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ORIGINAL ARTICLE

Case Control Study

Association between serum Sestrin2 level and diabetic peripheral neuropathy in type 2 diabetic patients

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Author contributions: Mao EW and Cheng XB performed the majority of experiments and wrote the manuscript, contributing equally to this article; Hou NN and Sun XD designed the study and corrected the manuscript; Li WC, Kan CX, Huang N, and Wang HS were involved in the sample collected and analytical tools.

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Abstract

BACKGROUND

Diabetic peripheral neuropathy (DPN) is a chronic and serious microvascular complication of diabetes linked to redox imbalance. Sestrin2, a novel inducible stress protein, participates in glucose metabolic regulation and redox homeostasis. However, the association between serum Sestrin2 and DPN is unknown.

AIM

To explore the association between serum Sestrin2 and DPN in patients with type 2 diabetes mellitus (T2DM).

METHODS

A total of 96 T2DM patients and 39 healthy volunteers, matched by age and sex, participated in this cross-sectional study. Clinical features and metabolic indices were identified. Serum Sestrin2 was measured by ELISA. The association between Sestrin2 and DPN was studied. Correlation and logistic regression analyses were used to evaluate the associations of different metabolic indices with Sestrin2 and DPN.

RESULTS

The 96 patients with T2DM were divided into DPN (n = 47) and patients without DPN (n = 49). Serum Sestrin2 was significantly lower in healthy volunteers than in all T2DM patients combined [9.10 (5.41-13.53) ng/mL *vs* 12.75 (7.44-23.80) ng/mL, P < 0.01]. T2DM patients without DPN also had significantly higher

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levels of Sestrin2 than healthy volunteers [14.58 (7.93-26.62) ng/mL *vs* 9.10 (5.41-13.53) ng/mL, $P < 0.01$]. However, T2DM patients with DPN had lower circulating Sestrin2 levels compared to T2DM patients without DPN [9.86 (6.72-21.71) ng/mL *vs* 14.58 (7.93-26.62) ng/mL, respectively, $P < 0.01$]. Bivariate correlation analysis revealed that serum Sestrin2 was positively correlated with body mass index ($r = 0.672$, $P = 0.000$), hemoglobin A1c (HbA1c) ($r = 0.292$, $P = 0.000$), serum creatinine ($r = 0.206$, $P = 0.016$), triglycerides ($r = 0.731$, $P = 0.000$), and fasting glucose ($r = 0.202$, $P = 0.040$), and negatively associated with estimated glomerular filtration rate ($r = -0.230$, $P = 0.007$). After adjustment for sex, age, HbA1c, and diabetes duration, multiple regression analysis revealed that Sestrin2 was independently correlated with body mass index and triglyceride levels ($P = 0.000$). Logistic regression analyses indicated that Sestrin2, diabetes duration, and high-density lipoprotein were strongly associated with DPN (odds ratio = 0.855, 1.411, and 0.041, respectively).

CONCLUSION
Our results show Sestrin2 is decreased in T2DM patients with DNP. As lower Sestrin2 is independently associated with DPN, Sestrin2 may contribute to progression of DPN in T2DM patients.

Key Words: Sestrin2; Diabetic peripheral neuropathy; Type 2 diabetes mellitus; Diabetic

Core Tip: This study demonstrated that serum Sestrin2 is increased in patients with type 2 diabetes but reduced in type 2 diabetic patients with diabetic peripheral neuropathy. Sestrin2 may be a novel modulatory factor for metabolic disturbances in diabetes complications.

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INTRODUCTION

Diabetes is associated worldwide with increased microvascular complications[1-3]. Diabetic peripheral neuropathy (DPN), a chronic and serious microvascular complication of diabetes, is the main cause of lower extremity amputation and loss of neuropathic pain, mainly characterized by numbness and hypoesthesia[4]. In severe cases, infection, gangrene, amputation, and even death may occur[4], but the underlying pathogenesis remains elusive. Most relevant studies have focused on potential causes, such as hyperglycemia, hypoxic injury, inflammation, oxidative stress, and activation of the hexosamine pathway[5,6]. In addition, patients with type 2 diabetes mellitus (T2DM) have a significantly increased risk of DPN, diabetic retinopathy, and hypertension compared with those with type 1 diabetes[7-9]. T2DM is regarded as an inflammatory disease, and controlling the accompanying systemic inflammation can improve these comorbidities and minimize complications[10,11]. However, more than 50% of patients with DPN are asymptomatic[12]. Additionally, controlling glucose in the normal range does not slow down progression of DPN[13], indicating that some other mechanism is involved in this process.

Sestrin2, part of the Sestrin family including Sestrin1 and Sestrin3, is a highly conserved protein induced by oxidative stress, inflammation, and DNA damage[14]. It maintains the integrity of cells under stress through metabolic reactions that generate energy and stimulation of the DNA repair system[14-16]. Hypoxia and ATP deficiency induce Sestrin2 expression[17,18]. Reduced intracellular levels of Sestrin2 can result in many undesirable sequelae including mitochondrial dysfunction, oxidative damage, and insulin resistance[19]. In addition, studies have found that Sestrin2 is also

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involved in atherosclerosis[20], diabetic nephropathy[21], and other chronic vascular complications of diabetes[22]. Sestrin2 is a new therapeutic target to reduce reactive oxygen species accumulation and enhance autophagy in the ischemic heart. Studies of Sestrin2 levels in diabetic patients have shown mixed results. Mohany *et al*[21] found that lower levels of serum Sestrin2 in T2DM patients when compared to healthy controls. In contrast, Chung *et al*[23] found high serum Sestrin2 levels in patients with obesity and T2DM. However, evidence is still unclear whether serum Sestrin2 levels has an association with DPN. Therefore, we aimed to explore the association between serum Sestrin2 levels and DPN in patients with T2DM.

MATERIALS AND METHODS

Participants

A total of 96 patients diagnosed with T2DM at our hospital from April to December 2020, and 39 healthy controls participated in this cross-sectional study. Informed consent was obtained prior to enrollment. The 96 T2DM patients were divided into T2DM patients with DPN (n = 47) and T2DM without DPN groups (n = 49). All of the patients met the World Health Organization diagnostic criteria for T2DM and diabetic neuropathies (a statement by the American Diabetes Association diagnostic criteria for DPN)[12]. The DPN criteria were as follows: Assessment included a detailed history; and symmetrical or unilateral limb numbness, spontaneous limb pain, dullness and physical tension, weakened or absent tendon reflexes, muscle weakness, and a considerable decrease in sensory and motor nerve conduction speed as shown by electromyography. During the assessment, patients with the following diseases were excluded: Severe acute complications such as diabetic ketoacidosis, peripheral neuropathy not caused by diabetes, or any endocrinal diseases (*e.g.*, infectious diseases, serious cardiovascular diseases, tumors, Cushing's syndrome, fever, cerebrovascular disease, connective tissue disease foot infections, edema, or depression). No subjects used neurotrophic drugs or other drugs that interfered with the experiment in the first three months of enrollment. The study was approved by the Medical Ethics Committee of Affiliated Hospital of Weifang Medical University.

Laboratory measurements

Data were recorded for sex, age, and other clinical characteristics. Blood samples were collected from the anterior cubital vein under fasting conditions, and serum samples were collected for analysis. Fasting plasma glucose (FPG) and blood lipids were measured using a Roche Cobas 8000 automatic biochemical analyzer. Hemoglobin A1c (HbA1c) levels were detected with a high-performance liquid chromatography system (Bio-Rad, United States). Insulin and C-peptide were tested by chemiluminescence (e601, Roche). Estimated glomerular filtration rate (eGFR) was calculated using a modified MDRD formula[24]. Serum Sestrin2 levels were determined by an ELISA Kit (SEC840Hu, Cloud-Clone Corp, China).

Statistical analysis

Statistical analysis was conducted using Graphpad Prism 8. Parametric data are expressed as the mean ± SE and were compared using Student's t-test. The non-parametric data are expressed as the median (interquartile range). Pearson's correlation coefficient was used to test the correlation between variables. Multivariate linear regression was used to evaluate the different metabolic indices with Sestrin2. Logistic regression analyses indicated the risk factors of DPN. The sample size was calculated by G. Power 3.1, with $\alpha = 0.05$ and $\beta = 0.2$. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

The characteristics of the participants are listed in Table 1. FPG, HbA1c, homeostasis model assessment of insulin resistance, blood pressure, and serum creatinine (Scr) were significantly higher in patients with T2DM compared to healthy controls ($P <$ 0.05). Triglyceride levels were higher and high-density lipoprotein cholesterol levels were lower in patients with T2DM than healthy controls. No significant differences in C-peptide, insulin, low-density lipoprotein cholesterol, blood urea nitrogen, and uric

Table 1 Clinical and metabolic characteristics of the three groups

Characteristics	NC	T2DM	DPN
n	39	49	47
Gender (M/F)	20/19	23/26	24/23
Age (yr)	52.31 ± 1.93	54.20 ± 1.58	58.87 ± 1.40
BMI (kg/m^2)	24.04 ± 0.45	27.91 ± 0.55[a]	26.67 ± 0.52[a]
Diabetes duration (yr)	-	1.00 (0.20-4.50)	10.00 (4.00-15.00)[c]
SBP (mmHg)	128 (119-133)	131 (118-146)[a]	141 (126-153)[a]
DBP (mmHg)	75.97 ± 0.89	85.96 ± 1.48[a]	86.79 ± 1.73[a]
FPG (mmoL/L)	5.31 (4.92-5.79)	9.02 (7.30-10.61)[a]	8.09 (6.77-9.89)[a]
HbA_{1c} (%)	5.50 ± 0.05	8.92 ± 0.29[a]	8.06 ± 0.26[a]
FCP (ng/mL)	1.65 (1.18-2.19)	1.24 (1.00-2.02)	1.31 (0.85-2.16)
FINS (uIU/mL)	6.87 (4.35-9.60)	5.85 (3.25-10.30)	6.84 (3.90-9.97)
HOMA-IR	1.49 (1.00-2.42)	2.42 (1.26-4.18)[a]	2.59 (1.23-4.50)[a]
TG (mmoL/L)	0.90 (0.62-1.24)	1.93 (1.32-3.87)[a]	1.89 (1.12-2.75)[a]
LDL (mmoL/L)	3.02 ± 0.13	3.07 ± 0.13	3.08 ± 0.17
HDL (mmoL/L)	1.36 ± 0.06	1.13 ± 0.04[a]	1.25 ± 0.05[a]
SCr (umoL/L)	50.33 ± 2.84	64.7 ± 2.01[a]	63.56 ± 1.96[a]
BUN (mmoL/L)	5.27 ± 0.25	3.41 ± 0.21	4.84 ± 0.15[c]
UA (mmoL/L)	300.90 ± 10.80	309.79 ± 10.48	282.58 ± 11.74
eGFR (mL/min/1.73m^2)	154.90 (122.90-214.60)	116.30 (101.40-140.30)[a]	114.00 (98.16-130.00)[a]
Sestrin2 (ng/mL)	9.10 (5.41,13.53)	14.58 (7.93-26.62)[a]	9.86 (6.72-21.71)[c]

[a]$P < 0.05$ *vs* normal control group.
[c]$P < 0.05$ *vs* type 2 diabetes mellitus group.
M: Male; F: Female; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HbA_{1c}: Glycosylated hemoglobin $A1_c$; FCP: Fasting C peptide; FINS: Fasting insulin; HOMA-IR: Homeostasis model assessment of insulin resistance; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Scr: Serum creatinine; BUN: Blood urea nitrogen; UA: Uric acid; eGFR: Estimated glomerular filtration rate; NC: Normal control; T2DM: Type 2 diabetes mellitus; DPN: Diabetic peripheral neuropathy.

acid were found among the groups ($P > 0.05$).

Serum Sestrin2 levels

Serum Sestrin2 levels of all T2DM patients were significantly higher than healthy controls [12.75 (7.44-23.80) ng/mL *vs* 9.10 (5.41-13.53) ng/mL, respectively, $P < 0.001$]. Serum Sestrin2 levels were significantly higher in T2DM patients without DPN than healthy controls [14.58 (7.93-26.62) ng/mL *vs* 9.10 (5.41-13.53) ng/mL, $P < 0.01$]. However, T2DM patients with DPN had decreased serum Sestrin2 levels compared to T2DM patients without DPN [9.86 (6.72-21.71) ng/mL *vs* 14.58 (7.93-26.62) ng/mL, $P < 0.0001$] (Table 1).

Correlations between serum Sestrin2 levels and clinical characteristics

Bivariate correlation analysis showed that serum Sestrin2 was significantly and positively correlated with HbA1c ($r = 0.292$, $P = 0.000$), body mass index (BMI; $r = 0.672$, $P = 0.000$), Scr ($r = 0.206$, $P = 0.016$), triglycerides ($r = 0.731$, $P = 0.000$), and FPG ($r = 0.202$, $P = 0.018$), and negatively associated with eGFR ($r = -0.230$, $P = 0.007$) (Table 2).

Multivariate correlations with serum Sestrin2 levels

After adjustments for sex, age, diabetes duration, and HbA1c levels, Sestrin2 levels were independently associated with BMI ($\beta = 0.422$, $P < 0.0000$) and triglyceride levels ($\beta = 0.443$, $P < 0.0000$), but not with Scr, FPG, or eGFR. Logistic regression analyses show that lower Sestrin2 levels were strongly correlated with DPN in patients with

Table 2 Correlation analysis between Sestrin2 and clinical characteristics

Characteristics	Sestrin2	
	r value	*P* value
Age	0.088	0.312
DD	0.134	0.122
BMI	0.672	0.000[a]
DBP	0.053	0.539
SBP	0.014	0.868
FPG	0.202	0.018[a]
HbA1c	0.292	0.000[a]
FCP	0.016	0.861
FINS	-0.008	0.927
HOMA-IR	0.115	0.183
TG	0.731	0.000[a]
TC	0.485	0.621
LDL	0.088	0.309
HDL	0.051	0.559
SCr	0.206	0.016[a]
BUN	0.094	0.281
UA	-0.002	0.980
eGFR	-0.230	0.007[a]

[a]$P < 0.05$.

DD: Diabetes duration; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin A1c; FCP: Fasting C peptide; TG: Triglyceride; TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; SCr: Serum creatinine; BUN: Blood urea nitrogen; UA: Uric acid; eGFR: Estimated glomerular filtration rate; FINS: Fasting insulin; HOMA-IR: Homeostasis model assessment of insulin resistance.

T2DM (OR = 0.855, $P = 0.019$) (Tables 3 and 4).

DISCUSSION

This case-control study shows that serum Sestrin2 levels increase in patients with T2DM but are reduced in T2DM patients with DPN. Notably, Sestrin2 levels are negatively associated with DPN. These results indicate that lower Sestrin2 is independently correlated with DPN in patients with T2DM, and suggests that the body may initially be able to self-regulate the abnormal metabolism. However, as T2DM progresses, the compensatory mechanism of Sestrin2 is insufficient to regulate the intracellular environment and progressively decreases. These changes may be related to developing diabetes-related complications.

Sestrin2 is an evolutionary, stress-inducing protein that plays a role in various cellular functions in metabolic diseases, including obesity and diabetes. Sestrin2 is inducible through oxidative stress, and is a recently discovered antioxidant molecule [25]. However, there have been few investigations into the relationship between Sestrin2 and DPN. The current study shows significantly higher serum Sestrin2 in patients with T2DM. This is in accordance with the findings of Chung *et al*[23], who found increased serum Sestrin2 levels in patients with obesity and T2DM. This paradoxical increase could be caused by a compensatory mechanism to overcome metabolic stress[26]. In contrast, Mohany *et al*[21] found low levels of serum Sestrin2 in patients with T2DM, and a reduction in Sestrin2 has been shown to lead to numerous adverse effects such as mitochondrial dysfunction, insulin resistance, and accelerated diabetes[19]. Indeed, these studies are unable to explain this contradiction. This study

Table 3 Unstandardized and standardized β-coefficients for associations of Sestrin2 with clinical characteristics in multivariate analysis

Sestrin2	B	SE	β	*t*	*P* value	95%CI
BMI	1.130	0.197	0.422	5.732	0.000	0.740-1.521
HbA1c	0.477	0.406	0.095	1.174	0.242	-0.327-1.281
TG	3.323	0.541	0.443	6.146	0.000	2.253-4.392
FPG	-0.417	0.286	-0.115	-1.460	0.147	-0.982-0.148
SCr	0.003	0.068	0.005	0.050	0.960	-1.131-0.138
eGFR	-0.006	0.023	-0.025	-0.243	0.808	-0.051-0.040

BMI: Body mass index; HbA1c: Glycosylated hemoglobin A1c; TG: Triglyceride; FPG: Fasting plasma glucose; SCr: Serum creatinine; eGFR: estimated glomerular filtration rate; CI: Confidence interval.

Table 4 Multivariate logistic analysis of risk factors for diabetic peripheral neuropathy

Risk factors	OR	95%CI	*P* value
Sestrin2	0.855	0.975-0.750	0.019
DD	1.411	1.695-1.175	0.000
HDL	0.041	0.880-0.002	0.041

DD: Diabetes duration; HDL: High-density lipoprotein; OR: Odds ratio; CI: Confidence interval.

suggests that Sestrin2 is positively associated with FBG and HbA1c in the subsequent analysis; thus, Sestrin2 transcription is appropriately up-regulated and participates in diabetes by modulating glucose levels under a variety of stresses. It is possible that Sestrin2 levels may vary at different stages of diabetes and the specific mechanism is worth exploring.

DPN is a common chronic complication affecting most patients with T2DM. The generation of oxygen-free radicals and oxidative stress due to the hyperglycemic condition causes endothelial dysfunction and ischemic nerve damage, promoting DPN pathogenesis[9,27]. Sestrin2 in neurons is induced by N-methyl-D-aspartic acid receptor activation, which stimulates the production of reactive oxygen species in a c/EBPβ-dependent manner[28]. Additionally, the AMPK/mTORC1 pathway is essential for maintaining the balance and stability of glucose and lipid metabolism under chronic hyperglycemia and excessive fat accumulation[29]. Modulation of AMPK/mTORC1 pathway over-activation can improve insulin resistance, glucose intolerance, and metabolic disorders[30]. Sestrin2 is a negative regulator of mTOR, and Sestrin2 may contribute to microvascular complications of diabetes. Reduced serum Sestrin2 levels have been associated with renal AMPK/mTORC1 activation and diabetic kidney disease[21]. The current study showed that, with the progression of diabetes, serum Sestrin2 levels decreased in patients with DPN. This finding suggests that the compensatory mechanism of Sestrin2 may be insufficient to regulate abnormal metabolism. The reduced Sestrin2 levels would induce abnormal mTOR activation and excess oxidative stress, thus leading to aggravated neuropathy in patients. Low levels of Sestrin2 have also been found to induce cancer, inflammation, and other neurological diseases, suggesting that low Sestrin2 is a risk factor for DPN and that Sestrin2 may participate in modulating nerve damage during DPN progression[17,31].

Although evidence strongly suggests that Sestrin2 is associated with metabolic disorders, there is no confirmed relationship between Sestrin2 and metabolic risk factors. We found that BMI and triglycerides are independently, positively correlated with serum Sestrin2 levels even after adjusting for other covariates. This indicates that Sestrin2 may be involved in body composition, thereby regulating metabolism and maintaining homeostasis under various stress conditions (such as T2DM and obesity). Few studies have examined the role of Sestrin2 in adipocyte and muscle cell biology. Li *et al*[32] have reported that Sestrin2 reverses palmitic acid-induced inhibition of autophagy signals in C2C12 muscle cells, leading to the recovery of insulin sensitivity. Further research is needed to clarify the effects of Sestrin2 on body composition,

including muscle and fat composition.

Our study has certain limitations; first, no definitive conclusions on causality can be drawn as this is a cross-sectional study. Further prospective studies are needed to clarify how Sestrin2 is involved in diabetes progression. Additionally, the small number of participants and selection bias may have affected the conclusion.

CONCLUSION

In summary, we found serum Sestrin2 is increased in patients with T2DM but reduced in T2DM patients with DPN. Sestrin2 may be a novel modulatory factor for metabolic disturbances in diabetes complications. Further analysis is needed to validate our findings and reveal the underlying mechanism of Sestrin2 on DPN pathophysiology.

ARTICLE HIGHLIGHTS

Research background

Diabetic peripheral neuropathy (DPN) is a chronic and serious microvascular complication of diabetes linked to redox imbalance. Sestrin2, a novel inducible stress protein, participates in glucose metabolic regulation and redox homeostasis. However, the association between serum Sestrin2 and DPN remains unclear.

Research motivation

Are there any correlations between serum Sestrin2 levels and DPN? Answering this question will provide significant insight into understanding the roles of Sestrin2 in DPN.

Research objectives

In this study, we explored the association between serum Sestrin2 and DPN in patients with type 2 diabetes mellitus (T2DM).

Research methods

Of 96 T2DM patients and 39 healthy individuals were enrolled in this case-control study. Clinical features and metabolic indices were identified. Serum Sestrin2 was measured. The association between Sestrin2 and DPN was studied.

Research results

Serum Sestrin2 was significantly lower in healthy volunteers than in all T2DM patients combined. T2DM patients without DPN also had significantly higher levels of Sestrin2 than healthy volunteers. However, T2DM patients with DPN had lower circulating Sestrin2 levels compared to T2DM patients without DPN. Bivariate correlation analysis revealed that serum Sestrin2 was positively correlated with body mass index, HbA1c, serum creatinine, triglycerides, fasting glucose, and negatively associated with estimated glomerular filtration rate. After adjustment for gender, age, HbA1c, and diabetes duration, multiple regression analysis revealed that Sestrin2 was independently correlated with body mass index and triglyceride levels. Logistic regression analyses indicated that Sestrin2, diabetes duration, and high-density lipoprotein were strongly associated with DPN.

Research conclusions

We have identified that lower serum Sestrin2 levels are independently associated with DPN.

Research perspectives

Sestrin2 mediates various effects on the complications of diabetes, including DPN. The value of the study promotes scientists to better understand the mechanisms of DPN for treatment.

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