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Association between serum asprosin and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus in the community

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Abstract. – OBJECTIVE: This study aimed to investigate the relationship between serum asprosin level and diabetic peripheral neuropathy (DPN) in community patients with type 2 diabetes mellitus (T2DM).

PATIENTS AND METHODS: A total of 498 patients with T2DM were recruited from Zhuoma Community Health Service Station and Chengbei West Street Community Health Service Center in Changzhi City of Shanxi Province between November 2019 and July 2021. Their height, weight, and body mass index (BMI), as well as fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), triglyceride (TG), and serum asprosin levels, were analyzed. Patients were divided into the DPN group (n = 329) and the non-DPN group (n = 169) according to the presence or absence of DPN. The *t*-test, Mann-Whitney U test, and χ^2 test were used to compare the indicators between the two groups. Pearson or Spearman correlation analysis was used to evaluate the correlation between serum asprosin and other clinical data. Multivariate logistic regression analysis was used to analyze the influencing factors of DPN.

RESULTS: Compared with the non-DPN group, the DPN group had higher serum asprosin ($p < 0.05$). The prevalence of DPN gradually increased according to the tertiles of asprosin (56%, 67%, and 75%; $p < 0.05$). Multivariate logistic regression analysis showed that after adjustment for covariates, patients with asprosin concentrations between 295.4-367.0 pg/ml and concentrations > 367.0 pg/ml had a higher risk of diabetic neuropathy compared than those with asprosin levels < 295.4 pg/ml ($p < 0.05$).

CONCLUSIONS: Serum asprosin was found to be positively correlated with DPN, and it resulted as an influencing factor for DPN in patients with T2DM in the community. With the increase of asprosin, the risk of DPN also increased.

Key Words:
Asprosin, Type 2 diabetes mellitus, Diabetic peripheral neuropathy, Community health services.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that can cause damage to multiple organs, whose various comorbidities have become the leading cause of death or disability in patients with diabetes mellitus (DM). Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications caused by DM, affecting up to 30-50% of cases[1]. Symptoms of DPN first appear in the distal limb, from where they distribute like a glove and gradually spread to the proximally, which can lead to many complications and has been associated with increased mortality[2]. The advancement of medical reform has made community centers the main medical institutions for DM patients, thus assigning them an important role in the early detection and prevention of diabetes and its complications.

Asprosin is a novel glucose-regulated proteinaceous hormone discovered by Romere et al[3] in 2016 when studying Marfanoid-progeroid-lipodystrophy syndrome. Asprosin is a secreted adipokine that can be released from white adipose tissue induced by a fasting state, encoded by exons 65 and 66 of the fibrillin-1 protein, and cleaved from the C-terminus of the fibrillin-1 gene. Although asprosin is mainly produced by white adipose tissue, its target organs are distrib-

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uted throughout the body. In the brain, asprosin receptors are mainly located in the arcuate nucleus of the hypothalamus, where they are bound by asprosin, which in turn promotes appetite. In the periphery, asprosin receptors are mainly located in the liver, pancreas, skeletal muscle, and myocardium, and can increase blood glucose levels by breaking down glycogen[3]. Previous studies[4,5] also showed that plasma asprosin level was positively correlated with waist circumference, glycosylated hemoglobin, fasting blood glucose level, total cholesterol level, 2-hour postprandial blood glucose, and insulin resistance[4]. In addition, asprosin is also closely associated with the occurrence and development of polycystic ovary syndrome, obesity, diabetes, and cardiovascular diseases[5].

Whether asprosin can serve as a predictor of DPN in community patients with T2DM remains to be investigated. Therefore, the present study aimed to investigate the relationship between asprosin level and DPN in patients with T2DM in Shanxi Province, to predict the risk of DPN in T2DM patients, and to provide a new theoretical basis for early screening and intervention of DPN.

Patients and Methods

Research Subjects

A total of 498 patients with T2DM were recruited in Zhuoma Community Health Service Station and Chengbei West Street Community Health Service Center in Changzhi City of Shanxi Province between November 2019 and July 2021.

The subjects of the present report were those of the previous study with the same inclusion criteria[6]. Clinical and biochemical data were taken from the previous study[6]. Inclusion criteria: patients fulfilled the 1999 World Health Organization diagnostic criteria for T2DM[7]. Exclusion criteria were: (1) the presence of other neurological diseases than DPN; (2) recurrent severe hypoglycemia; (3) acute complications such as diabetic ketoacidosis; (4) patients with a history of severe anxiety, depression, or mental illness; (5) visual impairment, hearing impairment or language communication impairment; (6) other serious somatic disorders.

The present study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University [approval number: 2019 (K056)], and all patients signed informed consent.

Clinical Data Collection

The height and weight of the patients were collected, and their body mass index (BMI) was calculated. The general data of the patients, such as gender, age, abdominal circumference, and systolic and diastolic blood pressure, were collected. Fasting venous blood of the patients was collected and examined for fasting blood glucose (FPG), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) (Beckman Automatic Biochemical analyzer, BK-200, USA). HbA1c was measured by high-pressure liquid chromatography (Roche 501, Basel, Switzerland). Clinical and biochemical data were taken from the previous study (methods outlined in Xu et al[6]) including research subjects, clinical data collection, detection of serum asprosin and grouping methods in the manuscript.

Detection of Serum Asprosin and Grouping

All patients fasted for 8-10 hours, after which their peripheral venous blood was collected and then centrifuged (3,000 rpm, centrifugation radius 13.5 cm) for 15 minutes. The supernatant was removed and stored frozen in the refrigerator at -80°C. Serum asprosin levels were measured by ELISA kit (Shanghai Hepeng, Shanghai, China) with an inter-assay difference of < 11% and intra-assay difference of < 8%. Samples were assayed in duplicate, and each assay was performed in strict accordance with the kit and instrument instructions. Patients with T2DM were divided into tertile groups according to serum asprosin (asprosin < 295.4 pg/ml, asprosin between 295.4-367.0 pg/ml, and asprosin > 367.0 pg/ml), and the risk of DPN was compared.

Diagnostic Criteria for DPN

According to the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017 edition)"[7], the following conditions were met: (1) have a clear history of diabetes; (2) neuropathy present at or after diagnosis of diabetes; (3) the clinical symptoms and signs were consistent with manifestations of DPN; (4) patients with clinical symptoms (pain, numbness, paresthesia, etc.), with at least one of the five examinations (ankle reflex, pinprick pain, vibration sensation, pressure sensation, and temperature sensation) being abnormal. (5) Neuropathy due

to other etiologies were excluded. If there were no clinical symptoms, minimally, two out of the five examinations were abnormal. If the above examination could not confirm the diagnosis, neuroelectromyography was performed for differential diagnosis.

Statistical Analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The Q-Q plots were employed for normality testing. Data with normal distribution was represented as mean±standard deviation (mean ± SD), and a comparison between groups was performed by *t*-test. Metrology data that did not conform to normal distribution were presented in M (Q1, Q3), and comparisons between the two groups were performed using the Mann-Whitney U test. Pearson and Spearman correlation analyses were used to evaluate the correlation between serum asprosin levels and other clinical data. Logistic regression was used to analyze the odds ratio (OR) and the 95% confidence interval (95% CI) of asprosin levels on the risk of DPN. $p < 0.05$ was considered statistically significant.

Results

Comparison of General Data, Biochemical Indexes, and Albumin Levels Between the Two Groups

A total of 498 T2DM patients were enrolled, including 329 patients with DPN and 169 without DPN. Their average age was (58.1 ± 13.6) years old, and 59.8% (298/498) were men. The median duration of diabetes was 11 (5, 17) years, and HbA1c was (9.15 ± 2.08)%. Compared with patients without DPN, patients with DPN had a longer duration of diabetes, older age, higher serum asprosin levels (all $p < 0.05$), and decreased levels of LDL-C, AST, and ALT (all $p < 0.05$). There were no statistically significant differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, TC, HDL-C, creatinine (CRE), estimated glomerular filtration rate (eGFR), BMI, FPG, and HbA1c ($p > 0.05$) (Table I).

Correlation of Serum Asprosin with General Data and Biochemical Parameters

Pearson or Spearman correlation analysis showed that serum asprosin was positively correlated with di-

Table I. Comparison of the clinical characteristics of patients with T2DM in the community between those with DPN and those without DPN.

Characteristics	Total			
	Non-DPN (n = 169)	DPN (n = 329)	χ^2/t	*p*-value
Age (y)	54.64 ± 14.93	59.90 ± 12.50	-3.928	< 0.001
*Duration (y)	8 (1, 14)	13 (8, 18)	42.478	< 0.001
BMI, kg/cm^2	26.24 ± 4.21	26.08 ± 4.03	0.408	0.684
SBP (mmHg)	134.05 ± 18.30	136.55 ± 19.30	-1.416	0.158
DBP (mmHg)	79.96 ± 11.74	79.83 ± 10.81	0.128	0.898
*AST (IU/L)	20 (15, 27)	17 (14, 23)	11.426	0.001
*ALT (IU/L)	20 (13, 33)	17 (12, 26)	7.718	0.005
*TG (mmol/L)	1.66 (1.14, 2.46)	1.67 (1.13, 2.42)	0.081	0.775
TC (mmol/L)	4.73 ± 1.31	4.57 ± 1.12	1.417	0.157
HDL-C (mmol/L)	0.94 ± 0.23	0.98 ± 0.25	-1.579	0.115
LDL-C (mmol/L)	2.82 ± 0.88	2.62 ± 0.83	2.385	0.018
FPG (mmol/L)	8.64 ± 3.35	8.35 ± 2.92	1.006	0.315
HbA1c (%)	9.17 ± 2.30	9.14 ±1.97	0.143	0.886
*CRE (μmol/L)	63 (55, 78)	67 (56, 83)	3.142	0.076
eGFR (mL/min/1.73 m^2)	144.67 ± 29.50	139.87 ± 34.33	1.546	0.122
Asprosin (pg/ml)	313.11 ± 85.98	346.95 ± 97.27	-3.819	< 0.001
Ca (mmol/L)	2.19 ± 0.11	2.15 ± 0.13	3.176	0.002

*Spearman correlation analysis was used for skewness distribution. BMI – Body Mass Index; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; AST – Aspartate Aminotransferase; ALT – Alanine Aminotransferase; TG – triglycerides; TC – total cholesterol; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; FPG – fasting blood glucose; PPG – blood glucose at 2 hours after meals; HbA1c – glycosylated haemoglobin; CRE – creatinine; eGFR – estimated glomerular filtration rate.

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

Covariates	Pearson correlation		Multiple Linear Regression	
	r	p	Standardized ß	p
*Duration (y)	0.222	0.000	0.159	0.000
Age (y)	0.120	0.007		
SBP (mmHg)	0.313	0.000	0.268	0.000
DBP (mmHg)	0.104	0.020		
BMI (kg/m^2)	0.087	0.053	-	-
TC (mmol/l)	0.124	0.006	0.101	0.027
*TG (mmol/l)	0.126	0.005		
LDL-C (mmol/l)	0.067	0.137	-	-
HDL-C (mmol/l)	0.033	0.469	-	-
FPG (mmol/l)	0.031	0.453	-	-
HbA1c (%)	0.128	0.004	0.167	0.000
*AST (IU/L)	-0.050	0.264	-	-
*ALT (IU/L)	-0.135	0.002	-0.097	0.024
*CRE (umol/l)	0.276	0.000	0.134	0.008
eGFR (mL/min/1.73 m^2)	-0.293	0.000	-0.186	0.000
Ca (mmol/L)	-0.166	0.010	-0.082	0.043

*Spearman correlation analysis was used for skewness distribution. BMI – Body Mass Index; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; AST – Aspartate Aminotransferase; ALT – Alanine Aminotransferase; TG – triglycerides; TC – total cholesterol; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; FPG – fasting blood glucose; PPG – blood glucose at 2 hours after meals; HbA1c – glycosylated hemoglobin; CRE – creatinine; eGFR – estimated glomerular filtration rate.

abetes duration, age, SBP, DBP, TC, TG, HbA1c, and CRE (both $p < 0.05$) but negatively correlated with ALT and eGFR (all $p < 0.05$) in 498 T2DM patients (Table II). Multiple linear regression analysis (using the stepwise method) revealed that T2DM duration, SBP, TG, HbA1c, ALT, eGFR, and Ca were independently associated with asprosin ($p < 0.05$, Table II). T2DM duration, SBP, TG, and HbA1c were positively correlated with asprosin, while ALT, eGFR, and Ca were negatively correlated with asprosin.

Prevalence of DPN in T2DM Patients Grouped by Tertiles of Asprosin

When all participants were analyzed together, the prevalence of DPN progressively increased from the lowest to the highest asprosin tertile (56%, 67%, and 75%; p for trend < 0.05) (Figure 1).

Multiple Stepwise Logistic Regression Analysis for the Ratio of Serum Asprosin to the Risk of DPN

The patients were subsequently divided into a low-level group (T1), middle-level group (T2), and high-level group (T3) according to the tertiles of serum asprosin levels (tertile, T). Multivariate logistic regression analysis (using asprosin tertile 1 as the reference group) was performed with or without the occurrence of DPN as the dependent variable, adjusting for DM, age, LDL-C, and AST. The analysis showed a significant increase in the incidence of DPN in T2 and T3 (all $p < 0.05$) (Table III). After further adjusting for DBP, BMI, FPG, and gender, patients in T2 and T3 groups were still at significantly higher risk of developing DPN compared with patients in the T1 group (all $p < 0.05$) (Table III).

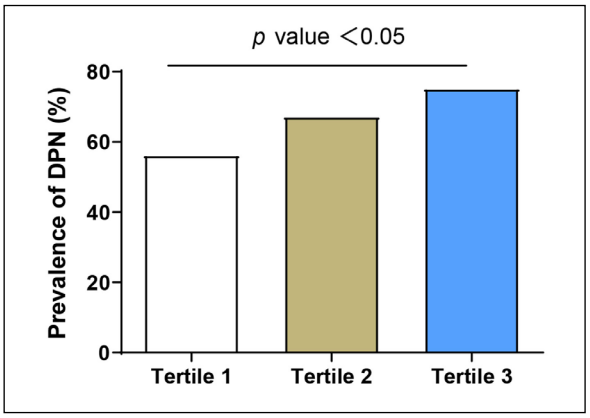

Figure 1. Prevalence of diabetic peripheral neuropathy (DPN) according to tertiles of serum asprosin.

Table III. Multiple stepwise Logistic regression analysis of the ratio of serum asprosin to risk of diabetic peripheral neuropathy.

	Tertile 1	Tertile 2	Tertile 3	*p*-value for trend
Model 1	1	1.598 (1.024-2.494)	2.374 (1.487-3.789)	< 0.001
Model 2	1	1.531 (0.954-2.455)	1.762 (1.075-2.837)	0.022
Model 3	1	1.529 (0.946-2.470)	1.706 (1.025-3.238)	0.037

Data are presented as odds ratio (95% confidence interval) compared with tertile 1. Participants without diabetic peripheral neuropathy (DPN) were defined as 0 and those with DPN as 1. Model 1, without adjusted variable; Model 2, with adjusted for duration of diabetes mellitus, age, low-density lipoprotein cholesterol (LDL-C), Aspartate Aminotransferase (AST); Model 3, model 2 with additional adjustment for diastolic blood pressure (DBP), body mass index (BMI), fasting blood glucose (FPG), sex.

Discussion

DPN is the most common cause of neuropathy, affecting the quality of life of about half of DM patients[8]. Individuals with advanced age and long duration of diabetes are at high risk of DPN incidence[9,10]. The present study found that compared with T2DM patients without DPN, T2DM patients with DPN were older and had a longer duration of diabetes, while their LDL-C was lower. The reduction of blood lipids may be associated with a higher proportion of patients taking aspirin and statins, which is consistent with the findings of Pan et al[11]. Serum-ionized calcium is one of the essential ions in the human body, which has a key role in regulating the normal function of cells. Serum-ionized calcium can promote intracellular and extracellular exchange through calcium-magnesium ATPases and calcium channels, thus maintaining the balance of intracellular and extracellular calcium *in vivo*. However, once the balance of calcium ions is broken, calcium metabolism becomes disordered, eventually leading to DPN in diabetes[12]. The present study's results showed that the serum ionized calcium level in the DPN group was lower than in the non-DPN group. Furthermore, the correlation analysis showed that serum asprosin was negatively correlated with serum calcium, which was consistent with the above results, suggesting that the decrease of serum ionized calcium level may be the basis of DPN in DM patients.

Adipose tissue is a functionally active endocrine organ that can produce and secrete a variety of adipokines. Among these adipokines, adiponectin and leptin have been confirmed to be closely related to diabetes and complications, participating in insulin sensitivity, lipid metabolism, and other processes. The decrease in serum adiponectin level and the increase in leptin level have an important role in the occurrence and development of diabetes[13]. Recently, asprosin has been identified as a fasting-induced glucogenic hormone[14]. Serum asprosin elevates blood glucose, regulates lipid metabolism, protects cardiomyocytes, and is closely related to diabetic macroangiopathy and microangiopathy[15]. Matsuda et al[16] proposed in 2004 that leptin, adiponectin, and tumor necrosis factors (TNFs) are closely related to the occurrence of DPN. Lim et al[17] found that leptin was related to the occurrence of DPN. However, there are also different conclusions. Kato et al[18] studied 198 Japanese patients with T2DM and found that neither serum high molecular weight adiponectin nor total adiponectin was significantly correlated with DPN. Therefore, the role of various adipokines in the occurrence and development of DPN remains unclear and should be further investigated. There is still no study on the association of asprosin with DPN. The present study found that the serum asprosin level of patients with DPN was higher than that of patients without DPN, while there was no significant difference in BMI between the two groups, which was consistent with the results of Li et al[19]. The inconsistencies in these findings may be due to the differences in subjects and expression sites of asprosin, which was found to be secreted in tissues such as the liver, heart, lung, muscle, and brain[3].

Multiple adipocytokines are associated with the complications of T2DM, which has certain similarities with the pathogenesis of DPN. DPN patients have abnormally elevated oxidative stress levels[20], which can activate glycation end products and protein kinase C pathway, mediate lipid peroxidation, promote the expression of transforming growth factor-β (TGF-β), interleukin-1 (IL-1), and other inflammatory factors, and induce nerve cell injury. Excessive reactive oxygen species (ROS) can accelerate the destruction of lipids, proteins, and nucleic acids. ROS clusters can also induce the pericytes contraction around endothelial cells, damage microvascular endothelial cells, pericytes, and astrocytes induce changes in the permeability of these cells, damage peripheral nerve cells, and promote the occurrence of DPN[21]. Our

results showed that after stepwise adjustment for covariates such as disease duration, age, LDL-C, AST, DBP, BMI, FPG, and gender, patients with asprosin between 295.4-367.0 pg/ml and asprosin > 367.0 pg/ml had a higher risk of developing DPN compared to patients with asprosin < 295.4 pg/ml, and elevated serum asprosin level was an important factor of DPN. The comparison between the tertiles of asprosin and the prevalence of DPN showed that the prevalence of DPN increased with asprosin levels, suggesting that early changes in serum asprosin levels should be given adequate attention, which may have a relevant role in slowing down the development of DPN.

Limitations

The present study has some limitations: (1) this is a cross-sectional study with a small sample size; (2) due to the influence of region, sample size, population characteristics, and other factors, future prospective studies are needed to confirm whether there is a causal relationship between serum asprosin and DPN; (3) the participants in the present study were T2DM patients. Asprosin level was higher in patients with DPN than those without DPN; however, there was no significant difference in BMI and TG between the two groups, suggesting that there may be other mechanisms between asprosin and DPN.

Conclusions

Higher serum levels of asprosin were associated with the presence of DPN in community-based T2DM patients in Changzhi, Shanxi Province, China, and the risk of developing DPN significantly increased with increasing serum levels of asprosin. Therefore, serum asprosin level is expected to become a predictor for early diagnosis of DPN.

Authors' Contributions

Dong Liang, Minggang Xu, and Jianhong Yin gathered the data. Guoliang Shi and Ping Li contributed to writing the discussion. Yan Wang and Jing Yang contributed to the experimental design. Linxin Xu wrote the paper. All authors approved the final version of the manuscript.

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Conflict of Interests

None.

Data Availability

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

Ethics Approval

The present study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University [approval number: 2019 (K056)].

Informed Consent

All patients signed informed consent.

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