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Circulating asprosin concentrations are increased in type 2 diabetes mellitus and independently associated with fasting glucose and triglyceride

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ABSTRACT

Background: Asprosin has been identified as a novel hormone enriched in white adipose tissue and is pathologically increased in insulin-resistant mice and humans. However, information regarding the role of asprosin in type 2 diabetes mellitus (T2DM) remains unavailable. Via conducting a hospital-based study, we purposed to ascertain the potential relationship between circulating asprosin concentrations and T2DM.

Methods: The study recruited 84 adults with T2DM and 86 controls with normal glucose tolerance. They matched in age, body mass index (BMI), and sex. Serum asprosin concentrations were measured via ELISA method.

Results: Compared to the controls, serum asprosin concentrations were significantly increased in the T2DM adults ($P < 0.001$). As asprosin concentrations increased across its tertiles, the percentage of T2DM increased (39.28, 37.50, and 70.68%; P value for trend < 0.001). Multivariate logistic regression models demonstrated that compared with the 1st tertile of asprosin, the odds ratio of T2DM was 3.278(95% CI 1.053–10.200, $P = 0.040$) for the 3rd tertile after adjustment for potential confounders. Area under ROC curve of asprosin (sex and age adjusted) for predicting the presence of T2DM was 0.707[95% CI 0.628–0.786]. Finally, multiple stepwise regression analysis indicated that fasting glucose and triglyceride were independently associated with serum asprosin in T2DM.

Conclusions: Asprosin concentrations are increased in adults with T2DM. The results suggest that asprosin might serve as a risk factor associated with the pathogenesis of T2DM, but not an ideal biomarker for predicting T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM), characterized by chronic hyperglycemia, has become a serious hazard to human health in the recent decades. A most recent report estimated that the prevalence of diabetes in adults is predicted to rise to 10.4% in 2040 [1]. The high global incidence of diabetes has brought considerable burden for treatment of its related complications [1]. Insulin resistance, characterized by impaired insulin action in skeletal muscle, adipose tissue, and the liver, is one of the major cause of T2DM. However, the pathogenesis of insulin resistance is not fully understood. For example, hyperinsulinemia and insulin resistance, who is the cart and who is the horse in the onset of diabetes remains controversial [2,3].

Obesity is linked to hyperinsulinemia and insulin resistance [4,5], and is an independent risk factor for the onset of T2DM [6,7]. Adipose tissue, traditionally known as an energy storage depot, also has endocrine function to secrete bioactive adipokines [8–10]. Many adipokines such as resistin, adiponectin, and leptin are implicated in the progress of glucose homeostasis, inflammation, and insulin sensitivity [8–10]. Conversely, excessive adiposity leads to dysfunction of adipokines and obesity-related disorders [2,11]. A variety of adipokines alter their concentrations under the condition of T2DM [12–16].

Asprosin recently has been identified as a novel hormone secreted by white adipose tissue (WAT) [17]. Romere et al. demonstrated that asprosin is a 140-amino-acid protein and is the C-terminal cleavage product of profibrillin (a pro-protein encoded by FBN1 gene) [17]. The team also found that asprosin peaks during fasting and modulates hepatic glucose release through G protein-cAMP-PKA pathway. Single injection of recombinant asprosin could lead to immediate increase of blood glucose and hyperinsulinemia [17]. In addition, asprosin was pathologically increased in mice models and humans with insulin resistance, while specific antibody of asprosin reduced plasma asprosin concentrations and improved insulin sensitivity in those mice [17]. Thus, attenuating asprosin activity or depleting asprosin may provide a new therapeutic potential for the treatment of T2DM and obesity. To our knowledge, literature is unavailable regarding the association of serum asprosin and T2DM in humans. Therefore, we conducted the hospital-based case-control study to explore the clinical relevance of the

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novel hormone in adults with newly diagnosed T2DM.

2. Material and methods

2.1. Subjects and study design

The work consisted of a total of 170 subjects (101 male; 69 female), including 86 adults with normal glucose tolerance (NGT) and 84 adults with newly diagnosed T2DM. Those with T2DM were screened from patients firstly attending the inpatient of department of Endocrinology and Metabolism at the First Affiliated Hospital of Soochow University, from March to June 2017. At first, we enrolled 86 T2DM cases in this study. Unfortunately, two patients suffered from respiratory tract infection and were excluded. After the oral glucose tolerance test, the NGT volunteers who matched in age, body mass index (BMI), and sex were recruited from the medical examination center in the same hospital. NGT and T2DM were defined in line with the criteria recommended by American Diabetes Association (ADA) in 2014 [18]. Those with Fasting glucose ≥ 7.0 mmol/l, or HbA1c $\geq 6.5\%$, or OGTT-2 h post-load plasma glucose ≥ 11.1 mmol/l were defined as diabetes. Fasting glucose < 6.1 mmol/l, HbA1c $< 5.7\%$ and OGTT-2 h post-load plasma glucose < 7.8 mmol/l were the criteria of NGT. The inclusion criteria for T2DM patients were: have not received any treatment for diabetes, including medication affecting insulin secretion or glucose tolerance, diet control, and exercise therapy. To collect data about drug use, history of diseases, smoking history, and alcohol consumption, a detailed questionnaire was completed by each subject. The exclusion criteria for all participants were the following: < 25 or > 70 y, BMI ≥ 40 kg/m^2, type 1 diabetes, cancer, Cushing's syndrome or thyroid disorders, treatment with systemic corticosteroids, medicine for hypertension or lipid-lowering drugs, acute or chronic virus hepatitis, liver, renal, or heart failure, infection or inflammation, pregnancy, drinking > 140 g alcohol/wk, and cigarettes smoking. Hypertension is not an exclusion criteria. The study protocol was approved by the Ethics Committee of Xinghua people's Hospital and the First Affiliated Hospital of Soochow University; each one signed an informed consent regarding the study. All human rights were observed in keeping with the Helsinki Declaration.

2.2. Anthropometric data collection

Anthropometric data including weight, height, waist circumference (WC), and hip circumferences (HC) were collected by our professional nurses. Waist-hip ratio (WHR) was calculated as WC divided by HC. Before blood pressure measured, every one kept a sitting position for rest at least 10 min. An electronic sphygmomanometer (Omron) was used to measure blood pressure for 3 times. The average of the three values was calculated.

2.3. Biochemical measurements

Following overnight fasting (at least 12 h), blood samples were taken (07:30–08:30 a.m.) and separated through centrifuge. Blood glucose, serum lipids including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol(LDL-C), triglyceride(TG), and total cholesterol(TC) were determined using a Hitachi 7600 analyzer(Hitachi, Ltd., Tokyo, Japan). An automated Immunoassay Analyzer was used to measure insulin concentrations (AIA-2000ST). HbA1c concentrations were determined via high performance liquid chromatography method (HLC-723G8). The rest fasting serum samples were stored -80 °C until asprosin measurement.

2.4. Indices of insulin secretion and insulin sensitivity/resistance

Homeostasis model assessment of insulin resistance index (HOMA-IR) was used to evaluate the status of insulin resistance. HOMA-IR formula = [fasting glucose (mmol/l) × fasting insulin (mIU/l)]/22.5 [19]. In 75-g OGTT, HOMA-β and Insulinogenic index were calculated as insulin secretion indices using the following formula [19,20]: HOMA-β = fasting insulin (mIU/l) × 20/[fasting glucose (mmol/l) − 3.5]; Insulinogenic index = [insulin (30 min) − fasting insulin (pmol/l)] / [glucose (30 min) − fasting glucose (mmol/l)]; quantitative insulin check index (QUICKI) was calculated as insulin sensitivity indices using the following formula [21]: QUICKI = $1/[\log_{10}$ fasting glucose (mg/dl) + $\log_{10}$ fasting insulin (mIU/l)].

2.5. Measurements of asprosin

Serum asprosin concentrations were measured via a human-exclusive ELISA kit (Catalogue No. abx257694; abbexa, Cambridge, UK). The measurement was performed following the instructions of the manufacturer. The assay is highly sensitive to human asprosin with a sensitivity of < 0.938 ng/ml. The intra-assay CV was $< 10\%$ and the inter-CV was $< 6\%$.

2.6. Statistical analysis

SPSS ver 23 and GraphPad Prism 5 Software were performed for all statistical analyses. To test characters of data distribution, Kolmogorov–Smirnov test and P–P plot were used. Data normally distributed were shown as mean ± SD and data with skewed distribution were shown as median (IQR, 25th–75th). Chi-square test was performed to compare categorical data. Mann-Whitney *U* test or independent samples *t*-test were performed to calculate differences of continues variables between two groups. For multiple testing among groups, one way ANOVA or Kruskal-Wallis test were performed and Bonferroni correction was used. To analyze bivariate correlation between asprosin and other variables, Pearson correlation analysis was conducted. To identify independent factors related to asprosin, multiple stepwise regression analysis was conducted to control the covariates. Data non-normally distributed were log-transformed (e.g., log-asprosin) before correlation analysis and multiple stepwise regression analysis. In the linear regression models, Variance inflation factor (VIF) was used to test multi-collinearity of independent variables. A variable with VIF ≥ 3.0 was considered to be collinear and was eventually removed from the model. To assess the correlation between asprosin concentrations and the prevalence of T2DM, trend Chi-square test was used. To control potential confounders which could be risk factors of T2DM (e.g. Sex, Age, BMI, etc.), multivariate logistic regression models were performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for T2DM. Asprosin concentrations for detecting T2DM were demonstrated by ROC curves. P value < 0.05 (2-side) was considered to be statistically significant.

Power analysis: According to the asprosin concentrations and subjects number of the two groups, the effect size was 0.7003, the power of the sample size was 0.9740, calculated by G*Power 3.0 software (Heinrich-Heine).

3. Results

3.1. General characteristics of the subjects

The clinical parameters of the 170 subjects are presented in Table 1. Naturally, sex, age and BMI, were similar between NGT and T2DM group. As expected, compared to the controls, patients with T2DM exhibited more disorders of lipids and glucose-associated parameters (fasting glucose, HbA1c, HOMA-IR, Insulinogenic index, HOMA-β, QUICKI, Fasting insulin, HDL-C, and LDL-C included, $P < 0.01$). In the T2DM group, WC and WHR were higher ($P < 0.01$). Between the two groups, other variables including Hypertension (%), SBP, DBP, TC, and TG showed no significant differences.

Table 1
General clinical and laboratory parameter in participants with and without type 2 diabetes.

Variable	NGT	T2DM	*P* value
N	86	84	
Sex (M/F)	49/37	52/32	NS
Age (y)[a]	47.60 ± 7.95	49.93 ± 10.99	NS
BMI (kg/m^2)[a]	24.81 ± 3.91	25.25 ± 4.20	NS
WC (cm)[a]	84.72 ± 10.26	91.61 ± 10.78	< 0.001
WHR[a]	0.87 ± 0.06	0.93 ± 0.06	< 0.001
SBP (mm Hg)[a]	126.80 ± 16.00	126.13 ± 14.65	NS
DBP (mm Hg)[a]	80.68 ± 13.70	79.03 ± 11.04	NS
Fasting glucose (mmol/l)[a]	5.26 ± 0.50	10.74 ± 4.10	< 0.001
Fasting insulin (mIU/l)[b]	6.29(4.13–8.87)	11.20(7.60–14.90)	< 0.001
HbA1c (%)[a]	5.2 ± 0.3	10.1 ± 2.5	< 0.001
HbA1c (mmol/mol)[a]	34 ± 3	87 ± 27	< 0.001
HOMA-IR[b]	1.49(0.95–2.15)	5.26(2.79–8.20)	< 0.001
HOMA-β[b]	74.33(51.89–105.31)	33.28(18.63–60.04)	< 0.001
Insulinogenic index[b]	70.68(49.67–91.99)	22.68(16.59–33.23)	< 0.001
QUICKI[a]	0.36 ± 0.03	0.30 ± 0.03	< 0.001
TG (mmol/l)[b]	1.45(0.94–2.02)	1.42(0.95–2.44)	NS
TC (mmol/l)[a]	4.79 ± 0.78	4.65 ± 1.28	NS
LDL-C(mmol/l)[a]	2.43 ± 0.79	2.80 ± 0.84	0.001
HDL-C(mmol/l)[a]	1.69 ± 0.35	1.15 ± 0.32	< 0.001
Hypertension (%)	27.91	38.10	NS

BMI body mass index; WC waist circumference; WHR waist-hip ratio; SBP systolic blood pressure; DBP diastolic blood pressure; QUICKI: Quantitative Insulin Check Index.
The enumeration data were compared with χ^2 test.
[a] Data normally distributed are shown as mean ± SD. Independent sample *t*-test was performed.
[b] Data with skewed distribution are shown as median (IQR). Mann–Whitney *U* test was performed.

3.2. Serum asprosin concentrations

As shown in Fig. 1(A), serum asprosin concentrations were significantly increased in the T2DM patients compared to the controls [3.52(1.50–7.17) vs. 1.77(1.24–3.45) ng/ml, median (25th–75th), $P < 0.001$]. Serum asprosin concentrations were not sexually dimorphic (NGT: 1.80(1.20–3.27) vs. 1.74(1.26–3.60) ng/ml, T2DM: 3.22(1.22–7.49) vs. 4.44(1.85–7.17) ng/ml, male vs. female, $P > 0.05$, respectively).

3.3. Correlations between serum asprosin concentrations and clinical parameters

As listed in Table 2, Pearson correlation analysis indicated that the concentrations of serum asprosin (log-transformed) were positively correlated with log-fasting glucose($r = 0.317$, $P = 0.003$), BMI ($r = 0.221$, $P = 0.044$), WC($r = 0.238$, $P = 0.030$), WHR($r = 0.250$, $P = 0.022$), log-TG($r = 0.250$, $P = 0.023$), log-HOMA-β($r = -0.220$, $P = 0.045$), QUICKI ($r = -0.256$, $P = 0.019$), and log-HOMA-IR ($r = 0.269$, $P = 0.013$) in the T2DM group. In the NGT group, serum asprosin concentrations were only correlated with log-TG($r = 0.223$, $P = 0.039$) and HDL-C($r = -0.256$, $P = 0.025$), while not with any adiposity index. As presented in Table 3, in the stepwise linear regression model, when adjusting for covariates which were associated with asprosin in the Pearson correlation analysis, BMI, WHR, HOMA-IR, HOMA-β, QUICKI were eventually excluded from the model. Fasting glucose and TG were the independent factors associated with asprosin concentrations in T2DM ($P = 0.004$, $P = 0.023$, respectively).WC didn't enter into the model due to its high multi-collinearity (VIF > 3.0).

Table 2
Bivariate correlation between serum asprosin levels and other variables.

Asprosin[a]	T2DM		NGT	
	r	*P*	*r*	*P*
Age	− 0.030	NS	0.045	NS
BMI	0.221	0.044*	0.110	NS
WC	0.238	0.030*	0.193	NS
WHR	0.250	0.022*	0.023	NS
SBP	0.171	NS	− 0.010	NS
DBP	0.176	NS	0.028	NS
Fasting glucose	0.317	0.003*	0.045	NS
Fasting insulin[a]	0.110	NS	0.121	NS
HbA1c	0.034	NS	0.167	NS
HOMA-IR[a]	0.269	0.013*	0.145	NS
HOMA-β[a]	− 0.220	0.045*	0.138	NS
Insulinogenic index[a]	0.187	NS	0.073	NS
QUICKI	− 0.256	0.019*	− 0.158	NS
TG[a]	0.250	0.023*	0.223	0.039*
TC	0.075	NS	0.010	NS
LDL-C	0.122	NS	− 0.104	NS
HDL-C	− 0.144	NS	− 0.256	0.025*

BMI body mass index; WC waist circumference; WHR waist-hip ratio; SBP systolic blood pressure; DBP diastolic blood pressure; QUICKI: Quantitative Insulin Check Index. Pearson correlation analysis was used.
[a] These variables were log-transformed before analysis.
* *P* value < 0.05 was considered significant.

3.4. Serum asprosin concentrations and T2DM

All subjects were stratified into trisection according to asprosin tertiles (T1: < 1.59 ng/ml; T2: 1.59–3.78 ng/ml; T3: ≥ 3.78 ng/ml). The clinical parameters of each category were listed in Table 4, variables including percentage of T2DM, BMI, WC, WHR, TG, HDL-C and

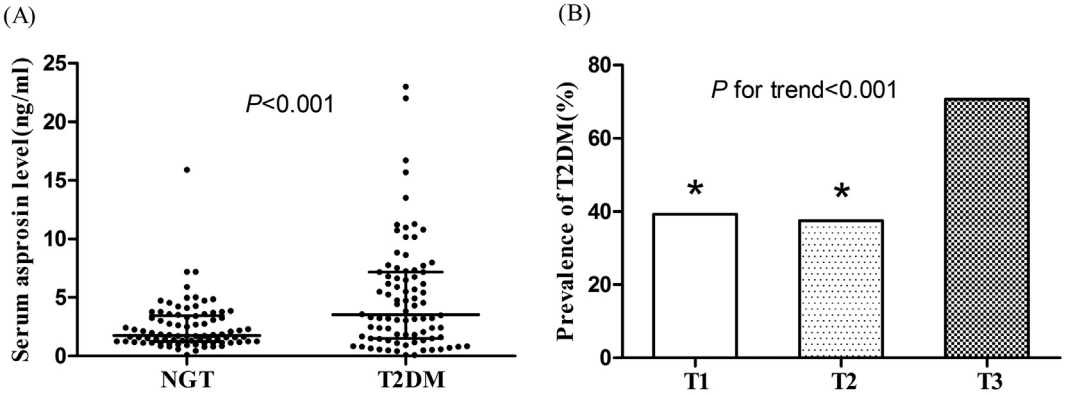

Fig. 1. (A) Serum asprosin levels (median (IQR) marked) in the NGT and T2DM Group.
(B) Prevalence (T1–T3: 39.28%, 37.50%, and 70.68%; $P < 0.001$) of T2DM according to asprosin tertiles; Chi-square test, trend Chi-square test and Bonferroni correction were used in the statistical analysis. Vs. T3, *$P < 0.001$.

Table 3
Multiple stepwise regression analysis: independent factors associated with serum asprosin levels in patients with T2DM.

Independent factors	β (unstandardized coefficient)	Std. error	*t*	*P* value
Fasting glucose	0.037	0.012	2.986	0.004
TG	0.349	0.151	2.314	0.023
Constant	0.018	0.143	0.124	NS

In this model, BMI, WHR, HOMA-IR, HOMA-β, QUICKI were also included as covariates, but they were not independently associated with asprosin. WC did not enter into the model due to its high multi-collinearity (VIF > 3.0). TG and asprosin were log-transformed before analysis. $P < 0.05$ was considered significant.

glucose-associated parameters presented an obvious variation tendency across the tertiles. As shown in Fig. 1(B), trend Chi-square test indicated that the percentage of T2DM increased, as asprosin concentrations increased across its tertiles (T1: 39.28%, T2: 37.50%, and T3: 70.68%; *P* value for trend < 0.001). As shown in Table 5, in logistic regression model 1 (reference, T1), an OR of 3.727 (95% CI 1.710–8.125, $P < 0.001$) in the 3rd tertile was observed for T2DM prevalence. OR of T2DM were not significantly different between the 1st and 2nd tertile of asprosin. In model 3, when further controlled age, sex, and adiposity indexes, the OR was 2.972 (95% CI 1.280–2.900, $P = 0.011$) for the 3rd tertile. In model 5, even after adjusting for sex, age, SBP, DBP, BMI, WC, hypertension, and lipids profiles, which could be confounders of asprosin, the tendency persisted with an OR of 3.278 (95% CI 1.053–10.200, $P = 0.040$) in the 3rd tertile.

As illustrated in Fig. 2, ROC curves of asprosin values for predicting the incidence of T2DM have been constructed. Unadjusted area under the curve (AUC) was 0.661(95%CI 0.576–0.746), $P < 0.001$; AUC adjusted for sex and age was 0.707(95%CI 0.628–0.786), $P < 0.001$.

4. Discussion

The main finding of the current research is that circulating asprosin concentrations were significantly increased in patients with newly diagnosed T2DM. Further, after adjustment for several confounders, the OR of having T2DM gradually increased following the increasing tertiles of asprosin. Besides, fasting glucose and TG were the independent factors associated with asprosin concentrations in T2DM. Collectively, these findings suggest that asprosin might be a risk factor associated with the development of T2DM.

Adipose tissue has the endocrine role to regulate metabolism and balance energy homeostasis [8–10]. Several adipose tissue-secreted molecules can either enhance or impair insulin action [8–10]. Insulin resistance, a major cause of T2DM, is one of the most remarkable changes which occur with excess adiposity. Thus, obesity is causally linked to a constellation of metabolic diseases such as T2DM and metabolic syndrome [6,7,22]. Asprosin, a novel protein hormone secreted by WAT, has the function to induce hepatic glucose release [17].

Table 5
ORs and 95% CIs for T2DM risk according to serum asprosin levels.

	OR(95%CI)		
	T1 (reference)	T2	T3
Model 1	1	0.927 (0.181–2.032)	3.727 (1.710–8.125)
P value		0.846	0.001
Model 2	1	0.994 (0.459–2.153)	3.794 (1.726–8.341)
P value		0.987	0.001
Model 3	1	0.950 (0.421–2.141)	2.972 (1.280–2.900)
P value		0.902	0.011
Model 4	1	1.034 (0.445–2.399)	3.486 (1.444–8.414)
P value		0.939	0.005
Model 5	1	0.549 (0.172–1.754)	3.278 (1.053–10.200)
P value		0.312	0.040

Model 1: crude.
Model 2: adjusted for age and sex.
Model 3: adjusted for Model 2 + BMI, waist circumference.
Model 4: adjusted for Model 3 + systolic blood pressure, diastolic blood pressure + hypertension (%).
Model 5: adjusted for Model 4 + triglyceride, Total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

Table 4
General clinical and laboratory parameter of all subjects according to serum asprosin levels.

Variable	T1	T2	T3	*P* value
Serum asprosin level (ng/ml)	< 1.59	1.59–3.78	≥ 3.78	
n	56	56	58	
Percentage of T2DM (%)	39.28	37.50	70.68[bd]	< 0.001
Sex (M/F)	34/22	31/25	36/22	NS
*Age (y)	49.46 ± 9.27	47.14 ± 9.29	49.62 ± 10.21	NS
*BMI (kg/m^2)	24.15 ± 3.54	24.88 ± 4.09	26.03 ± 4.30[a]	0.042
*WC (cm)	85.13 ± 9.50	86.41 ± 11.71	92.70 ± 11.91[a]	0.001
*WHR	0.89 ± 0.06	0.88 ± 0.07	0.93 ± 0.07[bd]	< 0.001
*SBP (mm Hg)	125.18 ± 15.63	125.55 ± 14.73	128.59 ± 15.54	NS
*DBP (mm Hg)	78.71 ± 11.23	79.11 ± 12.77	81.69 ± 13.22	NS
#Fasting glucose (mmol/l)	5.46(4.99–7.51)	5.50(5.02–7.95)	9.26(5.11–6.01)[bd]	< 0.001
#Fasting insulin (mIU/l)	7.80(4.56–10.62)	7.63(5.01–12.20)	6.40(5.52–13.50)	0.05
#HbA1c (%)	5.40(5.02–9.10)	5.55(5.20–9.45)	8.75(5.50–10.78)[bc]	0.001
#HbA1c (mmol/mol)	32 (31–76)	37 (33–80)	72 (37–94)	0.001
#HOMA-IR	2.01(1.06–3.19)	1.96(1.19–3.68)	4.61(1.75–7.16)	0.001
#HOMA-β	60.33(40.64–86.47)	66.96(38.47–104.89)	38.04(19.84–67.60) [bc]	< 0.001
#Insulinogenic index	42.33(28.08–84.99)	50.40(25.60–82.50)	38.19(19.57–61.31)	NS
*QUICKI	0.35 ± 0.04	0.34 ± 0.04	0.31 ± 0.03[bc]	< 0.001
#TG (mmol/l)	1.24(0.85–1.78)	1.51(0.92–2.40)	1.86(1.07–2.47)[b]	0.01
*TC (mmol/l)	4.60 ± 1.00	4.86 ± 0.89	4.73 ± 1.23	NS
*LDL-C (mmol/l)	2.44 ± 0.79	2.72 ± 0.81	2.60 ± 0.81	NS
*HDL-C (mmol/l)	1.53 ± 0.48	1.49 ± 0.39	1.25 ± 0.0.38[bc]	0.002
Hypertension (%)	32.14	25.57	36.21	NS

BMI body mass index; WC waist circumference; WHR waist-hip ratio; SBP systolic blood pressure; DBP diastolic blood pressure; QUICKI: Quantitative Insulin Check Index.
The category data were compared with Chi-square test.* Data normally distributed are shown as mean ± SD. One way ANOVA test was performed. #Data with skewed distribution are shown as median (IQR). Kruskal–Wallis was performed. Multiple comparisons were adjusted by Bonferroni correction.
Vs. T1, [a] $P < 0.05$, [b] $P < 0.01$.
Vs. T2, [c] $P < 0.05$, [d] $P < 0.01$.

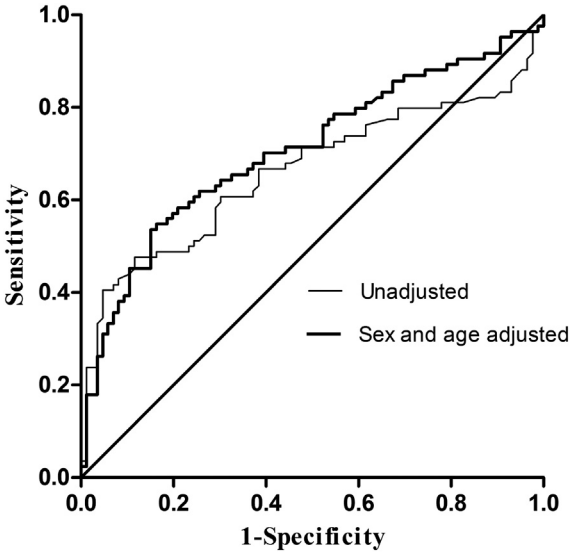

Fig. 2. ROC curves of asprosin values for T2DM diagnosis. Unadjusted: AUC = 0.661(95%CI 0.576–0.746), $P < 0.001$; Sex and age adjusted: AUC = 0.707(95%CI 0.628–0.786), $P < 0.001$.

Besides, asprosin was pathologically increased in mice models and humans with insulin resistance, while specific antibody of asprosin lowered plasma asprosin and improved insulin sensitivity in these mice [17]. However, information regarding the role of asprosin in T2DM remains unavailable.

Probably due to the race and sample type difference from the previous study [17], circulating asprosin levels in our subjects are relatively lower. In our research, compared to the controls, serum asprosin concentration was significantly increased in the T2DM group. It seems that participants in the 3rd tertile of asprosin increased approximately 3-fold possibility to suffer from T2DM. Furthermore, indices of insulin secretion and insulin sensitivity were correlated with asprosin concentrations. Fasting glucose was positively and independently related to asprosin concentrations. Besides, asprosin was positively correlated with HOMA-IR, consistent with previous findings [17]. While in the controls, fasting glucose or HOMA-IR was not significantly associated with asprosin concentrations. These observations reflect the strong relationship between asprosin and T2DM. However, the mechanism responsible for high asprosin concentrations in T2DM remains unclear. According to the work by Romere C et al. [17], asprosin is a glucogenic protein hormone and glucose serves as a suppressor of asprosin in a negative-feedback axis. Given the results that asprosin is pathologically increased in insulin-resistant individuals and lowering asprosin could improve insulin sensitivity, we speculate that the dysregulation of asprosin secretion by WAT might occur, which lead to pathologically increased asprosin concentrations in T2DM. Hepatic glucose production will be increased due to the abnormal asprosin concentrations, and then hyperinsulinemia might occur and worsen insulin resistance in the liver accordingly. The possibility also has been addressed by Romere et al. [17]. Indeed, glucose regulation disorder in the insulin-resistant liver is closely implicated in the pathogenesis of T2DM [23,24]. However, further studies are required to deeply explore the underlying mechanism.

Excessive adiposity leads to dysfunction of adipokines and metabolic disorders [2,11]. The present study also indicated that serum asprosin was positively associated with adiposity-related parameters in patients with T2DM, including BMI, WC, and WHR. Following the increased asprosin concentrations, BMI, WC, and WHR were gradually increased (Table 4). While, multiple stepwise regression analysis demonstrated that, these adiposity indexes were not independently associated with asprosin concentrations. Similarly, a recent study demonstrated that the alteration of serum adiponectin and chemerin concentrations in T2DM is independent of obesity [25]. One possible explanation is that the quantity of an adipokine within the tissue is unequal to the mount released into circulation [26]. In addition, although mainly secreted by WAT, asprosin also can be secreted by other tissues [17]. Hence, the association between obesity parameters and asprosin concentrations may be toned down.

Our data also suggest that serum asprosin has a strong relationship with lipids metabolism. Both in the controls and T2DM group, asprosin concentrations were positively correlated with TG. TG was independently related to asprosin concentrations in T2DM patients. Coupled with high hepatic glucose production in the insulin-resistant liver, dyslipidemia is a common status [23,27]. Considering the liver is the target organ of asprosin and insulin resistance can lead to dyslipidemia, we have reason to assume that asprosin may be involved in the pathogenesis of lipids disorder. This hypothesis requires more research to elucidate.

In our study, the crude AUC of the ROC curve of asprosin for detecting T2DM was 0.661, AUC adjusted for age and sex was only 0.707, suggesting that asprosin is not an ideal predictor for T2DM. On the other hand, our sample size is relatively small. The cut-off value of asprosin for T2DM diagnosis needs a large-scale study to confirm. Besides, unlike other adipokines such as leptin and adiponectin [28,29], serum asprosin concentrations were not sexually dimorphic, suggesting that asprosin concentrations might not be affected by sex hormone status.

This hospital-based observational study provides the first clinical evidence regarding the role of circulating asprosin in the development of T2DM. Nevertheless, several limitations to the present study should be addressed. First, the study was based on case-control and single-center design and the samples were relatively limited. The findings should be evidenced in other ethnicities through prospective cohort study. Second, as an observational study, cause-and-effect relationship could not be confirmed between serum asprosin and the physiopathologic mechanism of T2DM. Research in vitro and in vivo is required to ascertain the underlying mechanism. Third, due to the design of our research and limited funds, we only determined the fasting asprosin concentrations in adults with NGT and T2DM. Data during OGTT (0.5 h, 1 h, 2 h, and 3 h) and data in patients with pre-diabetes are not available.

In conclusion, serum asprosin concentrations are increased in humans with newly diagnosed type 2 diabetes. Our data suggest that asprosin might serve as a risk factor associated with the development of T2DM, but not an ideal biomarker for predicting T2DM. Our findings provide new clinical insights into the roles of adipokines in the pathogenesis of T2DM.

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