ORIGINAL ARTICLE

Increased serum level and impaired response to glucose fluctuation of asprosin is associated with type 2 diabetes mellitus

Xinyue Zhang, Hui Jiang, Xiaojing Ma, Hongyan Wu*

Health Management Center, Shandong Provincial Qianfoshan Hospital, The First Affiliated-Hospital of Shandong First Medical University, Jinan, China

ABSTRACT

Aims/Introduction: Asprosin is a novel secreted adipokine that is induced by fasting and promotes hepatic glucose release. In healthy humans, circulating asprosin shows circadian oscillation with an acute drop coinciding with the onset of eating. The present study investigated whether this circadian oscillation still exists in patients with type 2 diabetes mellitus.

Materials and Methods: We recruited 60 patients with type 2 diabetes mellitus and 60 individuals with normal glucose tolerance (NGT). All participants completed a 75-g oral glucose tolerance test. Fasting and 2-h postprandial serum asprosin concentrations were measured by the enzyme-linked immunosorbent assay method. Partial correlation coefficients were calculated to analyze the relationships between serum asprosin level and parameters of glucose metabolism. Multiple logistic regression analysis was used to determine the association of serum asprosin level with diabetes.

Results: Both fasting and postprandial asprosin levels were significantly higher in patients with type 2 diabetes mellitus. The postprandial asprosin level was apparently lower than fasting asprosin level in individuals with NGT. The fasting asprosin level closely correlated with type 2 diabetes mellitus after multiple adjustment (odds ratio 2.329, $P = 0.023$). Asprosin correlated negatively with change in blood glucose ($r = -0.502$, $P < 0.001$) and change in C-peptide ($r = -0.467$, $P < 0.001$) in individuals with NGT, but not in type 2 diabetes mellitus patients.

Conclusions: Serum asprosin level decreased coinciding with the onset of the oral glucose tolerance test in individuals with NGT, whereas this circadian oscillation was disturbed in type 2 diabetes mellitus patients. The impaired response of asprosin to glucose fluctuation in type 2 diabetes mellitus patients might be one of the reasons for the onset of type 2 diabetes mellitus.

INTRODUCTION

It is estimated that >451 million people worldwide are suffering from diabetes, and the International Diabetes Federation warned that these figures were expected to increase to 693 million by 2045[1]. Type 2 diabetes mellitus is one of the most common types of diabetes mellitus, accounting for >90% of the cases[2]. Apart from insulin resistance and β-cell dysfunction, elevated hepatic glucose output is also a typical characteristic of type 2 diabetes mellitus[3]. Several types of anti-type 2 diabetes mellitus drugs, such as metformin and glucagon-like peptide-1

receptor analogs, exert their hypoglycemic effect partly through reducing hepatic glucose output[2,4]. Suppression of hepatic glucose output should always be a good therapeutic target for type 2 diabetes mellitus.

Recently, asprosin – a novel secreted adipokine – was discovered, which is induced by fasting and targets the liver, promoting hepatic glucose release through the G protein–cyclic adenosine monophosphate–protein kinase A pathway[5,6]. Humans and mice with insulin resistance show pathologically elevated plasma asprosin, and its loss of function through immunological or genetic means has a profound glucose- and insulin-lowering effect secondary to reduced hepatic glucose

release[5]. Therefore, therapeutically targeting asprosin might be beneficial in type 2 diabetes mellitus patients. Up to now, several studies have investigated the level of circulating asprosin in type 2 diabetes mellitus patients, finding that fasting circulating asprosin concentrations are increased in type 2 diabetes mellitus [7–9]. Furthermore, circulating asprosin shows circadian oscillation with an acute drop in levels coinciding with the onset of eating in healthy humans and mice[5]. However, whether this circadian oscillation still exists in type 2 diabetes mellitus patients remains unclear.

In consideration of the therapeutic potential of asprosin in diabetes, it is necessary to further investigate the role of asprosin in the pathogenesis of type 2 diabetes mellitus, and clarify whether this circadian oscillation in healthy individuals still exists in type 2 diabetes mellitus patients. Therefore, we measured fasting and 2-h postprandial serum asprosin levels in patients with previously diagnosed type 2 diabetes mellitus, and compared the change in serum asprosin level in type 2 diabetes mellitus patients with that in individuals with normal glucose tolerance (NGT).

METHODS

Ethics statement
The present study was approved by the ethics committee of Shandong Provincial Qianfoshan Hospital; the study protocol conformed to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study participants
This observational study recruited 60 patients with previously diagnosed type 2 diabetes mellitus, and 60 age-, sex- and body mass index-matched individuals with NGT at Shandong Provincial Qianfoshan Hospital, Jinan, China from May 2018 to December 2018. The following exclusion criteria were applied: (i) patients with other types of diabetes and acute complications; (ii) patients with diabetic foot or infectious diseases; (iii) patients with diabetes durations <1 year or >20 years; (iv) patients with acute cardiovascular and cerebrovascular disease; and (v) patients with severely impaired liver or renal function. Diabetes was diagnosed according to the 2006 World Health Organization criteria: fasting blood glucose (FBG) ≥7.0 mmol/L and/or 2-h postprandial blood glucose (PBG) ≥11.1 mmol/L[10].

Data collection
The computerized patient record system of Shandong Provincial Qianfoshan Hospital was used to collect data regarding the demographic characteristics and previous medication histories. Antidiabetic medications were included in the following categories: insulin, insulin secretagogues and others (thiazolidinedione, metformin, alpha glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor etc.). Medication histories of antihypertensive drugs and statins were also collected. Somatometry was carried out to collect the data of height and weight. BMI was calculated as weight (kg) divided by height squared (m²). Blood

pressure (BP) was measured three times using the left arm consecutively, and the average reading was used for analysis. After at least 10 h of overnight fasting, venous blood samples were collected, and FBG, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, uric acid and creatinine were measured by using an automatic analyzer (ARCHITECT ci16200 Integrated System; Abbott, Abbott Park, IL, USA). Plasma PBG was measured after participants had completed a 75-g oral glucose tolerance test (OGTT). To eliminate the influence of insulin therapy, fasting and 2-h postprandial C-peptide levels were measured to reflect β-cell function in all participants. FBG and fasting C-peptide were used to calculate the homeostasis model assessment of β-cell function (HOMA2-%B), HOMA of insulin resistance (HOMA2-IR) and HOMA of insulin sensitivity (HOMA2-%S) by the computerized HOMA2 model downloaded from http://www.ocdem.ox.ac.uk/[11]. Fasting and 2-h postprandial serum asprosin levels were measured using enzyme-linked immunosorbent assay kits (Human ELISA kit; Wuhan EIAab Science Co. Ltd., Wuhan, China). The change (Δ) in asprosin (ng/mL) = postprandial asprosin – fasting asprosin, ΔBG (mmol/L) = PBG – FBG and ΔC-peptide (ng/mL) = postprandial C-peptide – fasting C-peptide.

Statistical analysis
The continuous variables with normal distribution are expressed as the mean ± standard deviation, and the continuous variables with non-normal distribution are expressed as the median (interquartile range). The categorical variables are presented as numbers (%). Normal distribution of the data was tested using the Kolmogorov–Smirnov test. Between-group differences were detected using Student's *t*-test or the Mann–Whitney *U*-test. The relationships between serum asprosin level and parameters of glucose metabolism were assessed using a partial correlation analysis by controlling for the covariates. Multiple logistic regression analysis was used to determine the association of serum asprosin level with diabetes. $P < 0.05$ was considered statistically significant. All the above statistical analyses were carried out with SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of study participants
The characteristics of participants with NGT and type 2 diabetes mellitus patients are shown in Table 1. Compared with the participants with NGT, the type 2 diabetes mellitus group had significantly higher systolic BP, diastolic BP, FBG, PBG, HbA1c, total cholesterol, triglyceride, low-density lipoprotein cholesterol, aspartate aminotransferase, creatinine and uric acid, and significantly lower fasting C-peptide and high-density lipoprotein cholesterol. The changes in blood glucose and C-peptide levels during OGTT were also shown in Figure 1. As expected, PBG and 2-h postprandial C-peptide were significantly elevated in both groups. The levels of

fasting asprosin and postprandial asprosin were also significantly higher in patients with type 2 diabetes mellitus. Interestingly, the postprandial asprosin level was apparently lower than the fasting asprosin level in participants with NGT, whereas the levels of postprandial asprosin and fasting asprosin were not significantly different in the type 2 diabetes mellitus group (Figure 2).

Multiple logistic regression analysis of fasting asprosin level with diabetes

The relationship between asprosin and diabetes was explored by multiple logistic regression analysis (Table 2). Before adjusting (model 1), fasting asprosin level showed significantly increased odds ratios (ORs) for type 2 diabetes mellitus (OR 2.058, $P < 0.001$). [Correction added on 16 October 2019, after first online publication: 'Meteorin-like level' has been replaced with 'asprosin level'.] After adjusting for age, sex and BMI (model 2), increased ORs also existed (OR 2.187, $P < 0.001$). Even after further adjustment for systolic BP, triglyceride, high-density lipoprotein cholesterol, creatinine, uric acid and fasting C-peptide in model 3, asprosin still showed significantly increased ORs for type 2 diabetes mellitus (OR 2.329, $P = 0.023$).

Partial correlation analysis of fasting asprosin level and parameters of glucose metabolism in participants (age, sex, BMI adjusted)

We investigated the relationship of fasting asprosin level with parameters of glucose metabolism using partial correlation analysis in participants (Table 3). When analyzed in all participants, fasting asprosin level positively correlated with FBG, PBG and HbA1c, whereas it negatively correlated with HOMA2-%B after adjusting for age, sex and BMI. However, when analyzed in participants with NGT or type 2 diabetes mellitus patients separately, fasting asprosin level was not associated with parameters of glucose metabolism both in participants with NGT and type 2 diabetes mellitus patients, except for HbA1c in participants with NGT.

Circadian oscillation of asprosin in response to OGTT in participants with NGT and type 2 diabetes mellitus patients

To explore the circadian oscillation of asprosin in response to eating, we carried out a 75-g OGTT for all participants. Interestingly, Δasprosin correlated negatively with ΔBG ($r = -0.502$, $P < 0.001$) and ΔC-peptide ($r = -0.467$, $P < 0.001$) after adjusting for age, sex and BMI in participants with NGT

Table 1 | Characteristics of participants with normal glucose tolerance and type 2 diabetes mellitus patients

Characteristics	NGT ($n = 60$)	T2DM ($n = 60$)	P-value
Female, n (%)	26 (43.3)	28 (46.7)	0.714
Age (years)	54.62 ± 5.97	56.40 ± 7.49	0.152
BMI (kg/m^2)	25.98 ± 2.73	26.32 ± 3.41	0.546
Systolic BP (mmHg)	129.58 ± 14.00	142.37 ± 22.26	**<0.001**
Diastolic BP (mmHg)	78.27 ± 7.86	83.20 ± 14.48	**0.023**
FBG (mmol/L)	5.22 ± 0.27	8.43 ± 1.60	**<0.001**
PBG (mmol/L)	6.02 ± 0.94	17.31 ± 3.45	**<0.001**
HbA1c (%)	5.05 ± 0.31	8.99 ± 1.27	**<0.001**
Fasting C-peptide (ng/mL)	1.74 (1.47–2.10)	1.40 (0.97–1.99)	**0.003**
Postprandial C-peptide (ng/mL)	3.61 (2.73–4.91)	3.59 (2.49–4.71)	0.985
TC (mmol/L)	4.50 ± 0.55	4.83 ± 1.06	**0.038**
TG (mmol/L)	0.97 (0.80–1.07)	1.78 (1.46–2.47)	**<0.001**
HDL-C (mmol/L)	1.38 ± 0.21	1.11 ± 0.30	**<0.001**
LDL-C (mmol/L)	2.88 ± 0.53	3.21 ± 0.85	**0.011**
ALT (U/L)	16.87 ± 5.09	18.78 ± 5.93	0.060
AST (U/L)	16.97 ± 3.56	18.58 ± 4.54	**0.032**
Creatinine (μmol/L)	62.11 ± 11.13	67.57 ± 18.08	**0.049**
UA (μmol/L)	273.37 ± 75.79	314.83 ± 82.22	**0.005**
Insulin secretagogues treatment, n (%)	–	35 (58.3)	–
Insulin treatment, n (%)	–	33 (55.0)	–
Other antidiabetic treatment, n (%)	–	53 (88.3)	–
Anti-hypertensive drugs, n (%)	14 (23.3)	30 (50.0)	**<0.001**
Statins treatment, n (%)	17 (28.3)	31 (51.7)	**<0.001**
Fasting asprosin (ng/mL)	5.22 ± 1.26	6.20 ± 1.13	**<0.001**
Postprandial asprosin (ng/mL)	3.79 ± 1.21	6.02 ± 1.10	**<0.001**

Data are presented as mean ± standard deviation or median (interquartile range). The bold values indicate the P-values which were <0.05. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; PBG, postprandial blood glucose; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; UA, uric acid.
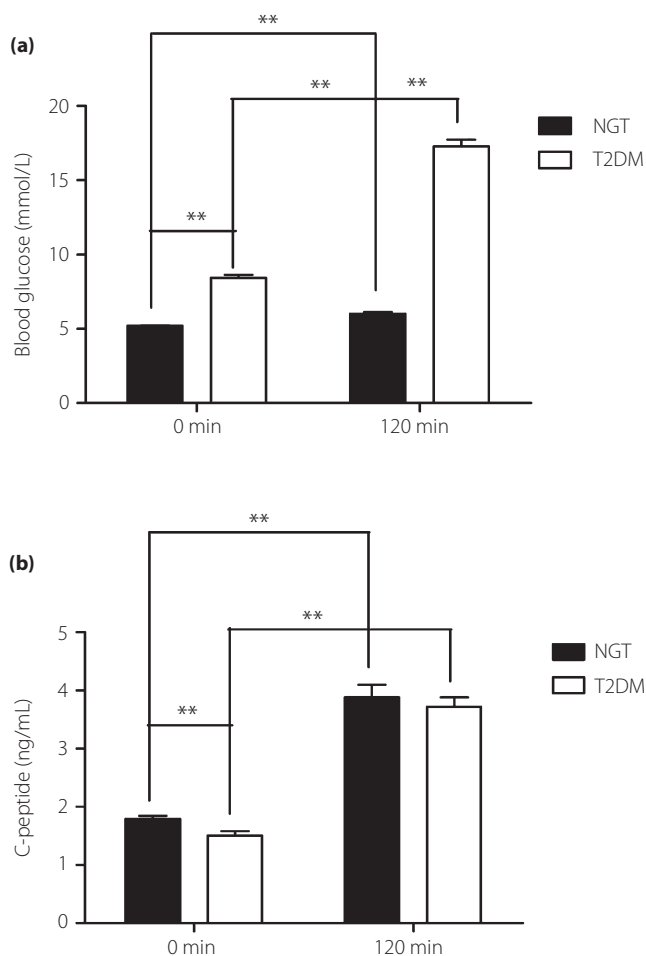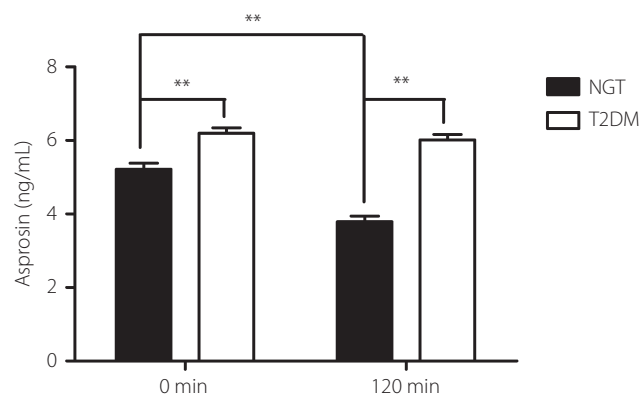
Figure 1 | Comparison of (a) blood glucose and (b) C-peptide levels in participants with normal glucose tolerance (NGT) and type 2 diabetes mellitus patients (T2DM) before and after a 75-g oral glucose tolerance test. **$P < 0.01$, data are given as mean ± standard error of the mean.

Figure 2 | Comparison of serum asprosin level in participants with normal glucose tolerance (NGT) and type 2 diabetes mellitus (T2DM) before and after a 75-g oral glucose tolerance test. **$P < 0.01$, data are given as mean ± standard error of the mean.

(Figure 3a b). However, Δasprosin was not associated with ΔBG ($r = 0.046$, $P = 0.735$) and ΔC-peptide ($r = 0.078$, $P = 0.564$) in type 2 diabetes mellitus patients (Figure 3c,d).

DISCUSSION

Asprosin is a new hormone, which is secreted by white adipose tissue and induces hepatic glucose release[5,6,12]. Fasting can increase the plasma asprosin level, whereas eating turns off its production[5]. The research team also found the plasma level of asprosin was increased in men and mice that had insulin resistance. An asprosin-specific monoclonal antibody could reduce the plasma level of asprosin in mice with insulin resistance, and improved insulin sensitivity[5]. All these findings made asprosin a potential target for new therapeutics for type 2 diabetes mellitus [5,6,12].

Since its discovery, several teams have investigated the level of circulating asprosin in type 2 diabetes mellitus patients. Zhang *et al.*[7], Wang *et al.*[8] and Li *et al.*[9] found that

circulating asprosin concentrations were increased in patients with type 2 diabetes mellitus, which was consistent with the present results (Table 1). Wang *et al.*[8] also found that plasma asprosin concentration was positively associated with FBG, PBG, HbA1c and HOMA-IR, but negatively correlated with HOMA-β in the study population that included impaired glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetes mellitus patients. However, when analyzing these correlations in participants with NGT and type 2 diabetes mellitus patients separately, Zhang *et al.*[7] only found the aforementioned relationships in type 2 diabetes mellitus patients, but not in participants with NGT. These observations reflect the strong relationship between asprosin and type 2 diabetes mellitus. Unfortunately, in the present study, the fasting serum asprosin level was not associated with parameters of glucose metabolism both in type 2 diabetes mellitus patients and participants with NGT, except for HbA1c in participants with NGT (Table 3). The conflicting results might be due to the different participants in the present study, as we included previously diagnosed type 2 diabetes mellitus patients rather than newly diagnosed type 2 diabetes mellitus patients. Zhang *et al.*[7] speculated that the dysregulation of asprosin secretion by white adipose tissue might occur in type 2 diabetes mellitus patients, which leads to pathologically increased asprosin concentrations in type 2 diabetes mellitus patients. We doubt that with the development of type 2 diabetes mellitus, this dysregulation might be worse and even affect the response of asprosin to glucose fluctuation, which leads to the impaired relationship between fasting circulating asprosin level and parameters of glucose metabolism in previously diagnosed type 2 diabetes mellitus patients.

To investigate the reactivity of asprosin to glucose fluctuation, we measured the 2-h postprandial serum asprosin level in participants with NGT and type 2 diabetes mellitus patients after all

Table 2 | Multiple logistic regression analysis of fasting asprosin level with diabetes

Models	Independent variable	B coefficient	Standard error of B coefficient	Wald statistic	Odds ratio (95% CI)	P-value
Model 1	Asprosin, per 1 ng/mL	0.722	0.189	14.561	2.058 (1.420–2.981)	**<0.001**
Model 2	Asprosin, per 1 ng/mL	0.783	0.203	14.846	2.187 (1.469 –3.257)	**<0.001**
Model 3	Asprosin, per 1 ng/mL	0.846	0.372	5.172	2.329 (1.124–4.827)	**0.023**

Model 1: not adjusted; model 2: adjusted for age, sex and body mass index; model 3: model 2 plus systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, creatinine, uric acid and fasting C-peptide. The bold values indicate the P-values which were <0.05. CI, confidence interval.

Table 3 | Partial correlation analysis of fasting asprosin level and parameters of glucose metabolism in participants (age, sex, body mass index adjusted)

Variable	All participants		NGT participants		T2DM participants	
	Coefficient (r)	P-value	Coefficient (r)	P-value	Coefficient (r)	P-value
FBG (mmol/L)	0.282	**0.002**	−0.174	0.195	−0.053	0.696
PBG (mmol/L)	0.340	**<0.001**	−0.069	0.611	−0.037	0.782
HbA1c (%)	0.364	**<0.001**	0.310	**0.019**	0.000	0.996
Fasting C-peptide (ng/mL)	−0.155	0.095	−0.204	0.128	0.021	0.874
Postprandial C-peptide (ng/mL)	−0.030	0.745	−0.029	0.829	0.036	0.788
HOMA2-%B	−0.346	**<0.001**	−0.088	0.517	0.078	0.567
HOMA2-IR	0.117	0.208	−0.214	0.111	0.016	0.903
HOMA2-%S	−0.073	0.432	0.196	0.144	−0.028	0.838

The bold values indicate the P-values which were <0.05. FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HOMA2-%B, homoeostasis model assessment of β-cell function; HOMA2-%S, homoeostasis model assessment of insulin sensitivity; HOMA2-IR, homoeostatic model assessment of insulin resistance; NGT, normal glucose tolerance; PBG, postprandial blood glucose; T2DM, type 2 diabetes mellitus.
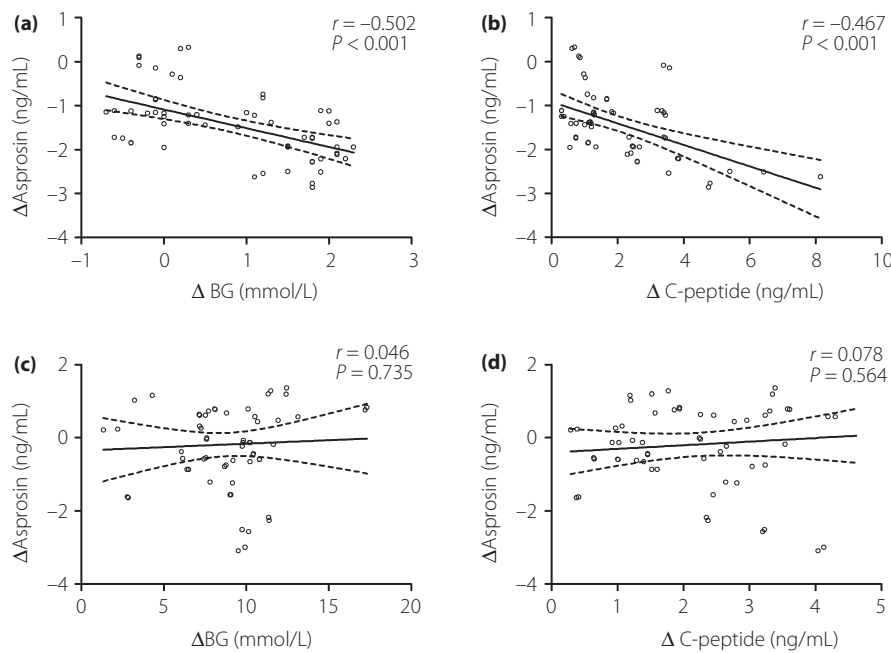
Figure 3 | Correlation between change in circulating asprosin level and glucose-related variables in (a,b) participants with normal glucose tolerance and (c,d) type 2 diabetes mellitus patients. (a,c) Change in (Δ) asprosin versus Δblood glucose (BG); (b,d) ΔAsprosin versus ΔC-peptide.

participants completed a 75-g OGTT. As expected, Δasprosin correlated negatively with ΔBG and ΔC-peptide in participants with NGT (Figure 3a,b), which was in keeping with the previous findings: plasma asprosin level showed an acute drop coinciding with the onset of eating[5]. However, this circadian oscillation was disturbed in type 2 diabetes mellitus patients, as we did not observe an apparent decrease of serum asprosin level after OGTT. ΔAsprosin was also not associated with ΔBG and ΔC-peptide in type 2 diabetes mellitus patients (Figure 3c,d). All these results support our hypothesis that the response of asprosin to glucose fluctuation was impaired in type 2 diabetes mellitus patients, which might be one of the reasons for the onset of type 2 diabetes mellitus and the sustained high level of blood glucose in type 2 diabetes mellitus patients.

There are still some questions about the physiological action of asprosin. For instance, the factors that regulate its secretion are unknown. Whether it is secreted just like glucagon remains unclear. Take glucagon secretion as an example, hypoglycemia can trigger glucagon secretion through a fall in the cytoplasmic adenosine triphosphate/ adenosine diphosphate ratio, leading to increased activity of the adenosine triphosphate- sensitive potassium channel and P/Q type Ca^{++} channels[13], which leads to glucagon secretory granules exocytosis. Extrinsic factors also play an important role in triggering glucagon secretion, including signals from the sympathetic and parasympathetic branches of the autonomic nervous system[14,15]. The intrinsic mechanism of asprosin secretion regulated by fasting and eating requires much deeper research.

Besides the relationship between asprosin and type 2 diabetes mellitus, the roles of asprosin in other diseases were also explored. Alan *et al.*[16] found that asprosin was also related to insulin resistance in women with polycystic ovary syndrome. Duerrschmid *et al.*[17] proved that asprosin was a centrally-acting orexigenic hormone. Asprosin in the circulation could cross the blood–brain barrier and directly activate orexigenic Agouti-related peptide neurons through a cyclic adenosine monophosphate-dependent pathway, leading to appetite stimulation and a drive to accumulate adiposity and bodyweight[17,18]. Acara *et al.*[19] suggested that asprosin might be a novel biochemical marker for predicting the severity of acute coronary syndrome with unstable angina pectoris. Wang *et al.*[20] showed that higher asprosin concentrations before bariatric surgery were associated with the weight reduction magnitude at 6 months after surgery. More pathophysiological roles of asprosin require further study.

Several limitations to the present study should be addressed. First, the study was an observational study, a cause-and-effect relationship between impaired asprosin response to glucose fluctuation and type 2 diabetes mellitus onset could not be confirmed. Second, the present study contained only Chinese participants, and the samples were relatively limited; therefore, the present study should be replicated in other ethnicities with larger samples. Third, we could not fully exclude other potential confounding factors, including exercise, as asprosin might be induced by acute anaerobic exercise[21]. In addition, as asprosin

was mainly produced by adipose tissue, body percentage of fat mass should also be assessed and adjusted in statistical analyses. Finally, we only detected two time points (0 min and 120 min) for blood glucose, C-peptide and serum asprosin during OGTT, the more detailed changes in serum asprosin during OGTT in type 2 diabetes mellitus patients needed to be assessed at more time points.

In conclusion, we found that both the levels of fasting asprosin and postprandial asprosin were higher in patients with type 2 diabetes mellitus. Serum asprosin levels decreased coinciding with the onset of OGTT in participants with NGT, whereas this circadian oscillation was disturbed in type 2 diabetes mellitus patients. The response of asprosin to glucose fluctuation was impaired in type 2 diabetes mellitus patients, which might be one of the reasons for the onset of type 2 diabetes mellitus. Future in-depth studies are required to explore the pathophysiological mechanisms and clinical implications of asprosin in type 2 diabetes mellitus patients.

DISCLOSURE
The authors declare no conflict of interest.

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