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Circulating asprosin, irisin, and abdominal obesity in Chinese patients with type 2 diabetes mellitus: a case-control study

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Abstract

Introduction: Studies have suggested that serum asprosin and irisin were involved in type 2 diabetes mellitus (T2DM) and obesity. This study evaluated circulating levels of asprosin and irisin and their associations with anthropometric and metabolic parameters, especially the visceral fat area (VFA) in T2DM patients with abdominal obesity (AO).

Material and methods: In this case-control study, 131 patients with T2DM were grouped into an AO group (n = 68) and a non-AO group (NAO) (n = 63) based on their VFA. Anthropometric and metabolic parameters as well as serum asprosin and irisin levels were measured and compared between the 2 groups.

Results: Compared to the NAO group, the AO group had significantly higher serum asprosin and irisin concentrations (3.67 ± 1.76 ng/mL *vs*. 2.85 ± 0.90 ng/mL, p = 0.001; 154.62 ± 61.87 pg/mL *vs*. 130.54 ± 34.89 pg/mL, p = 0.008, respectively) and greater VFA (p < 0.001). Serum asprosin in the AO group was positively associated with weight, waist circumference (WC), hipline, body mass index, fasting blood glucose (FBG), glycated haemoglobin (HbA_{1c}), VFA, subcutaneous fat area, and total abdominal fat area (TAFA), and the serum irisin concentration in the AO group was positively correlated with WC, waist-to-hip ratio (WHR), VFA, and TAFA and negatively correlated with FBG. Stepwise logistic regression analysis suggested that FBG and VFA were independent factors positively associated with serum asprosin, and that FBG was independently, negatively associated with serum irisin, while VFA was independently, positively associated with serum irisin.

Conclusions: Elevated serum asprosin and irisin levels in T2DM patients with AO and their correlations with other metabolic parameters suggest that both are potential therapeutic agents/targets in treating obesity and its related disorders. **(Endokrynol Pol 2023; 74 (1): 55–62)**

Key words: *type 2 diabetes mellitus; abdominal obesity; asprosin; irisin; visceral fat area*

Introduction

Obesity is a well-established risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs) characterized by excessive accumulation of lipid in the adipose tissue [1–4]. In recent years, accumulating evidence has suggested that compared with whole body fat, visceral fat accumulation is more important in the development of T2DM, CVDs, and metabolic syndrome (MetS), especially in Asian countries [1–4]. Abdominal obesity (AO) is fundamental in the pathogenesis of MetS [3]. Therefore, it is important to measure visceral fat accumulation as a marker for obesity-related disorders [4]. Waist circumference (WC) and/or waist-to-hip ratio (WHR) are often used to define AO [3]. However, neither could distinguish visceral fat accumulation from subcutaneous fat accumulation (SFA) [3]. Visceral fat area (VFA) quantification has become a good surrogate marker for obesity-related disorders, and the 2019 Chinese Guideline for primary care of obesity states that VFA quantification is more accurate than WC in defining AO and that a diagnosis of AO for Chinese patients could be made with a VFA ≥ 80 cm^2 [5].

Besides lipid storage, adipose tissue is also an endocrine organ that secrets various adipokines, many of which are important in maintaining glucose homeostasis and insulin sensitivity [6–8]. Excessive adipose tissue could alter the balance among adipokines, change their concentrations, and lead to dysfunction of adipokines [6–8]. Asprosin is a 140-amino acid fasting-induced protein hormone secreted by white adipose tissue (WAT) [6–9]. It peaks during fasting, circulates to liver, and induces rapid hepatic glucose release into the circulation via activation of the G protein–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) pathway [6–9]. It also activates the orexigenic Augoti-related protein (AgRP+) neuron directly because it can pass the blood-brain barrier and thus can stimulate appetite and lead to adiposity accumulation [10]. Some studies found pathologically elevated asprosin in obese humans

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and mice as well as in humans and mice with insulin resistance [6, 9, 10]. Meanwhile, reducing circulating asprosin by asprosin-specific antibody could reduce appetite and body weight, improve insulin sensitivity, and protect against MetS [6, 9, 10]. Asprosin has been suggested as a potential therapeutic target for T2DM and obesity [6, 9, 10]. Elevated asprosin levels in patients with T2DM have been reported [6, 11, 12]; however, studies on whether the circulating asprosin level is elevated in obese patients drew conflicting conclusions [10, 13, 14]. It has been suggested that studies on adipokines in different populations, especially populations of different ethnicities, could produce different results [8].

Irisin is an adipomyokine consisting of a cleaved fragment of fibronectin type III domain-containing 5 (FNDC5) secreted by muscle tissue, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) [15, 16]. It is induced in response to exercise and could induce browning of white adipose tissue (WAT) by activating uncoupling protein 1 (UCP 1) to increase energy expenditure, and thus could account for at least part of the beneficial effect of exercise [15, 16]. In addition, its overexpression in obese mice increased energy expenditure, improved insulin sensitivity, and decreased blood glucose and insulin levels, and subcutaneous perfusion of irisin could reduce blood glucose level and improve hyperlipidaemia and insulin resistance [15–19]. Thus, irisin could be useful in the development of therapeutic strategies for metabolic disorders such as T2DM and obesity [17, 18]. Studies on the association between circulating irisin levels and metabolic disorders such as T2DM and obesity have reported different findings [18–25].

Studies on changes in circulating levels of asprosin and irisin in subjects with AO are lacking. Although Yilmaz et al. found that the circulating irisin level was associated with WC and total fat mass in non-diabetic patients under haemodialysis [26], they did not address whether VFA, a recommended surrogate marker of AO, was associated with serum levels of asprosin and irisin. In the current case-control study, we evaluated circulating levels of asprosin and irisin as well as their relationships with various anthropometric and metabolic parameters such as VFA in T2DM patients with AO. Such a study potentially provides new insights into asprosin and irisin's roles in metabolic disorders as well as their values as potential therapeutic targets in treating various metabolic disorders.

Material and methods

Study design and patients

In this single centre, case-control study, except for patients who fit the exclusion criteria below, all patients with T2DM who visited the National Metabolic Management Centre (MMC) of the Third Affiliated Hospital of Anhui Medical University from 1 February 2021 to 20 June 2021 and who signed an informed consent form were recruited. A diagnosis of diabetes was made according to the 2020 Chinese Guideline for the prevention and treatment of type 2 diabetes mellitus [27], and it was consistent with the 2020 American Diabetes Association Standards of Medical Care in Diabetes (the 2020 ADA guideline) [28]. Exclusion criteria: 1) patients with infection, tumour, type 1 diabetes (T1DM), diabetic ketoacidosis, diabetic hyperosmolar syndrome, severe cardiac, and hepatic and/or pulmonary disease(s); 2) patients with specific types of diabetes due to other causes, such as patients who were serum insulin antibody-positive or anti-glutamic acid decarboxylase antibody-positive; and 3) pregnant or lactating female patients (thus excluding gestational diabetes). The exclusion criteria were set to only include patients with T2DM in the study. Differential diagnosis of T1DM and T2DM was made according to the Chinese guideline [27] and was also consistent with the 2020 ADA guideline [28].

The recruited patients with T2DM were grouped into an AO group (VFA ≥ 80 cm^2) and a NAO group (VFA < 80 cm^2) according to the 2019 Chinese Guideline for primary care of obesity [5].

This study was approved by the Ethics Committee of The Third Affiliated Hospital of Anhui Medical University and was carried out in accordance with the principles laid down in the Declaration of Helsinki. All patients gave written informed consent before any study-related data collection, testing, or measurement.

Clinical and biochemical data collection

Individual age, gender, duration of T2DM, and blood pressure (systolic blood pressure and diastolic blood pressure) were recorded. After 8–12 hours of overnight fasting, individual's height and weight were measured and their body mass index (BMI) (weight/height) (kg/m^2) was calculated. WC (cm), hipline (cm), and WHR were measured for each patient.

After the overnight fasting a peripheral venous blood sample was collected in the morning and serum was obtained by centrifugation. Fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured with a Cobas C702 (Roche Diagnostics, Indianapolis, IN, United States). Glycated haemoglobin (HbA1c) was measured using high-performance liquid chromatography with a VARIANT II TURBO Hemoglobin Testing System (Bio-Rad Laboratories, Inc., Hercules, California, United States). Fasting C-peptide (FCP) level was determined with chemiluminescent microparticle immunoassays (Abbott i2000, Abbott, Abbott Park, IL, United States). The remaining serum samples were kept at -80°C for further asprosin and irisin measurements.

The serum levels of asprosin and irisin of all included patients were measured in one batch using commercial enzyme linked immunosorbent assay (ELISA) kits (Wuhan ColorfulGene Biological Technology Co., LTD, Wuhan, China).

VFA and SFA were determined using dual bioelectrical impedance analysis (BIA) with an Omron DUALSCAN HDS-2000 visceral fat analyser (Omron, Kyoto, Japan). Briefly, following 8-hour fasting, each patient was asked to assume a supine position and breathe calmly, with his/her wrist, ankle, and abdominal skin exposed. The patient was asked to hold his/her breath at the end of expiration, and the abdominal cross-sectional area at the level of the umbilicus was measured. Limb electrodes consisting of 4 clap-on electrodes were placed on the patient's wrists and ankles, and truncal electrodes consisting of 8 pairs of electrodes fixed to an adjustable belt were placed around the patient's waist so that the positions of the electrodes were centred on the mid-sagittal line at the level of the umbilicus. The patient was asked to breathe calmly and hold his/her breath at the end of expiration, and the VFA and SFA were measured [29]. The total abdominal fat area (TAFA) was calculated (VFA + SFA).

Statistical analysis

SPSS 26.0 software (IBM, Armonk, NY, USA) was used for all statistical analyses in the study. Data are expressed as means ± standard deviations (SD) for continuous variables. The independent samples t-test was used to compare continues variables between AO and NAO. Pearson's correlation analysis was used to evaluate the correlation between serum asprosin/irisin and other variables for the AO group, the NAO group, and all patients (AO + NAO). Forward stepwise logistic regression analysis was performed to identify factors independently associated with levels of asprosin and irisin by calculating odd ratios (OR) with 95% confidential intervals (CI). Independent variables were variables significantly associated with asprosin or irisin according to Pearson's correlation analysis, and dependent variables were whether the asprosin/irisin level in a patient was elevated based on the mean asprosin/irisin level in the study. Statistical significance was achieved with a p value < 0.05.

Results

Demographic and clinical characteristics

A total of 131 patients with T2DM were included in the study. Among them, 92 patients were male and 39 were female. Sixty-eight of the 131 patients were in the abdominal obesity group (AO) (VFA ≥ 80 cm^2) and 63 were in the non-abdominal obesity group (NAO) (VFA < 80 cm^2). Their demographic and clinical characteristics are listed in Table 1. Compared to the NAO group, patients with AO were significantly taller and heavier, had a significantly higher BMI, FCP, TG, and VLDL-C, and greater WC, hipline, WHR, VFA, SFA, and TAFA.

Compared to the NAO group, the AO group had significantly elevated levels of circulating asprosin (3.67 ± 1.76 ng/mL *vs*. 2.85 ± 0.90 ng/mL, p = 0.001) and irisin (154.62 ± 61.87 pg/mL *vs*. 130.54 ± 34.89 pg/mL, p = 0.008) (Tab. 1).

Differences in age, disease duration, systolic blood pressure, diastolic blood pressure, FBG, HbA_{1c}, TC, LDL-C, and HDL-C between the 2 groups were not statistically significant (Tab. 1).

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Table 1. *Demographic and clinical characteristics of the included patients*

Variables	T2DM-AO [n = 68]	T2DM-NAO [n = 63]	p value
Ages [years]	52.03 ± 11.41	53.73 ± 11.65	0.400
Disease duration [years]	5.67 ± 5.26	7.37 ± 5.50	0.074
Height [cm]	170.40 ± 7.94	165.31 ± 8.40	0.001*
Weight [kg]	77.36 ± 10.37	64.48 ± 9.27	< 0.001*
BMI [kg/m^2]	26.59 ± 2.77	23.54 ± 2.53	< 0.001*
WC [cm]	96.59 ± 6.85	86.81 ± 7.17	< 0.001*
Hipline [cm]	101.42 ± 4.92	95.04 ± 7.21	< 0.001*
WHR	0.95 ± 0.05	0.91 ± 0.06	< 0.001*
SBP [mmHg]	129.46 ± 16.91	127.57 ± 17.46	0.532
DBP [mmHg]	83.44 ± 11.48	81.24 ± 9.86	0.243
FBG [mmol/L]	8.44 ± 2.57	7.86 ± 2.41	0.181
HbA_{1c} (%)	8.67 ± 1.82	8.74 ± 1.93	0.849
FCP [ng/mL]	1.72 ± 0.90	1.27 ± 0.64	0.001*
TG [mmol/L]	2.65 ± 2.41	1.60 ± 1.01	0.002*
TC [mmol/L]	4.82 ± 1.85	4.42 ± 0.94	0.128
LDL-C [mmol/L]	2.74 ± 1.34	2.65 ± 0.83	0.644
HDL-C [mmol/L]	1. 07 ± 0.29	1.13 ± 0.28	0.243
VLDL-C [mmol/L]	1.06 ± 0.97	0.64 ± 0.40	0.002*
VFA [cm^2]	104.96 ± 17.07	57.86 ± 16.76	< 0.001*
SFA [cm^2]	209.60 ± 55.05	164.10 ± 48.22	< 0.001*
TAFA [cm^2]	314.56 ± 64.98	221.95 ± 58.69	< 0.001*
Asprosin [ng/mL]	3.67 ± 1.76	2.85 ± 0.90	0.001*
Irisin [pg/mL]	154.62 ± 61.87	130.54 ± 34.89	0.008*

Values are expressed as means ± standard deviations unless otherwise indicated; *p value < 0.05; T2DM — type 2 diabetes mellitus; AO — abdominal obesity; NAO — non-abdominal obesity; BMI — body mass index; WC — waist circumference; WHR — waist-hip ratio; SBP — systolic blood pressure; DBP — diastolic blood pressure; FBG — fasting blood glucose; HbA_{1c} — glycated haemoglobin; FCP — fasting C-peptide; TG — triglyceride; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; VLDL-C — very low-density lipoprotein cholesterol; VFA — visceral fat area; SFA — subcutaneous fat area; TAFA — total abdominal fat area

Table 2. *Correlations between serum asprosin level and other variables*

Variables	T2DM-AO (n = 68)		T2DM-NAO (n = 63)		All T2DM patients (n = 131)	
	r	p value	r	p value	r	p value
Weight	0.301	0.013*	0.101	0.432	0.342	< 0.001*
WC	0.382	0.001*	–0.078	0.544	0.333	< 0.001*
Hipline	0.409	0.001*	–0.300	0.017*	0.220	0.012*
WHR	0.144	0.241	0.327	0.009*	0.271	0.002*
BMI	0.408	0.001*	0.069	0.592	0.386	< 0.001*
FBG	0.377	0.002*	0.271	0.032*	0.349	< 0.001*
HbA_{1c}	0.338	0.005*	0.217	0.087	0.264	0.002*
VFA	0.310	0.010*	0.064	0.618	0.353	< 0.001*
SFA	0.323	0.007*	–0.046	0.721	0.297	0.001*
TAFA	0.355	0.003*	–0.019	0.880	0.350	< 0.001*
Irisin	0.184	0.134	0.039	0.760	0.208	0.017*

Pearson's correlation analysis was used; *p value < 0.05; T2DM — type 2 diabetes mellitus; AO — abdominal obesity; NAO — non-abdominal obesity; r — Pearson's correlation coefficient; WC — waist circumference; WHR — waist-to-hip ratio; BMI — body mass index; FBG — fasting blood glucose; HbA_{1c} — glycated haemoglobin; VFA — visceral fat area; SFA — subcutaneous fat area; TAFA — total abdominal fat area

Correlation between serum asprosin concentration and other anthropometric and metabolic parameters

According to Pearson's correlation analysis, in the AO group the serum asprosin concentration was positively associated with weight ($r = 0.301$, $p = 0.013$), WC ($r = 0.382$, $p = 0.001$), hipline ($r = 0.409$, $p = 0.001$), BMI ($r = 0.408$, $p = 0.001$), FBG ($r = 0.377$, $p = 0.002$), HbA_{1c} ($r = 0.338$, $p = 0.005$), VFA ($r = 0.310$, $p = 0.010$), SFA ($r = 0.323$, $p = 0.007$), and TAFA ($r = 0.355$, $p = 0.003$). Meanwhile, the serum asprosin concentration in the NAO group was positively correlated with WHR ($r = 0.327$, $p = 0.009$) and FBG ($r = 0.271$, $p = 0.032$) and was negatively correlated with hipline ($r = –0.300$, $p = 0.017$) (Tab. 2).

Correlation between serum irisin concentration and other anthropometric and metabolic parameters

Pearson's correlation analysis indicated that the serum irisin concentration in the AO group was positively correlated with WC ($r = 0.249$, $p = 0.040$), WHR ($r = 0.259$, $p = 0.033$), VFA ($r = 0.359$, $p = 0.003$), and TAFA ($r = 0.259$, $p = 0.033$) and was negatively correlated with FBG ($r = –0.468$, $p < 0.001$). In the NAO group, the serum irisin concentration was positively correlated with weight ($r = 0.272$, $p = 0.031$), VFA ($r = 0.331$, $p = 0.008$), and FCP ($r = 0.301$, $p = 0.017$) (Tab. 3).

Independent factors associated with serum concentration of asprosin or irisin

In the AO group, according to forward stepwise logistic regression analysis using weight, WC, hipline, BMI, FBG, HbA_{1c}, VFA, SFA, and TAFA (Tab. 2) as independent variables and whether serum asprosin concentration was elevated above the mean asprosin level of 3.67 ng/mL (Tab. 1) in patients in the AO group as dependent variable, FBG and VFA were independent factors positively associated with serum asprosin concentration in T2DM-AO (OR: 1.273, 95% CI: 1.021–1.586, $p = 0.032$; OR: 1.044, 95% CI: 1.010–1.079, $p = 0.011$, respectively) (Tab. 4).

For all of the T2DM patients included in the study, according to forward stepwise logistic regression analysis using weight, WC, hipline, WHR, BMI, FBG, HbA1c, VFA, SFA, TAFA, and irisin (Tab. 2) as independent variables and whether the serum asprosin concentration was elevated above the mean asprosin level of 3.28 ng/mL in all included patients as dependent variable, FBG (OR: 1.377, 95% CI: 1.145–1.656, $p = 0.001$), VFA (OR: 1.020, 95% CI: 1.003–1.037, $p = 0.023$), and irisin (OR: 1.012, 95% CI: 1.002–1.022, $p = 0.016$) were factors independently, positively associated with the serum asprosin concentration in patients with T2DM (Tab. 4).

Forward stepwise logistic regression analysis using WC, WHR, FBG, VFA, and TAFA (Tab. 3) as independent variables and whether the serum irisin concentration was elevated above the mean level of 154.62 pg/mL in the AO group (Tab. 1) as a dependent variable revealed that FBG was an independent factor negatively associated with serum irisin (OR: 0.559, 95% CI: 0.399–0.782, $p = 0.001$) and that VFA was independently, positively associated with serum irisin (OR: 1.062, 95% CI: 1.018–1.107, $p = 0.005$) in T2DM-AO (Tab. 4).

Table 3. *Correlations between serum irisin level and other variables*

Variables	T2DM-AO (n = 68)		T2DM-NAO (n = 63)		All T2DM patients (n = 131)	
	r	p value	r	p value	r	p value
Weight	0.132	0.285	0.272	0.031*	0.268	0.002*
WC	0.249	0.040*	0.206	0.106	0.312	< 0.001*
Hipline	0.095	0.443	0.068	0.597	0.172	0.049*
WHR	0.259	0.033*	0.205	0.107	0.284	0.001*
FBG	–0.468	< 0.001*	–0.114	0.374	–0.303	< 0.001*
VFA	0.359	0.003*	0.331	0.008*	0.380	< 0.001*
SFA	0.195	0.111	0.117	0.362	0.242	0.005*
TAFA	0.259	0.033*	0.191	0.135	0.320	< 0.001*
Asprosin	0.184	0.134	0.039	0.760	0.208	0.017*
FCP	0.216	0.076	0.301	0.017*	0.287	0.001*

Pearson's correlation analysis was used; *p value < 0.05; T2DM — type 2 diabetes mellitus; AO — abdominal obesity; NAO, non-abdominal obesity; r — Pearson's correlation coefficient; WC — waist circumference; WHR — waist-to-hip ratio; FBG — fasting blood glucose; VFA — visceral fat area; SFA — subcutaneous fat area; TAFA — total abdominal fat area; FCP — fasting C-peptide

Table 4. *Independent factors associated with serum concentration of asprosin or irisin in the abdominal obesity (AO) group and in all the type 2 diabetes mellitus (T2DM) patients (AO + NAO) according to forward stepwise regression analysis*

Serum asprosin in the AO group						Serum asprosin in all the included T2DM patients (AO+NAO)					
Variables	B	Wald χ^2	p value	Odd ratio	95% CI	Variables	B	Wald χ^2	p value	OR	95% CI
FBG	0.241	4.621	0.032	1.273	1.021–1.586	FBG	0.320	11.565	0.001	1.377	1.145–1.656
VFA	0.043	6.443	0.011	1.044	1.010–1.079	VFA	0.019	5.144	0.023	1.020	1.003–1.037
						Irisin	0.012	5.846	0.016	1.012	1.002–1.022
Serum irisin in the AO group						Serum irisin in all the included T2DM patients (AO + NAO)					
Variables	B	Wald χ^2	p value	Odd ratio	95% CI	Variables	B	Wald χ^2	p-value	OR	95% CI
FBG	–0.582	11.531	0.001	0.559	0.399–0.782	FBG	–0.295	9.669	0.002	0.774	0.618–0.897
VFA	0.060	7.943	0.005	1.062	1.018–1.107	VFA	0.015	4.236	0.040	1.015	1.001–1.030
						Asprosin	0.000	6.342	0.012	1.000	1.000–1.001

NAO — non-abdominal obesity; FBG — fasting blood glucose; CI, confidential interval; VFA — visceral fat area

As for all of the patients with T2DM included in the study, according to forward stepwise logistic regression analysis using weight, WC, hipline, WHR, FBG, VFA, SFA, TAFA, asprosin, and FCP (Tab. 3) as independent variables and whether the serum irisin concentration was elevated above the mean irisin level of 143.04 pg/mL of all patients as a dependent variable, VFA (OR: 1.015, 95% CI: 1.001–1.030, p = 0.040) and asprosin (OR: 1.000, 95% CI: 1.000–1.001, p = 0.012) were independent factors positively associated with serum irisin concentration in patients with T2DM, while FBG was independently, negatively associated with the serum irisin concentration in patients with T2DM (OR: 0.774, 95% CI: 0.618–0.897, p = 0.002) (Tab. 4).

Discussion

The main finding of this single-centre, case-control study is that serum concentrations of asprosin and irisin were significantly elevated in T2DM patients with AO compared with those without AO. Additionally, compared to the NAO group, the AO group had an unfavourable anthropometric and metabolic profile. Pearson's correlation analysis revealed that serum asprosin in the AO group was positively associated with weight, WC, hipline, BMI, FBG, HbA_{1c}, VFA, SFA, and TAFA, and that the serum irisin concentration in the AO group was positively correlated with WC, WHR, VFA, and TAFA and negatively correlated with FBG. According to forward stepwise logistic regression,

FBG and VFA were independent factors positively associated with serum asprosin concentration, and FBG was independently, negatively associated with serum irisin while VFA was independently, positively associated with serum irisin.

Abdominal obesity is characterized by excessive fat accumulation in the abdomen and increased volume of visceral adipose tissue, which is more cardio-metabolically dangerous than subcutaneous adipose tissue [2, 4, 5, 30–32]. It has recently been reported that VFA quantified by dual BIA is highly correlated with VFA estimated by CT and that dual BIA could be an alternative method of VFA quantification [4]. In this study, we used VFA quantified by dual BIA to define patients with AO. In line with previous studies [2, 11, 14, 19, 30, 33], we found that compared to T2DM patients without AO, T2DM patients with AO had an unfavourable anthropometric and metabolic profile, i.e. the AO group had higher BMI and greater WC, hipline, WHR, VFA, SFA, TAFA, FCP, TG, and VLDL-C, indicating that T2DM patients with AO had more severe derangement of lipid metabolism, possibly due to increased lipolysis and free fatty acid metabolism associated with increased VFA [34]. Therefore, it is important to monitor whether T2DM patients with AO have dysregulation of lipid metabolism.

Asprosin is a WAT-secreted adipokine capable of driving fat accumulation and increasing body weight by inducing the release of hepatic glucose into the circulation and stimulating the appetite [6–10]. Neonatal progeroid syndrome (NPS) is a congenital lipodystrophic disease leading to heterozygous depletion of asprosin [9], and patients with NPS have normal glucose level, and reduced fasting insulin and subcutaneous fat [9]. Administration of a single dose of asprosin led to an immediate increase in blood glucose levels and compensatory hyperinsulinemia in mice [9], while asprosin sequestration with asprosin-specific antibody in mouse models of insulin resistance improved insulin resistance and maintained normal blood glucose levels [9]. Elevated circulating asprosin levels have been found in patients with impaired glucose regulation [12], newly diagnosed T2DM [8, 12], and established T2DM [6]. Additionally, it has been reported that FBG and HbA1c are positively correlated with serum asprosin levels [6–8] and that FBG is an independent factor positively associated with serum asprosin levels in patients in T2DM [6, 8]. Consistent with these previous studies, we found that serum asprosin was positively correlated to FBG and HbA1c in both the AO and NAO group and that FBG was independently, positively associated with serum asprosin in T2DM with AO, as well as in all the included T2DM patients, indicating a role of asprosin in regulating blood glucose homeostasis. It has been suggested that pathologically elevated asprosin level in patients with T2DM could lead to increased production and the release of hepatic glucose, leading to hyperinsulinaemia and worsened insulin resistance [6, 9]. Studies on whether circulating asprosin levels are elevated in obese patients reported different findings [10, 13, 14]. Consistent with Sünnetçi Silistre et al., Liu et al. [13, 14], and other studies [6, 8], our study found elevated circulating asprosin in the AO group and a positive correlation between serum asprosin and adiposity-related parameters such as WC, hipline, and BMI. A relationship between serum asprosin and abdominal fat distribution has not been reported previously. We found that serum asprosin levels were positively correlated with VFA, SFA, and TAFA in the AO group and that only VFA was an independent factor positively associated with serum asprosin levels in T2DM patients with AO as well as in all the included T2DM patients, suggesting that VFA might affect circulating asprosin levels in patients with T2DM, probably because visceral fat is more metabolically active than subcutaneous fat [2, 4, 27, 31].

The adipomyokine irisin secreted by muscle tissue, VAT, and SAT could induce WAT browning and increase energy expenditure [15, 16]. Its overexpression or subcutaneous perfusion decreased body weight and corrected deranged glucose/lipid metabolism in obese mice [15–19]. Studies on the association between circulating irisin levels and metabolic disorders such as T2DM and obesity drew different conclusions [18–25]. For example, Zhang et al. found that compared to normal controls, serum irisin levels were lower in patients with T2DM without obesity and higher in obese patients without T2DM, whereas the levels of serum irisin in obese patients with T2DM were between those in patients with T2DM without obesity and obese patients without T2DM [23]. In addition, Zhang et al. also found that serum irisin levels had positive correlation with gender, BMI, WC, and fat mass and negative correlation with HbA1c and FBG [23]. On the other hand, studies such as the one by AlKhairi et al. found elevated serum irisin in patients with T2DM and in obese patients, and that serum irisin levels were higher in obese patients with T2DM than in T2DM patients with normal weight [19]. AlKhairi et al. further found that serum irisin was positively correlated with BMI, TC, FBG, and HbA_{1c} [19]. Rana et al. found higher irisin levels in patients with T2DM than in healthy subjects, and they observed that serum irisin had a positive correlation with BMI, body fat percentage, and HbA_{1c} and a negative correlation with visceral fat score [20]. Wang et al. found decreased circulating irisin levels in patients with newly diagnosed T2DM compared to healthy controls, as well as positive correlations between se-

rum irisin level and body weight, WC, WHR, and VFA [35]. Our study found that elevated serum irisin levels were greater in T2DM patients with AO compared to those without AO, that serum irisin levels had positive correlations with WC, WHR, VFA, and TAFA and negative correlation with FBG in T2DM patients with AO, and that serum irisin in the NAO group had a positive correlation with weight, VFA, and FCP. These findings are more in line with those of Zhang et al. and Wang et al. [23, 24]. Furthermore, in line with Al-Daghri et al. and Wang et al. [32, 35], the stepwise logistic regression analysis revealed that FBG was an independent factor negatively associated with serum irisin levels while VFA was an independent factor positively associated with serum irisin levels in T2DM patients with AO as well as in all the included T2DM patients. It has been suggested that increased irisin secretion in obese subjects is compensatory in nature, in order to counteract the obesity-induced metabolic derangement by increasing energy expenditure and lowering blood glucose; however, once obesity progresses to diabetes, such compensatory irisin secretion would transit to failure in irisin secretion [23].

Both asprosin and irisin can be secreted by adipose tissue, and it has been reported that subcutaneous infusion of irisin increased serum asprosin levels in male obese rats but not in female obese rats [36], while intraperitoneally administered asprosin decreased serum irisin in healthy and diabetic mice [37]. In addition, a positive correlation between asprosin and irisin in healthy subjects and a positive correlation between asprosin increase and irisin increase 30 minutes after acute anaerobic exercise have been reported [38]. Our study found no correlation between asprosin and irisin in the AO group or the NAO group; however, when all of the 131 T2DM patients (AO + NAO) were included in the analysis, serum asprosin and irisin were independent factors positively associated with each other. This is most likely to be because AO is a confounder in determining whether there is correlation between asprosin and irisin. Whether there is any meaningful correlation between asprosin and irisin in different populations needs to be further explored.

Our study has certain limitations. First, it is a case-control observational study, and the associations identified in the study do not represent an actual cause-and-effect relationship. Secondly, this is a single-centre study with a modest sample size.

Conclusions

Elevated serum levels of asprosin and irisin in T2DM patients with abdominal obesity and their correlations with other anthropometric and metabolic parameters indicate that asprosin and irisin are potential therapeutic agents or targets in treating obesity and its related disorders.

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Conflict of interest
None of the authors have any potential conflicts of interest associated with this research.

Author contributions
L.V. contributed to study conception, design and coordination, and data interpretation. H.G. contributed to study conception and design, secured funding for the study, participated in specimen and data collection, analysis and interpretation, and wrote the first draft of this manuscript. S.W. and Z.Q. participated in specimen and data collection, analysis, and interpretation. All authors revised the manuscript critically for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethical approval and consent to participate
This study was approved by the Ethics Committee of The Third Affiliated Hospital of Anhui Medical University and was carried out in accordance with the principles laid down in the Declaration of Helsinki. All patients gave written informed consent before any study-related data collection, testing, or measurement.

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