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ORIGINAL ARTICLE

The correlation between serum asprosin and left ventricular diastolic dysfunction in elderly patients with type 2 diabetes mellitus in the community

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ABSTRACT

Aims/Introduction: Serum asprosin is expected to become a screening indicator in early-stage diabetic heart disease. The relationship between serum asprosin and left ventricular diastolic dysfunction (LVDD) was studied in elderly patients with type 2 diabetes mellitus in the community.

Materials and Methods: A total of 252 elderly patients with type 2 diabetes mellitus were recruited from Zhuoma Community Care Station and Chengbei West Street Community Care Service Center in Changzhi City of Shanxi Province from November 2019 to July 2021. Patients were divided into the LVDD group (n = 195) and the non-LVDD group (n = 57). The t-test, Mann–Whitney U test, and χ^2 test were used to compare indicators between the LVDD group and the non-LVDD group. Pearson or Spearman correlation analysis was adopted to evaluate the correlation between serum asprosin and other clinical data. Multivariate logistic regression analysis was applied to analyze the influencing factors on LVDD.

Results: Compared with patients without LVDD, patients with LVDD had a higher level of low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FPG), and asprosin, but a lower level of early diastolic movement speed (A) to diastolic movement velocity (E) (E/A). Asprosin was positively associated with waist circumference (WC), body mass index (BMI), creatinine, triglycerides ($P < 0.05$), and negatively associated with E/A and high density lipoprotein cholesterol HDL-C ($P < 0.05$). The risk of LVDD increased with elevated asprosin levels after adjustment for age, systolic blood pressure (SBP), BMI, FPG, and LDL-C. Compared with patients in the lowest tertile of serum asprosin (<275.25 pg/mL), a serum level of asprosin between 275.25–355.08 pg/mL [OR (95% CI) is 2.368 (1.169–4.796), $P < 0.05$] and asprosin >355.08 pg/mL [OR (95% CI) is 2.549 (1.275–5.095), $P < 0.05$] patients have a higher risk of left ventricular diastolic dysfunction.

Conclusions: Serum asprosin was positively associated with left ventricular diastolic dysfunction, and the risk of LVDD increased significantly with increased serum levels of asprosin.

INTRODUCTION

In the past 20 years, the global number of patients with diabetes has soared from 151 million to 537 million in 2021, of which 90–95% are patients with type 2 diabetes[1]. Some 70–80% of diabetic patients died from cardiovascular disease, which is 2–3 times that of the heart disease mortality of non-diabetic patients[2]. Thus it is imperative to detect cardiovascular disease events caused by diabetes as soon as possible. But a

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large number of patients with diabetic cardiovascular disease do not have any clinical symptoms at the initial stage of onset especially elderly patients whose neurosensitivity is declining progressively[3], increasing the difficulty of diagnosis. Left ventricular diastolic dysfunction (LVDD) has been reported to be the earliest cardiac structural change in diabetic cardiopathy and cardiac Doppler ultrasound could detect this change through measuring the early diastolic movement speed (A)/diastolic movement velocity (E) (E/A)[4]. However, though cardiac Doppler ultrasound has become a widely used screening method to evaluate the left ventricular diastolic function, it cannot be used as a means of extensive screening for patients with type 2 diabetes mellitus with early-stage diabetic heart disease, especially in some old people with impaired mobility.

Asprosin is a novel fasting-induced glucogenic protein hormone mainly secreted by white adipose tissue. Recent research has found that asprosin plays a significant and complicated part in metabolic diseases. Studies have shown that this glucogenic protein adipokine is closely related to the onset of diabetes, obesity, polycystic ovarian syndrome (PCOS), and cardiovascular disease[5]. Additionally, an elevated level of asprosin also increases the risk of diabetic retinopathy[6] and diabetic nephropathy[7]. Further studies by our research group have found that the risk of diabetic nephropathy caused by elevated asprosin was closely related to gender, especially being female[8]. Nevertheless, its specific mechanisms are not yet fully understood. Therefore, based on its important role in diabetes and cardiovascular disease, serum asprosin is expected to become a screening indicator in early-stage diabetic heart disease. Until now, there has been no study on whether asprosin can be a predictor of left ventricular diastolic dysfunction in the elderly community of patients with type 2 diabetes mellitus. In this research, we analyzed the relationship between the asprosin level and E/A in elderly patients with type 2 diabetes mellitus in Changzhi City, Shanxi Province, to predict the risk of LVDD in patients with type 2 diabetes mellitus, aiming to provide a new theoretical basis for early screening and intervention of diabetes-related cardiovascular diseases.

MATERIALS AND METHODS

Study design and subjects

In our cross-sectional research, detailed clinical data of elderly patients with type 2 diabetes mellitus were collected retrospectively from a community health care center (Zhuoma Community Care Station and Chengbei West Street Community Care Service Center in Changzhi City of Shanxi Province) in southeastern Shanxi Province from November 2019 to July 2021. Patients who met the WHO diagnostic criteria for type 2 diabetes mellitus in 1999[9], ≥65 years old[10], and presenting with available clinical and asprosin data were included in this study, whereas subjects were excluded if they had (1) type 1 diabetes mellitus; (2) diabetic ketoacidosis and diabetic hypertonic coma; (3) severe liver and kidney dysfunction, serious infection, and malignant tumors; (4) communication disorders, for example mental diseases; (5) were unable to cooperate with the researcher, diabetes caused by other endocrine diseases; (6) patients with left ventricular systolic insufficiency [ejection fraction (EF) ≤50%] with a history of ischemic heart disease (previous history of myocardial infarction, history of coronary revascularization, or coronary angiography for definite coronary artery stenosis >50%).

Data collection

The waist circumference, weight, height, and blood pressure (systolic blood pressure and diastolic pressure) of the patients were gathered, and using the results of weight and height, the body mass index (BMI) (weight/(height × height)) was calculated. The diagnosis of hypertension was based on the Chinese Guidelines for the Prevention and Treatment of Hypertension (2010) criteria: systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg (1 mmHg = 0.133 kPa). All participants were fasted for 8–10 h before the collection of 2–3 mL blood samples by a nurse. These samples were used to measure important laboratory indicators, including fasting blood glucose (FPG) (reference range 3.9–6.1 mmol/L), total cholesterol (TC) (reference range 64–104 μmol/L), low-density lipoprotein cholesterol (LDL-C) (reference range 0–3.12 mmol/L), high-density lipoprotein cholesterol (HDL-C) (reference range ≧1.04 mmol/L), creatinine (CRE) (reference range 64–104 μmol/L), triglycerides (TG) (reference range 0.2–1.7 mmol/L), glycosylated hemoglobin (HbA1c) (reference range 4.8–5.9%). In addition, serum asprosin levels were also measured.

Grouping and serum asprosin detection

Blood for asprosin measurement was taken and centrifuged (3,000 rpm, 13.5 cm radius) for 15 min. Then the supernatant was taken and stored at −80°C. The serum asprosin level was measured by enzyme-linked immunosorbent assay (ELISA) with a ready-to-use detection kit by Herb (Shanghai, Biotechnology Co., Ltd, Shanghai, China). The standards for the kit were an inter-batch difference of <11% and an intra-batch difference of <8%, all samples were tested by double-well repetition. The participants were divided into three subgroups according to the tertile of serum asprosin: the low-level asprosin group (T1), the medium-level group (T2), and the high-level asprosin group (T3). Furthermore, patients in a supine position were examined by medical staff with a color Doppler ultrasound which has a Philips IE33 probe of 2.5–4.0 MHz. The early diastolic movement speed (E) and late diastolic movement velocity (A) were measured, and the E/A was calculated. The above data were averaged over three cardiac cycles and synchronously recorded in the image acquisition system of the ultrasound workstation for playback analysis. According to Appleton[11], a value of E/A < 1 was defined as left heart dysfunction in the early diastolic phase. Using this criterion, patients with an E/A < 1 were identified as being in the LVDD group, the rest were assigned to the non-LVDD group.

Statistical analysis

SPSS 22.0 (International Business Machines Corporation, Amonk, NY, USA) was used to analyze the data and the Q-Q plots to test for normality. The data are represented as the form of mean ± standard deviation (mean ± SD) when consistent with a normal distribution, while those not consistent with a normal distribution are shown as the median (range). As for the categorical data, this was shown as the presence of frequency (constituent ratio or percentage). To compare the statistical differences of the quantitative data, analysis of variance or the Kruskal–Wallis H-test was used, and categorical data were suitable for the Chi-square test or Fisher exact test. Regarding the relationship between serum asprosin and other variables of the participants, the Pearson correlation coefficient was calculated when the data met a bivariate normal distribution, if they did not meet this distribution, the Spearman correlation coefficient was calculated. Multivariate stepwise linear regression was adopted to analyze the correlations of asprosin with BMI, waistline, age, SBP, DBP, FPG, HbA1c, CRE, TC, TG, LDL-C, HDL-C, E/A, and EF. Univariate and multivariate logistic regression analyses were used to determine factors independently related to LVDD in patients with type 2 diabetes mellitus. In addition, the multivariate logistic regression analysis used the 'enter' method (i.e., all factors entered the logistic regression equation at the same time), through which 95% confidence intervals (95% CIs) odds ratios (ORs) were calculated. Three models were used for the multivariate logistic regression analyses: Model 1, no adjusted variable; Model 2, adjusted for age, systolic blood pressure, body mass index, fasting blood glucose; Model 3, model 2 with additional adjustment for low-density lipoprotein cholesterol; serum asprosin tertile 1, <275.25 pg/mL; serum asprosin tertile 2, range 275.25–355.08 pg/mL; serum asprosin tertile 3, >355.08 pg/mL. $P < 0.05$ was considered statistically significant. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 252 elderly patients with type 2 diabetes mellitus were studied, 57 without left ventricular dysfunction and 195 with left ventricular dysfunction. The age was 71.85 ± 4.80 years, and 52.2% (105/252) were men. The median duration of diabetes was 15 (10, 20) years, and the HbA1c was 8.77 ± 1.78%. The levels of LDL-C, FPG, and asprosin ($P < 0.05$) were significantly higher in patients with LVDD than in those without LVDD, while the E/A ($P < 0.05$) was significantly lower than in patients without LVDD ($P < 0.05$). The detailed characteristics of the included patients are shown in Table 1.

Pearson correlation analysis showed that the serum asprosin level was positively associated with WC, BMI, creatinine (CRE), triglycerides (TG) ($P < 0.05$), and negatively associated with E/A and HDL-C ($P < 0.05$). Multiple linear regression analysis revealed that TG, CRE, E/A were independently related to asprosin. Specifically, asprosin was positively correlated with TG, CRE, and negatively correlated with E/A (Table 2).

Table 1 | Comparison of the clinical characteristics of patients with type 2 diabetes mellitus in the community between those with LVDD and those without LVDD

Characteristics	Total			
	Without LVDD (n = 57)	LVDD (n = 195)	$\chi^2/Z/t$	P for trend
Age (years)	71.22 ± 4.86	72.15 ± 4.75	−1.442	0.069
Duration† (years)	15.0 (10, 20)	15.0 (8, 20.0)	0.173	0.677
BMI, kg/cm^2	24.94 ± 3.61	25.59 ± 3.46	−1.385	0.503
SBP (mmHg)	134.38 ± 21.50	134.13 ± 16.79	0.092	0.04
DBP (mmHg)	74.83 ± 9.64	75.64 ± 9.95	−0.613	0.987
Waistline (cm)	92.51 ± 13.0	95.18 ± 9.80	−1.626	0.002
TG† (mmol/L)	1.39 (1.02, 2.15)	1.45 (1.07, 1.85)	2.667	0.102
TC (mmol/L)	4.41 ± 1.13	4.64 ± 1.07	−2.493	0.134
HDL-C (mmol/L)	1.04 ± 0.30	1.03 ± 0.25	0.342	0.911
LDL-C (mmol/L)	2.48 ± 0.79	2.82 ± 0.90	−3.414	0.036
FPG (mmol/L)	7.38 ± 2.57	8.14 ± 2.81	−1.145	0.531
HbA1c (%)	8.52 ± 1.71	8.89 ± 1.80	−2.20	0.897
CRE† (μmol/L)	63 (55.75, 78.25)	67 (57.0, 80.0)	0.136	0.712
E/A	1.11 (0.85, 1.25)	0.68 (0.61, 0.77)	131.80	<0.001
Asprosin (pg/mL)	283.57 ± 112.34	332.17 ± 91.28	−5.412	0.034
EF (%)	68.94 ± 5.16	67.69 ± 5.52	1.072	0.231

†Kruskal–Wallis H-test. BMI, body mass index; CRE, creatinine; DBP, diastolic blood pressure; E/A, early diastolic movement speed (A)/diastolic movement velocity (E); EF, ejection fraction; FPG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

In multiple stepwise logistic regression analysis (using asprosin 1 as the reference group), the risk of left ventricular diastolic dysfunction increased with elevated asprosin levels after adjustment for age, SBP, BMI, and FPG variables (Table 3). Compared with the patients in the lowest tertile of serum asprosin (<275.25 pg/mL), asprosin between 275.25–355.08 pg/mL [OR (95% CI) is 2.368 (1.169–4.796), $P < 0.05$] and asprosin >355.08 pg/mL [OR (95% CI) is 2.549 (1.275–5.095), $P < 0.05$] patients have a higher risk of LVDD.

Moreover, the diagnostic ability of asprosin to detect LVDD in elderly patients with type 2 diabetes mellitus was tested using receiver operating characteristic (ROC) curve analysis. The results showed that the area under the curve was 0.723. A calculated cutoff value of 231.5 pg/mL yielded a sensitivity of 89.7%, specificity of 50.9%, positive predictive value of 77.4%, and a negative predictive value of 22.6% ($P < 0.001$, Figure 1).

DISCUSSION

The prevalence of diabetes in the elderly in China has been increasing year by year in recent years. According to the data of the International Diabetes Federation in 2019, the number of elderly patients with diabetes in China has reached 35.5 million,

Table 2 | Association between serum asprosin and other covariates in patients with type 2 diabetes

Variable	Total			
	Pearson correlation		Multiple linear regression	
	R correlation coefficient	*P*	Standardized β	*P*
Duration (years)†	0.059	0.348	-	-
Age (years)	0.100	0.112	-	-
SBP (mmHg)	−0.086	0.176	-	-
DBP (mmHg)	0.091	0.151	-	-
Waistline	0.351	<0.001	0.122	0.154
BMI (kg/m^2)	0.345	<0.001	0.107	0.202
FPG (mmol/L)	−0.044	0.490		
HbA1c (%)	−0.010	0.868		
TC (mmol/L)	0.037	0.555	-	-
TG† (mmol/L)	0.340	<0.001	0.167	0.005
LDL-C (mmol/L)	0.026	0.679		
HDL-C (mmol/L)	−0.251	<0.001	−0.056	0.349
CRE†	0.494	<0.001	0.329	<0.001
E/A	−0.211	0.001	−0.151	0.007
EF	−0.031	0.621		

†Spearman correlation analysis was used for skewness distribution.

Table 3 | Multiple stepwise logistic regression analysis of the ratio of serum asprosin to risk of LVDD

	Tertile 1	Tertile 2	Tertile 3	*P* value for trend
Model 1				
Total	1	2.368 (1.169–4.796)	2.549 (1.275–5.095)	0.008
P value		0.017	0.008	
Model 2				
Total	1	2.333 (1.113–4.891)	2.404 (1.130–5.115)	0.023
P value		0.025	0.023	
Model 3				
Total	1	2.309 (1.092–4.881)	2.577 (1.189–5.587)	0.016
P value		0.028	0.017	

Data are presented as odds ratio (95% confidence interval) compared with tertile 1. Participants without LVDD were defined as 0 and those with LVDD as 1. Model 1, without adjusted variable; Model 2, adjusted for age, systolic blood pressure, body mass index, fasting blood glucose; Model 3, model 2 with additional adjustment for low-density lipoprotein cholesterol; serum asprosin tertile 1, <275.25 pg/mL; serum asprosin tertile 2, 275.25–355.08 pg/mL; serum asprosin tertile 3, >355.08 pg/mL.

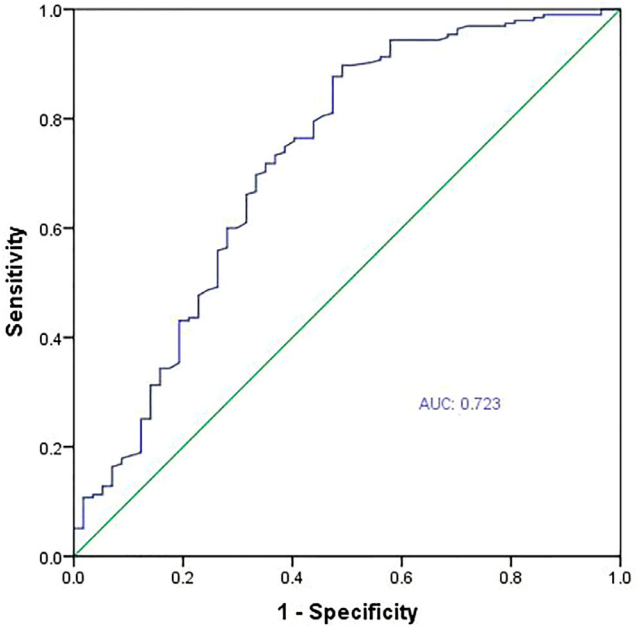

Figure 1 | ROC analysis for asprosin levels in detecting left ventricular diastolic dysfunction in elderly patients with type 2 diabetes mellitus.

accounting for a quarter of the overall number of elderly patients with diabetes in the world (135.6 million), so ranking first in the world. Its complications are often underestimated. Among the serious outcomes caused by diabetes, cardiovascular disease accounts for about 65% of diabetes-related mortality, and is the main cause of death in diabetic patients. The Framingham Heart Study[12,13] showed that compared with the age-equivalent control team, heart failure occurred five times more frequently in diabetic women and two times more frequently in diabetic men, suggesting that diabetic patients are more likely to develop congestive heart failure than normal blood glucose controls. Thus early, active prevention and treatment is needed. In the early stage of congestive heart failure, the left ventricular diastolic function is mainly impaired, while in the later stage of the disease, myocardial systolic dysfunction occurs, and eventually leads to congestive heart failure. A cohort study in a non-diabetic population showed that left ventricular diastolic dysfunction is an independent risk factor for developing heart failure[14], and other studies showed that the prevalence of LVDD in diabetic patients without clinical cardiac disease symptoms was 60%[15]. E/A is a relatively stable and reliable method, and can reflect LVDD, and has been used widely in clinical practice.

This study found that the prevalence of LV diastolic dysfunction in elderly patients with type 2 diabetes mellitus in the community was 77.4%. Compared with elderly patients with type 2 diabetes mellitus without LVDD, patients with LVDD had a higher LDL-C, FPG, asprosin, hypertension, and a lower E/A. Meanwhile, the results of correlation analysis suggested that serum asprosin in type 2 diabetes mellitus was positively correlated with waist circumference and BMI, and negatively correlated with E/A and HDL-C, suggesting that asprosin may be involved in the process of left ventricular dysfunction in patients with type 2 diabetes, which is consistent with the results of a study by Chen *et al.*[16] Therefore, early screening with cardiac Doppler ultrasound in diabetic patients, especially in those who already have left ventricular diastolic dysfunction but without clinical symptoms, can reduce the mortality of cardiovascular complications of diabetes. However, this method is not ideal for

large-scale screening of patients since it is still inconvenient for elderly patients when repeated examination is needed.

Hyperglycemia could lead to diabetic cardiomyopathy (DCM) and cardiovascular diseases through the increased generation of reactive oxygen species (ROS) and apoptosis of cardiomyocytes[17–19]. Studies showed that the level of asprosin was higher in hyperglycemia than normal ones[20]. Herein, we speculate that asprosin may play a relevant role in the process of myocardial injury. Retrospective studies showed that serum asprosin might be used as a risk biomarker in patients with coronary artery heart disease[21] and unstable angina pectoris[22]. Our study presumed that asprosin plays an important role in predicting type 2 diabetes mellitus patients with early-stage cardiovascular disease, which is consistent with two research studies, suggesting that asprosin could be a predictor or biomarker in both asymptomatic and symptomatic heart disease.

Prospective research[23] suggested that asprosin exerted cardiac protective effects in patients with dilated cardiomyopathy, indicating the higher the level of asprosin, the fewer the adverse cardiovascular events that occurred. In addition, this beneficial function of asprosin was confirmed by further cardiomyoblast studies that showed that asprosin could enhance mitochondrial respiration under hypoxia in dilated cardiomyopathy, which was contrary to our previous conclusion. The reason for the different conclusions may be related to the different ethnicity of the population, the number of samples, and the experimental design methods. To explore the function of asprosin in the hyperglycemic status of patients with impaired myocardial function, we analyzed the results of several cellular experiments with asprosin in diabetic cardiomyopathy. Zhang[24] reported that asprosin could improve the survival of mesenchymal cells in myocardial infarction through the ERK1/2 SOD2 pathway. Chen[25] pointed out that asprosin inhibited the oxidative stress response of myocardial microvascular endothelial cells (CMECs) by upregulating the Spatin pathway in diabetic mice, and improved myocardial microvascular endothelial injury in diabetic mice. Another related study[26] similarly showed that asprosin reduced cardiomyocyte apoptosis in mice by reducing the MDA and ROS levels in cardiomyocytes under high glucose conditions and played a preprotective function by increasing the levels of cAMP and PKA. All these detailed protective mechanisms of asprosin were concluded from *vitro* experiments when treating cells with asprosin. Thus we suppose that the asprosin level could be a warning indicator of heart disease in diabetes, and also could be a promising therapeutic method *in vitro*.

For the past few years, there have been no reports on whether asprosin could be used as a predictor of LV diastolic dysfunction in community-based elderly patients with type 2 diabetes mellitus, but a reduced serum adiponectin level has been confirmed to be an independent risk factor for LV diastolic dysfunction[27,28]. Fukuta[29] found that a decrease in the adiponectin level was related to cardiac diastolic dysfunction. Hong *et al.*[30] found that the serum level of adiponectin was positively correlated with the E/A, suggesting that increasing the adiponectin level could improve cardiac diastolic function and could be used as a new target for treatment and examination. Our study found that after controlling for covariates such as age, SBP, BMI, FPG, and LDL, patients with an asprosin level of 275.25–355.05 pg/mL and >355.05 pg/mL have a higher risk of developing left ventricular dysfunction, suggesting that an increased serum asprosin level is an influencing factor for left ventricular dysfunction. Therefore, attention should be paid to changes in serum asprosin levels at an early stage, which may play a role in slowing the development of left ventricular dysfunction.

However, this study has some limitations, this study is a cross-sectional study with a small sample size and whether there is a causal relationship between serum asprosin and left ventricular dysfunction needs to be further confirmed by future prospective studies, animal and cellular studies.

Elevated serum asprosin was associated with the occurrence of left ventricular diastolic dysfunction in community-based elderly patients with type 2 diabetes mellitus in Changzhi, Shanxi Province, China. Additionally, the risk of LVDD was obviously increased with the raise of asprosin. Therefore, we speculate that serum asprosin could be used as a predictor of LVDD and thus reduce the economic burden to society.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: The research protocol is applicable by the ethics committee of the First Hospital of Shanxi Medical University (No. 2019 [K056]).
Informed consent: All study participants provided informed written consent. The study kept patient data confidential and complied with the Declaration of Helsinki. There is no conflict of interests among all authors.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

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