**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 69784

**Manuscript Type:** ORIGINAL ARTICLE

***Case Control Study***

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

Mao EW *et al*. Sestrin2 and DPN

En-Wen Mao, Xue-Bing Cheng, Wen-Chao Li, Cheng-Xia Kan, Na Huang, Hong-Sheng Wang, Ning-Ning Hou, Xiao-Dong Sun

**En-Wen Mao, Cheng-Xia Kan, Xiao-Dong Sun,** Department of Endocrinology and Metabolism, Clinical Research Center, The Affiliated Hospital of Weifang Medical University, Weifang 261031, Shandong Province, China

**Xue-Bing Cheng, Wen-Chao Li, Na Huang, Hong-Sheng Wang, Ning-Ning Hou,** Department of Endocrinology and Metabolism, The Affiliated Hospital of Weifang Medical University, Weifang 261031, Shandong Province, China

**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.

**Supported by** National Natural Science Foundation of China, No. 81870593; Natural Science Foundation of Shandong Province of China, No. ZR2020MH106; Medical Health Science and Technology Project of Shandong Province, No. 202003060396 and No. 202003060400; and Quality Improvement of Postgraduate Education in Shandong Province, No. SDYAL19156.

**Corresponding author: Xiao-Dong Sun, MD, PhD, Chief Physician,** Department of Endocrinology and Metabolism, Clinical Research Center, The Affiliated Hospital of Weifang Medical University, No. 2428 Yuhe Road, Weifang 261031, Shandong Province, China. xiaodong.sun@wfmc.edu.cn

**Received:** July 12, 2021

**Revised:** September 6, 2021

**Accepted: November 14, 2021**

**Published online:**

**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 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

Mao EW, Cheng XB, Li WC, Kan CX, Huang N, Wang HS, Hou NN, Sun XD. Association between serum Sestrin2 level and diabetic peripheral neuropathy in type 2 diabetic patients. *World J Clin Cases* 2021; In press

**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.

**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 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 α = 0.05 and β = 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 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 (β = 0.422, *P* < 0.0000) and triglyceride levels (β = 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 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 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.

**REFERENCES**

1 **Benn M**. Peripheral Neuropathy-Time for Better Biomarkers? *Clin Chem* 2020; **66**: 638-640 [PMID: 32300787 DOI: 10.1093/clinchem/hvaa075]

2 **The Lancet**. Diabetes: a dynamic disease. *Lancet* 2017; **389**: 2163 [PMID: 28589879 DOI: 10.1016/S0140-6736(17)31537-4]

3 **Huang JX**, Liao YF, Li YM. Clinical Features and Microvascular Complications Risk Factors of Early-onset Type 2 Diabetes Mellitus. *Curr Med Sci* 2019; **39**: 754-758 [PMID: 31612393 DOI: 10.1007/s11596-019-2102-7]

4 **Selvarajah D**, Kar D, Khunti K, Davies MJ, Scott AR, Walker J, Tesfaye S. Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention. *Lancet Diabetes Endocrinol* 2019; **7**: 938-948 [PMID: 31624024 DOI: 10.1016/S2213-8587(19)30081-6]

5 **Ellulu MS**, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017; **13**: 851-863 [PMID: 28721154 DOI: 10.5114/aoms.2016.58928]

6 **Berbudi A**, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. *Curr Diabetes Rev* 2020; **16**: 442-449 [PMID: 31657690 DOI: 10.2174/1573399815666191024085838]

7 **Rolim LC**, da Silva EM, Flumignan RL, Abreu MM, Dib SA. Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy. *Cochrane Database Syst Rev* 2019; **6**: CD011265 [PMID: 31201734 DOI: 10.1002/14651858.CD011265.pub2]

8 **Sattar N**, Preiss D. Research digest: the risks of type 2 diabetes at a young age. *Lancet Diabetes Endocrinol* 2017; **5**: 331 [PMID: 28395877 DOI: 10.1016/S2213-8587(17)30117-1]

9 Diabetic neuropathy. *Nat Rev Dis Primers* 2019; **5**: 42 [PMID: 31197183 DOI: 10.1038/s41572-019-0097-9]

10 **Zhu CL**, Zhao WY, Qiu XD, Zhao SW, Zhong LZ, He N. A meta-analysis of surgical decompression in the treatment of diabetic peripheral neuropathy. *Medicine (Baltimore)* 2018; **97**: e12399 [PMID: 30213013 DOI: 10.1097/MD.0000000000012399]

11 **Prabodha LBL**, Sirisena ND, Dissanayake VHW. Susceptible and Prognostic Genetic Factors Associated with Diabetic Peripheral Neuropathy: A Comprehensive Literature Review. *Int J Endocrinol* 2018; **2018**: 8641942 [PMID: 29736170 DOI: 10.1155/2018/8641942]

12 **Pop-Busui R**, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; **40**: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]

13 **Rodriguez-Gutierrez R**, Gonzalez-Gonzalez JG, Zuñiga-Hernandez JA, McCoy RG. Benefits and harms of intensive glycemic control in patients with type 2 diabetes. *BMJ* 2019; **367**: l5887 [PMID: 31690574 DOI: 10.1136/bmj.l5887]

14 **Kim M**, Sujkowski A, Namkoong S, Gu B, Cobb T, Kim B, Kowalsky AH, Cho CS, Semple I, Ro SH, Davis C, Brooks SV, Karin M, Wessells RJ, Lee JH. Sestrins are evolutionarily conserved mediators of exercise benefits. *Nat Commun* 2020; **11**: 190 [PMID: 31929512 DOI: 10.1038/s41467-019-13442-5]

15 **Shin BY**, Jin SH, Cho IJ, Ki SH. Nrf2-ARE pathway regulates induction of Sestrin-2 expression. *Free Radic Biol Med* 2012; **53**: 834-841 [PMID: 22749810 DOI: 10.1016/j.freeradbiomed.2012.06.026]

16 **Cordani M**, Sánchez-Álvarez M, Strippoli R, Bazhin AV, Donadelli M. Sestrins at the Interface of ROS Control and Autophagy Regulation in Health and Disease. *Oxid Med Cell Longev* 2019; **2019**: 1283075 [PMID: 31205582 DOI: 10.1155/2019/1283075]

17 **Sun W**, Wang Y, Zheng Y, Quan N. The Emerging Role of Sestrin2 in Cell Metabolism, and Cardiovascular and Age-Related Diseases. *Aging Dis* 2020; **11**: 154-163 [PMID: 32010489 DOI: 10.14336/AD.2019.0320]

18 **Bae SH**, Sung SH, Oh SY, Lim JM, Lee SK, Park YN, Lee HE, Kang D, Rhee SG. Sestrins activate Nrf2 by promoting p62-dependent autophagic degradation of Keap1 and prevent oxidative liver damage. *Cell Metab* 2013; **17**: 73-84 [PMID: 23274085 DOI: 10.1016/j.cmet.2012.12.002]

19 **Fan X**, Zeng Y, Song W, Li J, Ai S, Yang D, Mao X, Yang M. The role of Sestrins in the regulation of the aging process. *Mech Ageing Dev* 2020; **188**: 111251 [PMID: 32389691 DOI: 10.1016/j.mad.2020.111251]

20 **Sundararajan S**, Jayachandran I, Subramanian SC, Anjana RM, Balasubramanyam M, Mohan V, Venkatesan B, Manickam N. Decreased Sestrin levels in patients with type 2 diabetes and dyslipidemia and their association with the severity of atherogenic index. *J Endocrinol Invest* 2021; **44**: 1395-1405 [PMID: 33048307 DOI: 10.1007/s40618-020-01429-9]

21 **Mohany KM**, Al Rugaie O. Association of serum sestrin 2 and betatrophin with serum neutrophil gelatinase associated lipocalin levels in type 2 diabetic patients with diabetic nephropathy. *J Diabetes Metab Disord* 2020; **19**: 249-256 [PMID: 32548072 DOI: 10.1007/s40200-020-00498-0]

22 **Sun X**, Han F, Lu Q, Li X, Ren D, Zhang J, Han Y, Xiang YK, Li J. Empagliflozin Ameliorates Obesity-Related Cardiac Dysfunction by Regulating Sestrin2-Mediated AMPK-mTOR Signaling and Redox Homeostasis in High-Fat Diet-Induced Obese Mice. *Diabetes* 2020; **69**: 1292-1305 [PMID: 32234722 DOI: 10.2337/db19-0991]

23 **Chung HS**, Hwang HJ, Hwang SY, Kim NH, Seo JA, Kim SG, Kim NH, Baik SH, Choi KM, Yoo HJ. Association of serum Sestrin2 level with metabolic risk factors in newly diagnosed drug-naïve type 2 diabetes. *Diabetes Res Clin Pract* 2018; **144**: 34-41 [PMID: 30099048 DOI: 10.1016/j.diabres.2018.07.024]

24 **Cheng Y**, Huang L, Han Y, Vanisha C, Ge S, Xu G. A novel nomogram to predict the reliability of estimated glomerular filtration rate formulae in oncology patients. *BMC Cancer* 2020; **20**: 530 [PMID: 32513123 DOI: 10.1186/s12885-020-06997-w]

25 **Kumar A**, Dhiman D, Shaha C. Sestrins: Darkhorse in the regulation of mitochondrial health and metabolism. *Mol Biol Rep* 2020; **47**: 8049-8060 [PMID: 32888126 DOI: 10.1007/s11033-020-05769-w]

26 **Shen T**, Alvarez-Garcia O, Li Y, Olmer M, Lotz MK. Suppression of Sestrins in aging and osteoarthritic cartilage: dysfunction of an important stress defense mechanism. *Osteoarthritis Cartilage* 2017; **25**: 287-296 [PMID: 27693501 DOI: 10.1016/j.joca.2016.09.017]

27 **Yao RQ**, Ren C, Xia ZF, Yao YM. Organelle-specific autophagy in inflammatory diseases: a potential therapeutic target underlying the quality control of multiple organelles. *Autophagy* 2021; **17**: 385-401 [PMID: 32048886 DOI: 10.1080/15548627.2020.1725377]

28 **Papadia S**, Soriano FX, Léveillé F, Martel MA, Dakin KA, Hansen HH, Kaindl A, Sifringer M, Fowler J, Stefovska V, McKenzie G, Craigon M, Corriveau R, Ghazal P, Horsburgh K, Yankner BA, Wyllie DJ, Ikonomidou C, Hardingham GE. Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. *Nat Neurosci* 2008; **11**: 476-487 [PMID: 18344994 DOI: 10.1038/nn2071]

29 **Steinberg GR**, Carling D. AMP-activated protein kinase: the current landscape for drug development. *Nat Rev Drug Discov* 2019; **18**: 527-551 [PMID: 30867601 DOI: 10.1038/s41573-019-0019-2]

30 **Chai D**, Wang G, Zhou Z, Yang H, Yu Z. Insulin Increases Sestrin 2 Content by Reducing Its Degradation through the PI 3 K/mTOR Signaling Pathway. *Int J Endocrinol* 2015; **2015**: 505849 [PMID: 25792980 DOI: 10.1155/2015/505849]

31 **Kowalsky AH**, Namkoong S, Mettetal E, Park HW, Kazyken D, Fingar DC, Lee JH. The GATOR2-mTORC2 axis mediates Sestrin2-induced AKT Ser/Thr kinase activation. *J Biol Chem* 2020; **295**: 1769-1780 [PMID: 31915252 DOI: 10.1074/jbc.RA119.010857]

32 **Li Y**, Zhang J, Zhou K, Xie L, Xiang G, Fang M, Han W, Wang X, Xiao J. Elevating sestrin2 attenuates endoplasmic reticulum stress and improves functional recovery through autophagy activation after spinal cord injury. *Cell Biol Toxicol* 2021; **37**: 401-419 [PMID: 32740777 DOI: 10.1007/s10565-020-09550-4]

**Footnotes**

**Institutional review board statement:** The study was approved by the Medical Ethics Committee of Affiliated Hospital of Weifang Medical University.

**Informed consent statement:** Informed consent was obtained prior to enrollment.

**Conflict-of-interest statement:** The authors have nothing to disclose.

**Data sharing statement:** The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review started:** July 12, 2021

**First decision:** September 5, 2021

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cardoso C **S-Editor:** Yan JP **L-Editor:** A **P-Editor:** Yan JP

**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/m2) | 24.04 ± 0.45 | 27.91 ± 0.55a | 26.67 ± 0.52a |
| 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 ± 1.48a | 86.79 ± 1.73a |
| FPG (mmoL/L) | 5.31 (4.92-5.79) | 9.02 (7.30-10.61)a | 8.09 (6.77-9.89)a |
| HbA1c (%) | 5.50 ± 0.05 | 8.92 ± 0.29a | 8.06 ± 0.26a |
| 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 ± 0.04a | 1.25 ± 0.05a |
| SCr (umoL/L) | 50.33 ± 2.84 | 64.7 ± 2.01a | 63.56 ± 1.96a |
| BUN (mmoL/L) | 5.27 ± 0.25 | 3.41 ± 0.21 | 4.84 ± 0.15c |
| UA (mmoL/L) | 300.90 ± 10.80 | 309.79 ± 10.48 | 282.58 ± 11.74 |
| eGFR (mL/min/1.73m2) | 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; HbA1c: Glycosylated hemoglobin A1c; 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.

**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 | 0.000a |
| DBP | 0.053 | 0.539 |
| SBP | 0.014 | 0.868 |
| FPG | 0.202 | 0.018a |
| HbA1c | 0.292 | 0.000a |
| FCP | 0.016 | 0.861 |
| FINS | -0.008 | 0.927 |
| HOMA-IR | 0.115 | 0.183 |
| TG | 0.731 | 0.000a |
| TC | 0.485 | 0.621 |
| LDL | 0.088 | 0.309 |
| HDL | 0.051 | 0.559 |
| SCr | 0.206 | 0.016a |
| BUN | 0.094 | 0.281 |
| UA | -0.002 | 0.980 |
| eGFR | -0.230 | 0.007a |
|  |  |  |

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.

**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.