose load blood glucose (2 h OGTT) ($P < 0.05$ and $P < 0.01$), but negatively with fasting plasma insulin (FINS), 2 h plasma insulin after glucose overload (PINS), High-density lipoprotein cholesterol (HDL-C) and HOMA-beta-cell insulin secretion index (HOMA-IS) ($P < 0.05$ and $P < 0.01$). However, no significant relationships were observed between plasma Fetuin-A levels and estimated glomerular filtration rate (eGFR), age and gender in nT2DM subjects. In a multiple linear regression analysis, Fetuin-A levels were independently associated with FBG, 2 h OGTT, HOMA-IS, TG, and CIMT ($R^2 = 0.6760$). CIMT were negatively associated with FINS and HDL-C ($r = -0.33$, $P = 0.008$; $r = -0.31$, $P = 0.01$, respectively) in the Pearson's analyses. Moreover, they were positively associated with HOMA-IR ($r = 0.28$, $P = 0.03$). It showed significant correlations of plasma CIMT with FINS, PINS and HOMA-IR ($R^2 = 0.6760$). Conclusions: Our study suggests that the plasma Fetuin-A levels may be associated with macroangiopathies in nT2DM patients. Therefore, detecting early plasma Fetuin-A levels nT2DM provides an opportunity to intervene of carotid artery disease in diabetic patients and giving timely treatment for the prevention of diabetic vascular complications.

**Keywords:** New-onset type 2 diabetes mellitus, Fetuin-A, carotid intima-media thickness

## Introduction

Atherosclerosis (AS) may be the most common macrovascular complication of type 2 diabetes (T2DM) and therefore, will emerge as the leading causes of death in these patients. The risk of AS patients with T2DM is higher than those with normal glucose tolerance [1]. Patients with new-onset type 2 diabetes mellitus (nT2DM) do not have typical of clinical manifestations, some patients with almost no symptoms. The high blood sugar is only for the main performance of nT2DM. So, early detection in high-risk groups can take effective preventive measures to reduce cardiovascular mortality in patients with nT2DM.

Atherosclerosis, which mainly affects the medium-sized and large arteries of the heart, brain, kidney, peripheral artery and other large vessels. It is characterized by plaque deposits that block the flow of blood. An early sign of lesions are increases intima-media thickness (IMT) of arterial wall. The Study showed that the carotid artery intima-media thickness (CIMT) can be as a surrogate marker of coronary artery disease

in diabetes [2]. Thus, it seems that CIMT has important significance for early detection and intervention of carotid artery disease in diabetic patients and giving timely treatment for the prevention of diabetic vascular complications.

Fetuin-A, which is a glycoprotein secreted by the liver, has emerged as a promising candidate biomarker for diabetes risk [3-8]. High levels of Fetuin-A appear to be related with insulin resistance [9]. A previous study showed that Fetuin-A induces insulin resistance by inhibiting insulin receptor autophosphorylation [10]. Additionally, enhanced insulin sensitivity was observed in mice null for the Fetuin gene [11]. Also, Fetuin-A is shown to inhibit ectopic calcium deposition and protect from vascular calcification [12]. However, contradictory results have been reported regarding the role of novel biomarker Fetuin-A in macroangiopathies in T2DM [13, 14]. Insulin resistance (IR) is a one of the key pathophysiological mechanisms of T2DM, which may contribute to the development of T2DM and associated vascular complications. IR also is considered to be the common cause of dyslipidemia and hypertensive diseases [15]. However, the role of Fetuin-A and its involvement in IR remains unclear.

Thus, the aim of this study was to investigate plasma Fetuin-A levels in patients with nT2DM and to analyze the association of plasma Fetuin-A levels with clinical characteristics in patients with nT2DM. In addition, possible factors related to increased plasma Fetuin-A concentration were investigated.

## Materials and methods

### *Ethics statement*

The patient with type 2 diabetes is not treated with oral medications or insulin. This study was approved by the institutional ethics committee at the First Affiliated Hospital of Shihezi University School of Medicine and conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Written informed consents were obtained from all patients and healthy controls before they entered the study.

### *Patients*

100 patients with nT2DM (nT2DM group) and 100 normal glucose tolerance (NGT group) controls were evaluated in the study. The diagnostic criteria of T2DM was based on a 75 g oral glucose tolerance test (OGTT) recommended by World Health Organization criteria [16]. nT2DM was defined prospectively as at least 2 post-baseline FBG measurements ≥ 7.0 mmol/l (126 mg/dl) and at least 1 post-baseline glucose > 2 mmol/l (36 mg/dl) above baseline [17]. The study was performed on 100 nT2DM group (54 male and 46 female; mean age = 55.11 ± 12.84 years). The NGT group, age and BMI matched with nT2DM group (44 male and 56 female; mean age = 52.39 ± 13.79 years). Exclusion criteria comprised patients who had renal dysfunction, severe cardiac problems, uncontrolled hypertension, or type 1 diabetes.

### *Blood sampling*

Blood samples were drawn from the antecubital vein between 09:30 and 10:00 AM after > 8 h of overnight fasting at the time of OGTT. HbA1c was more sensitive, whereas OGTT was more specific. Thus, we think that a single measurement to diagnose diabetes is unwarranted. HbA1c was measured from a blood sample obtained on the same day by an automated ion-exchanged chromatography (BIO-RAD mini column). Blood tubes were centrifuged for 10 minutes at 1500 × g after clotting for 30 minutes at room temperature. Plasma samples were subsequently stored at -80°C until further analysis of insulin and Fetuin-A levels.

### *Clinical data*

The gender, age, height, body weight, systolic pressure and diastolic pressure of the patients were recorded, the body mass index (BMI), the homeostatic model assessment index of IR(HOMA-IR) and HOMA-beta-cell insulin secretion index = 20 × FINS/(FBG-3.5) [18] were calculated in all subjects.

### *Measurement of plasma Fetuin-A levels*

Plasma Fetuin-A levels were measured with a commercially available ELISA kit (R&D Systems, Minneapolis, MN, USA).

### *Measurement of carotid intima-media thickness*

The subjects underwent a Doppler Ultrasound system (iE33; Philips Healthcare) with a 3-11MHz linear-array transducer. Methods for measurements of CIMT have been described in

**Table 1.** Characteristic of the study subjects and Fetuin-A levels

| Characteristic | nT2DM | NGT |
|---|---|---|
| Gender (male/female) | 54/46 | 44/56 |
| Age (years) | 55.11 ± 12.84 | 52.39 ± 13.79 |
| BMI (kg/m$^2$) | 25.32 ± 2.97 | 24.38 ± 2.19 |
| SBP(mmHg) | 134.07 ± 15.02 | 137.39 ± 11.68 |
| DBP (mmHg) | 77.00 ± 8.96 | 81.39 ± 8.13 |
| FPG (mmol/L) | 8.52 ± 3.10 | 4.85 ± 0.48** |
| 2Hogtt (mmol/L) | 11.64 ± 4.28 | 5.13 ± 0.48** |
| PINS (pmol/L) | 40.65 ± 27.02 | 69.68 ± 28.87** |
| FINS (pmol/L) | 21.12 ± 4.52 | 35.51 ± 3.65** |
| TC (mmol/L) | 4.92 ± 0.92 | 4.43 ± 0.94** |
| TG (mmol/L) | 2.12 ± 1.81 | 1.39 ± 0.83** |
| LDL-C (mmol/L) | 3.00 ± 0.83 | 2.62 ± 0.72** |
| HDL-C (mmol/L) | 1.14 ± 0.28 | 1.29 ± 0.33** |
| HOMA-IR# | 1.61 ± 0.79 | 0.65 ± 0.05** |
| HOMA-IS | 18.49 ± 1.72 | 9.93 ± 1.76* |
| HbA1C (%) | 8.78 ± 1.8 | 5.2 ± 0.05** |
| Hs-CRP (mg/L) | 38.5 ± 10.3 | 23.8 ± 16.5 |
| CIMT (mm)# | 0.26 ± 0.21 | 0.13 ± 0.08** |
| eGFR (MDRD, mL/min) | 105.2 ± 10.8 | 122.5 ± 16.5** |
| Fetuin-A (mg/ml) | 368.5 ± 15.6 | 152.7 ± 7.1* |

Data are mean ± SD. NGT, normal glucose tolerance; T2DM, type 2 diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2 h OGTT, 2 h post-glucose load blood glucose; FINS, fasting plasma insulin; PINS, 2 h plasma insulin after glucose overload; TC, total cholesterol; TG, triglyceride; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol. HOMA-IR, HOMA-insulin resistance index. HOMA-IS, HOMA-beta-cell insulin secretion index. CIMT, carotid intima media thickness. eGFR, estimated glomerular filtration rate. #Data with a non-Gaussian distribution that were transformed by natural logarithmic before analysis. *P < 0.01, **P < 0.001 compared with NGT group.

detail previously [19]. The measurement of CIMT was made by the same experienced ultrasonic experts in every case.

*Statistical analysis*

Data were expressed as mean ± SD. Differences between groups were assessed by Student's unpaired *t* test, Mann-Whitney U test, or Chi-square test as appropriate. Pearson's correlations analysis were used to examine the association between plasma Fetuin-A levels and clinical characteristics. Variables with a non-Gaussian distribution were logarithmically transformed before statistical analysis. Multiple linear regression analysis was performed to evaluate the independent contribution to plasma Fetuin-A level and CIMT. Differences were considered to be statistically significant at two-sided $P < 0.05$. All calculations were performed using the SPSS 15.0 software (Chicago, IL).

## Results

*The clinical characteristics and plasma Fetuin A levels*

The clinical characteristics of the two groups showed significant difference in FBG, 2 h OGTT, FINS, PINS, TC, TG, LDL-C, HDL-C, HOMA-IR, HOMA-IS, HbA1c, eGFR, and CIMT (**Table 1**). Gender distribution, age, WHR, BMI, SBP, DBP and Hs-CRP in nT2DM group were no statistically significant differences than NGT group.

*Plasma Fetuin-A levels*

There was significant difference in plasma Fetuin-A levels between the nT2DM and NGT groups (368.5 ± 15.6 versus 152.7 ± 7.1 mg/L, $P < 0.01$).

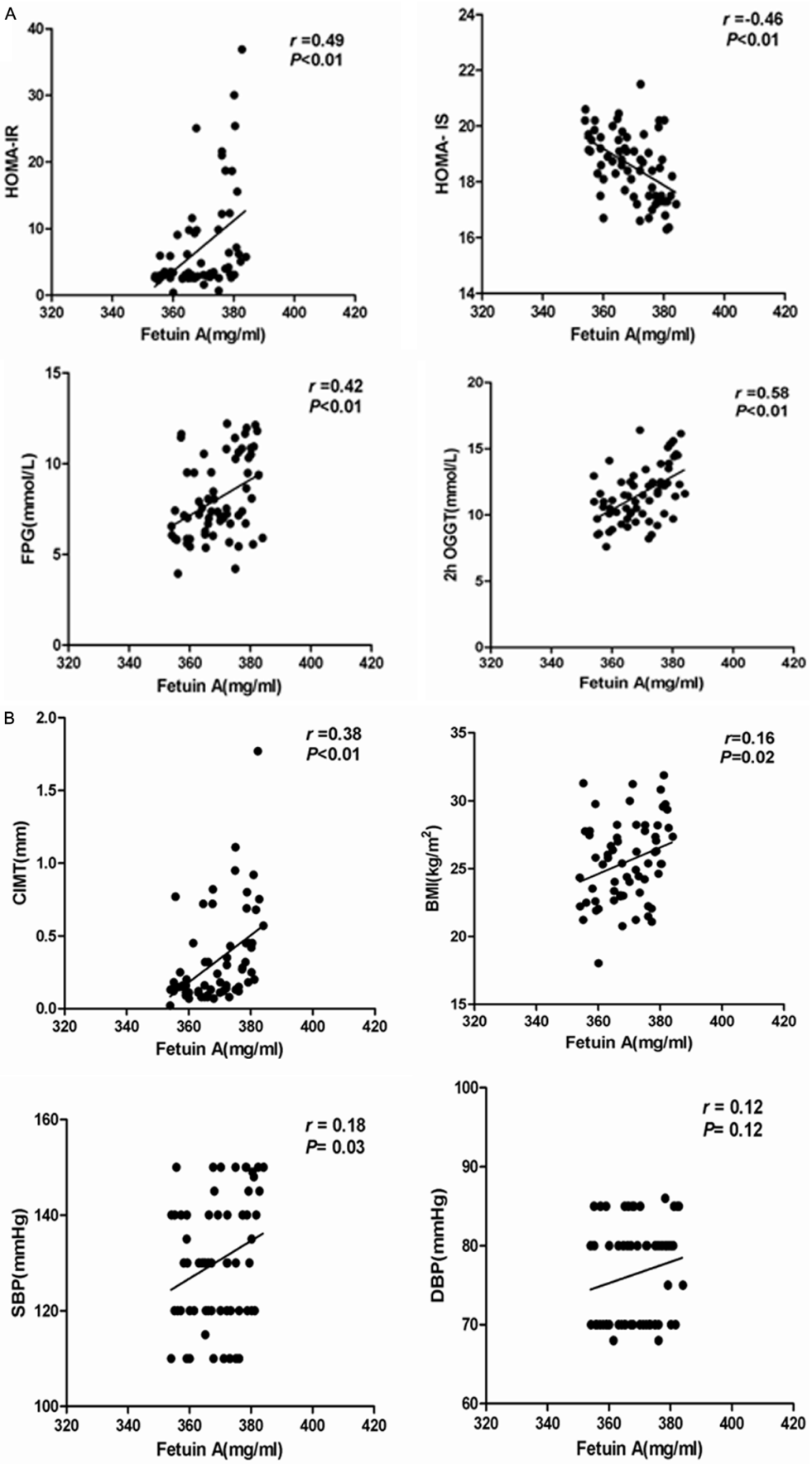
*Correlation of plasma Fetuin A levels with clinical parameters*

Pearson's correlation analysis were performed to assess relationships between plasma Fetuin-A levels and clinical parameters. Plasma Fetuin-A levels was found to correlate positively and significantly with HOMA-IR ($r = 0.49$, $P < 0.01$), CIMT ($r = 0.38$, $P < 0.01$), HbA1c ($r = 0.15$, $P < 0.05$), SBP ($r = 0.18$, $P < 0.05$), LDL-C ($r = 0.11$, $P < 0.05$), triglyceride ($r = 0.35$, $P < 0.01$), BMI ($r = 0.16$, $P < 0.05$), FBG ($r = 0.42$, $P < 0.01$) and 2 h OGTT ($r = 0.58$, $P < 0.01$), but negatively with FINS ($r = -0.15$, $P < 0.01$), PINS ($r = -0.42$, $P < 0.01$), HDL-C ($r = -0.18$, $P < 0.05$) and HOMA-IS ($r = -0.46$, $P < 0.01$), but no significant correlation with the eGFR by MDRD, age and gender (**Figure 1A-D**).

Multiple linear regression analysis showed Fetuin-A levels were independently associated with FBG, 2 h OGTT, HOMA-IS, TG, and CIMT ($R^2 = 0.6760$, seen in **Table 2**).

*Correlation of CIMT with clinical parameters*

We further investigated the association of CIMT with clinical parameters by pearson's correlation analyses. CIMT were negatively associated


A
HOMA-IR
r =0.49
P<0.01
Fetuin A(mg/ml)
HOMA- IS
r =-0.46
P<0.01
Fetuin A(mg/ml)
FPG(mmol/L)
r =0.42
P<0.01
Fetuin A(mg/ml)
2h OGGT(mmol/L)
r =0.58
P<0.01
Fetuin A(mg/ml)
B
CIMT(mm)
r =0.38
P<0.01
Fetuin A(mg/ml)
BMI(kg/m2)
r=0.16
P=0.02
Fetuin A(mg/ml)
SBP(mmHg)
r = 0.18
P= 0.03
Fetuin A(mg/ml)
DBP(mmHg)
r = 0.12
P= 0.12
Fetuin A(mg/ml)

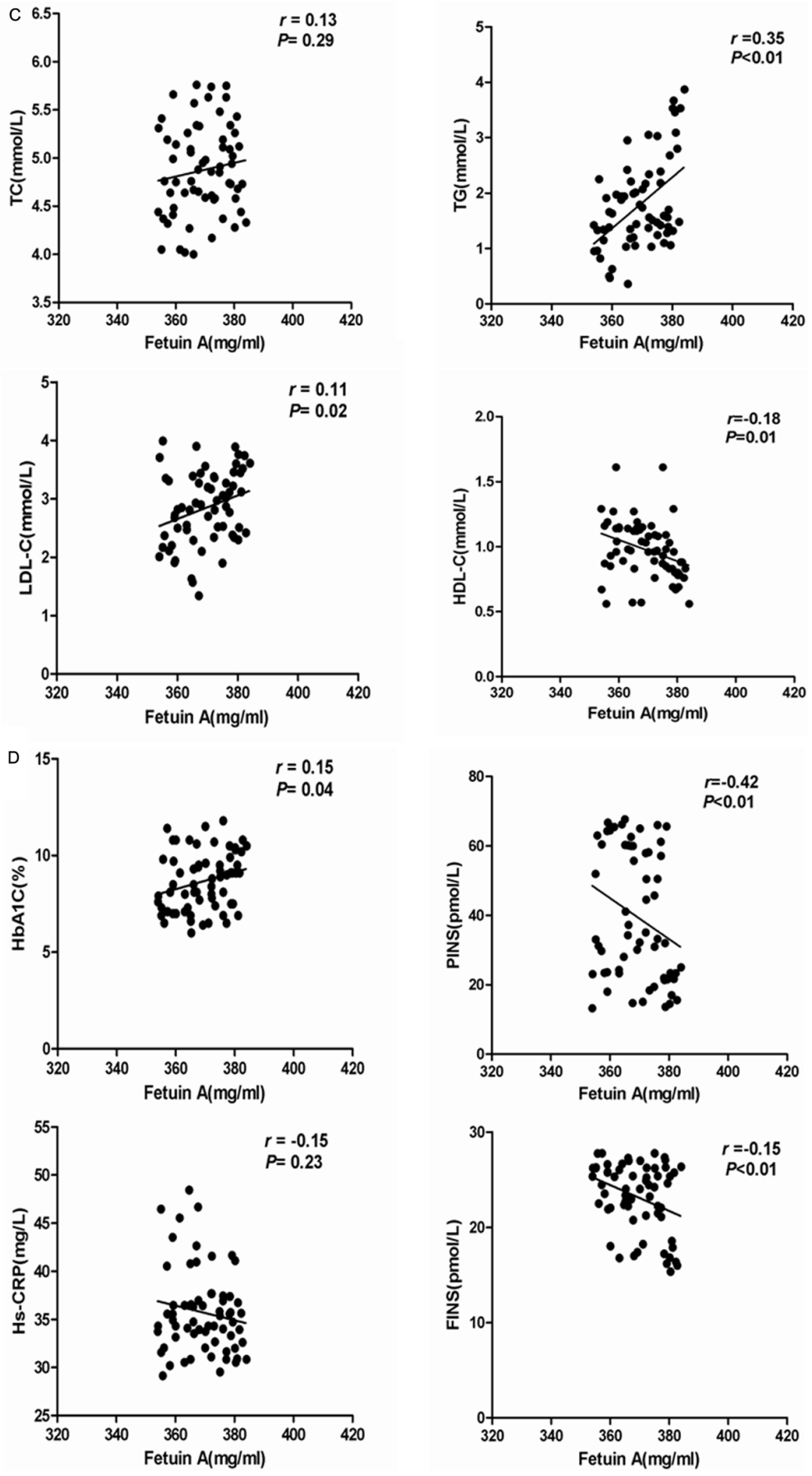

C
r = 0.13
P= 0.29
TC(mmol/L)
Fetuin A(mg/ml)
r =0.35
P<0.01
TG(mmol/L)
Fetuin A(mg/ml)
r = 0.11
P= 0.02
LDL-C(mmol/L)
Fetuin A(mg/ml)
r=-0.18
P=0.01
HDL-C(mmol/L)
Fetuin A(mg/ml)
D
r = 0.15
P= 0.04
HbA1C(%)
Fetuin A(mg/ml)
r=-0.42
P<0.01
PINS(pmol/L)
Fetuin A(mg/ml)
r = -0.15
P= 0.23
Hs-CRP(mg/L)
Fetuin A(mg/ml)
r=-0.15
P<0.01
FINS(pmol/L)
Fetuin A(mg/ml)

Figure 1. Correlations between plasma Fetuin-A levels with clinical parameters (A-D. Pearson correlation analysis).

Table 2. Multiple linear regression analysis of plasma Fetuin-A

| $R^2$ | 0.6760 | | | |
|---|---|---|---|---|
| Independent variables | Coefficient | Std. Error | t | *P* |
| 2 h OGTT | 1.0902 | 0.4273 | 2.552 | 0.0140* |
| BMI | -0.06342 | 0.3082 | -0.206 | 0.8379 |
| CIMT | 4.9443 | 2.8620 | 1.728 | 0.0406* |
| Hs-CRP | -0.1670 | 0.1829 | -0.913 | 0.3660 |
| SBP | -0.03548 | 0.07659 | -0.463 | 0.6453 |
| DBP | 0.1786 | 0.1418 | 1.260 | 0.2140 |
| FINS | -0.07923 | 0.2322 | -0.341 | 0.7344 |
| PINS | 0.01322 | 0.04713 | 0.280 | 0.7804 |
| FPG | 0.7933 | 0.3837 | 2.067 | 0.0342* |
| HBA1C | 0.5748 | 0.5333 | 1.078 | 0.2867 |
| HOMA-IS | -1.9766 | 0.7421 | -2.664 | 0.007** |
| HOMA-IR | 0.1410 | 0.1173 | 1.202 | 0.2353 |
| HDL | -3.2576 | 4.6716 | -0.697 | 0.4890 |
| LDL | 1.1070 | 1.4033 | 0.789 | 0.4342 |
| TC | -0.4555 | 1.8962 | -0.240 | 0.8112 |
| TG | 2.3216 | 1.1241 | 2.065 | 0.030* |
| eGFR | -0.07659 | 0.1627 | -0.471 | 0.6400 |

*$P < 0.05$, **$P < 0.01$.

with FINS and HDL-C (r = -0.33, $P = 0.008$; r = -0.31, $P = 0.01$, respectively, **Figure 2**) in the Pearson's analyses. Moreover, they were positively associated with HOMA-IR (r = 0.28, $P = 0.03$, **Figure 2**).

Multiple linear regression analysis showed significant correlations of CIMT with FINS, PINS and HOMA-IR ($P < 0.05$) (**Table 3**).

## Discussion

Fetuin-A is a multifunctional molecule secreted by the liver [20]. In the context of previous studies have demonstrated that Fetuin-A has emerged as a biomarker for risk of type 2 diabetes [3-8]. However, none of these studies investigated the relationships between plasma Fetuin-A level with clinical characteristics in patients with nT2DM.

Type 2 diabetes mellitus is a major risk factor for cardiovascular disease [15, 16]. In the present study, we found that plasma Fetuin-A levels were elevated in patients with nT2DM compared with NGT group. Dyslipidemia is elevation of total cholesterol, triglyceride and small dense LDL-C concentrations with a low plasma HDL-C levels. HDL-C has a protective role in atherosclerosis, because it can remove cholesterol from cells in the artery wall [21]. A previous study have demonstrated that plasma Fetuin-A levels is absolutely related with visceral obesity and dyslipidemia [22]. In agreement with previous studies, we demonstrated that higher fetuin-A concentrations were independently associated with clinical parameters. In the current study, we found that plasma Fetuin-A levels was positively and significantly correlated with LDL-C and triglyceride, but negatively with HDL-C. In addition, plasma Fetuin-A levels were associated with BMI, SBP, HbA1c, FBG and 2 h OGTT. However, in contrast to our study, a previous study reported that Fetuin-A showed positive association with ABI and no significant correlations with metabolic parameters [23]. Another study reported that Fetuin-A levels do not correlate with some clinical and metabolic parameters as BMI, BP, total cholesterol, HDL and triglyceride in T2DM patients with early diabetic nephropathy [24]. Moreover, in our study, multivariate regression analysis indicated that Fetuin-A levels were independently associated with FBG, 2 h OGTT, HOMA-IS, TG, and CIMT. However, we found that fetuin-A concentrations were not significantly associated with (eGFR), age and gender in our study. Thus, reviewing the existing data as well as the results obtained in our study, the significance of plasma Fetuin-A levels is controversial whether it is a good marker for diabetic micro- and macrovascular complications.

In addition, it had been demonstrated that plasma Fetuin-A level was related with insulin resistance [9, 25, 26]. In the present study, we also found that plasma Fetuin-A levels was positively and significantly correlated with HOMA-IR, but negatively with FINS, PINS and HOMA-IS. These findings indicated that Fetuin-A might have a role in triggering the processes leading to insulin resistance in nT2DM patients. This result is in line with previous data concerning the relationship of between Fetuin-A and IR. However, there are no associations of Fetuin-A with CIMT in previous studies. In our study, we also found that CIMT were negatively associated with FINS and HDL-C in the Pearson's analy-

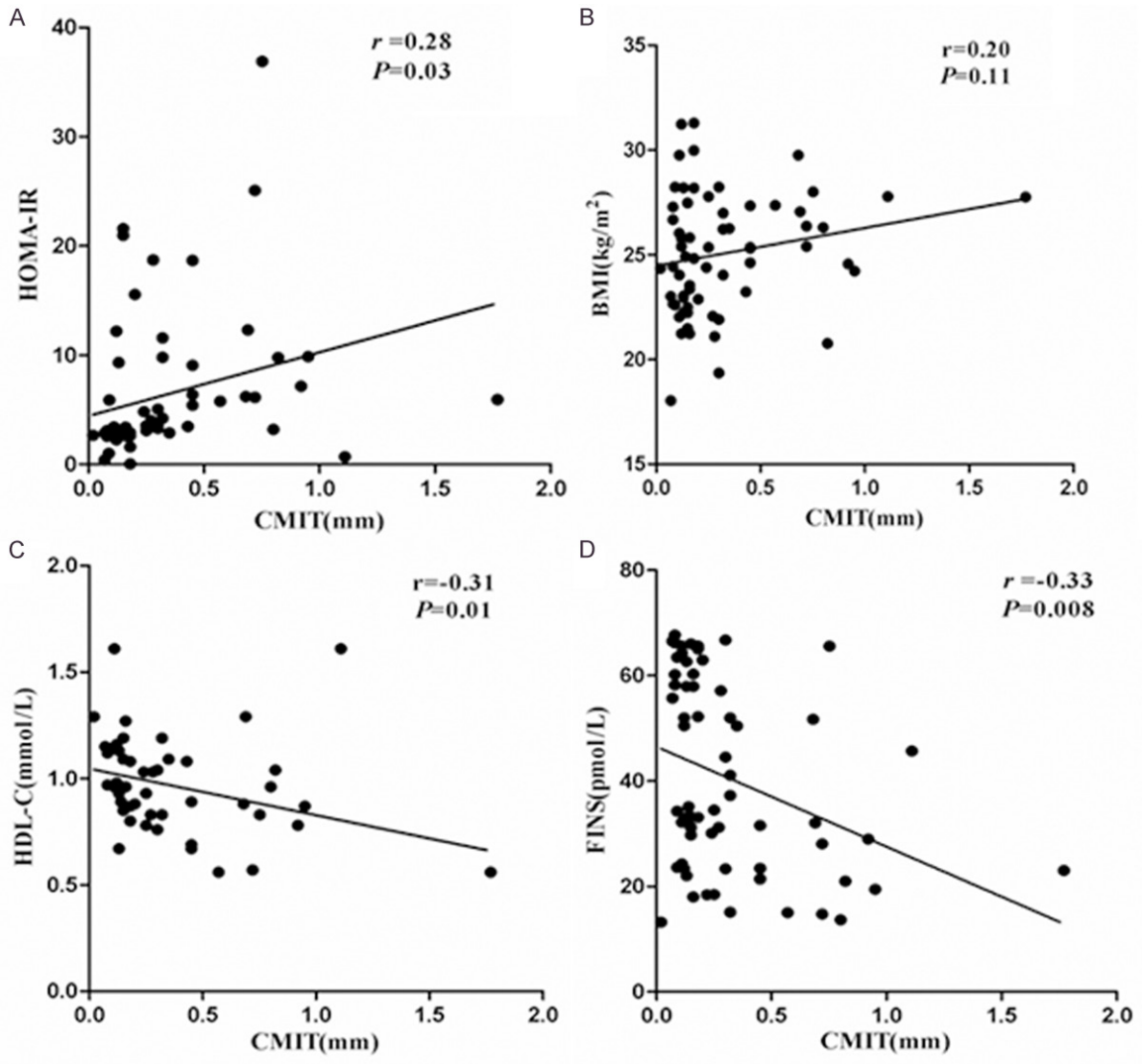



**Figure 2.** Correlations between CIMT with clinical parameters (Pearson correlation analysis).

**Table 3.** Multiple linear regression analysis of CIMT

| $R^2$ | 0.3145 | | | |
|---|---|---|---|---|
| Independent variables | Coefficient | Std. Error | t | *P* |
| BMI | -0.002821 | 0.01174 | -0.240 | 0.8111 |
| CRP | -0.006731 | 0.007685 | -0.876 | 0.3857 |
| DBP | 0.01097 | 0.005477 | 2.002 | 0.0513 |
| FINS | -0.005876 | 0.002270 | -2.589 | 0.0129* |
| PINS | 0.005856 | 0.002287 | 2.561 | 0.0139* |
| FPG | 0.01312 | 0.01611 | 0.814 | 0.4197 |
| HbA1C | 0.03003 | 0.02221 | 1.352 | 0.1831 |
| HOMA-IS | -0.02832 | 0.02778 | -1.019 | 0.3134 |
| HOMA-IR | 0.01206 | 0.005804 | 2.078 | 0.0434* |
| HDL | 0.1426 | 0.1715 | 0.831 | 0.4101 |
| LDL | -0.007733 | 0.1037 | -0.0746 | 0.9409 |
| TC | 0.05891 | 0.1034 | 0.570 | 0.5716 |
| TG | -0.009138 | 0.02506 | -0.365 | 0.7171 |

*$P < 0.05$.

ses. Moreover, they were positively associated with HOMA-IR. It showed significant correlations of plasma CIMT with FINS, PINS and HOMA-IR. This result suggests that the plasma Fetuin-A levels may be associated with macroangiopathies in nT2DM patients. Thus, early detecting plasma Fetuin-A levels nT2DM provides an opportunity to intervene of carotid artery disease in diabetic patients and giving timely treatment for the prevention of diabetic vascular complications.

In conclusion, our study found that plasma Fetuin-A levels are significantly increased and significantly associated with clinical characteristics in nT2DM. More importantly, early detecting plasma Fetuin-A levels nT2DM provides an opportunity to intervene of carotid artery disease in diabetic patients and can be

used as independent markers in the diagnosis of macroangiopathies in nT2DM.

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## Disclosure of conflict of interest

None.

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