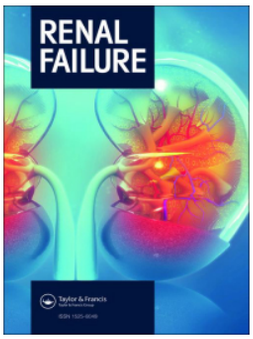

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Asprosin is positively associated with metabolic syndrome in hemodialysis patients: a cross-sectional study

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CLINICAL STUDY

Asprosin is positively associated with metabolic syndrome in hemodialysis patients: a cross-sectional study

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ABSTRACT

Introduction: Metabolic syndrome (MS) has a high prevalence in hemodialysis patients. High asprosin levels are associated with the accumulation of adiposity and an increase in body weight, which may drive the development of this syndrome. The relationship between asprosin and MS in patients on hemodialysis has not been investigated.

Materials and Methods: We enrolled hemodialysis patients at the hemodialysis center of one hospital in May 2021. MS was defined by the International Diabetes Federation. Fasting serum asprosin levels were measured. ROC curve, multivariate logistic regression and Spearman's rank correlation analyses were performed.

Results: In total, 134 patients were included, with 51 with MS and 83 without MS. Among the patients with MS, there was a significantly higher proportion of women (54.9%), prevalence of DM ($p < 0.001$), waist circumference ($p < 0.001$), BMI ($p < 0.001$), triglycerides ($p < 0.001$), and low-density lipoprotein cholesterol($p < 0.050$), and PTH ($p < 0.050$) contents and a lower diastolic pressure($p < 0.050$) and high-density lipoprotein cholesterol level ($p < 0.001$) than those in patients without MS. The patients with MS exhibited significantly higher serum asprosin levels than the non-MS patients [502.2 ± 153.3 ng/ml vs. 371.5 ± 144.9 ng/ml, $p < 0.001$]. The AUC for the serum asprosin level was 0.725 (95% confidence interval: 0.639, 0.811). Multivariate logistic regression analysis revealed that asprosin was independently and significantly positively associated with MS (OR = 1.008, $p < 0.010$). Asprosin levels tended to rise as the number of diagnostic criteria of MS increased (p for trend <0.001).

Conclusions: Fasting serum asprosin is positively correlated with MS and could be an independent risk factor for MS in hemodialysis patients.

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KEYWORDS
Asprosin; metabolic syndrome; hemodialysis

End-stage renal disease is a very common disease, and in most new cases, hemodialysis is a prevalent modality of renal replacement treatment [1]. The number of hemodialysis patients with diabetes and hypertension increases with age, and metabolic syndrome (MS) is highly prevalent in such patients, up to 50% [2–5].

Asprosin is a glucogenic protein hormone discovered by Chase Romere in 2016. It is a 140-amino-acid long C-terminal cleavage product of profibrillin (encoded by FBN1) and is mainly synthesized and released by white adipose tissue during fasting. Asprosin promotes glucose production in the liver through the olfactory receptor OLFR734 [6]. Moreover, asprosin in the circulation, which can cross the blood–brain barrier, directly activates orexigenic AgRP + neurons and inhibits anorexigenic POMC neurons, thus leading to appetite stimulation. It is a driver of adiposity accumulation and body weight increase [7].

Asprosin plays a complex role in metabolic diseases, including obesity, insulin, and diabetes [8]. It is associated with MS features such as glucose and lipid metabolism, insulin resistance, obesity and inflammation [9]. Some studies have shown that asprosin concentrations are increased in obesity [10] and type 2 diabetes mellitus [11,12]. Asprosin-induced overfeeding and hepatic glucogenesis may drive the development of metabolic syndrome [13]. However, the association between asprosin and metabolic syndrome in hemodialysis patients remains unknown. The purpose of this study was to explore how asprosin is related to metabolic syndrome, to thus determine whether asprosin is an independent risk factor for metabolic syndrome in hemodialysis patients.

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Materials and methods

Patients

This cross-sectional study was conducted in May 2021 at the hemodialysis center of a hospital in Chuangzhou City, Jiangsu, China. Patients older than 18 years who received hemodialysis treatment three times a week for 3.5–4 h, used standard bicarbonate dialysate on a hollow fiber dialyzer and had been on dialysis for at least 3 months were enrolled in our study. Patients were excluded if they had any acute disease, infection, malignancy, liver disease, ascites, polycystic kidney, or parathyroidectomy or if they refused to sign a written informed consent form for the study. Each patient signed an informed consent form prior to participating in the study. The present study was approved by the hospital ethics review board and was conducted in accordance with the principles of the Declaration of Helsinki.

Metabolic syndrome was diagnosed according to the 2005 International Diabetes Federation's definition: (a) waist circumference ≥90 cm (Chinese males) or ≥80 cm (Chinese females), plus two or more of the following: (b) fasting serum glucose ≥5.6 mmol/L or previously confirmed type 2 diabetes mellitus or having received corresponding hypoglycemic therapy; (c) systolic BP ≥130 or diastolic BP ≥85 mmHg, or having received antihypertensive treatment or previous clear diagnosis with hypertension; (d) TG ≥1.7 mmol/l, or having received corresponding lipid-conditioning treatment; and (e) HDL cholesterol ≤1.03 mmol for males or 1.29 mmol/L for females, or having received corresponding lipid-conditioning treatment. Those with three or more of the above items can be diagnosed with metabolic syndrome [14].

Anthropometric data and biochemical measurements

Participants' weight was derived from the routinely recorded dry weight, patients' height was measured without shoes, and waist circumference was measured with a tape measure between the lowest ribs and the hip bone. The measurements were performed by the same operator. Body mass index (BMI) was calculated as body weight divided by height squared.

Fasting blood samples were collected before starting dialysis after one day without a dialysis session. Blood was added to tubes containing procoagulant to obtain serum. Samples were processed within 2 h of collection and centrifuged at 3000 × g for 5 min. Serum albumin, transaminase, urea nitrogen, creatinine, lipids, calcium, phosphate and iPTH levels were determined by routine laboratory methods. Aliquots of serum were prepared and immediately stored at −20 °C until assay. Serum asprosin levels were determined using a commercially available enzyme-linked immunosorbent assay (Cat: AE59067HU, Abebio, Wuhan, China). Samples were diluted 500-fold, following the manufacturer's recommendations. All samples were analyzed in duplicate and the average of these values was used for calculations.

Statistical analysis

Numerical variables are expressed as the mean ± standard deviation or median and interquartile range. First, data were tested for normal distribution using the Kolmogorov–Smirnov test. Student's independent *t* test (2-tailed) was used to test the two groups for normally distributed data. The Mann–Whitney *U* test was used to compare non-normally distributed data between the two groups. Categorical variables were analyzed using the X^2-test. The ROC curve was used to calculate the area under the curve (AUC). Binary logistic regression analysis was performed to assess the independent effects of the variables significantly associated with MS. Simple linear regression analysis was used to evaluate the association of asprosin with each diagnostic criterion of MS. Spearman rank correlation was analyzed to evaluate the correlation between the asprosin concentration and the number of metabolic syndrome criteria. A probability value of less than 0.05 was statistically significant. Data were analyzed using SPSS 25.0, and graphs were generated using GraphPad Prism 7.0.

Results

A total of 134 hemodialysis patients were recruited for this study, including 79 males (59%) and 55 females (41%), with a mean age of 57.24 ± 15.09 years, and 44 patients had diabetes (32.8%). The mean dialysis duration was 54.50 (26.75, 98.25) months. Fifty-one (38.1%) patients were diagnosed with metabolic syndrome, and 83 were diagnosed with non-metabolic syndrome. Among the patients with MS, there was a significantly higher proportion of women (54.9%), prevalence of DM ($p < 0.001$), waist circumference ($p < 0.001$), BMI ($p < 0.001$), triglycerides ($p < 0.001$), low-density lipoprotein cholesterol ($p < 0.050$), and PTH ($p < 0.050$), and a lower diastolic pressure($p < 0.050$) and high-density lipoprotein cholesterol($p < 0.001$) than in those without MS. No statistically significant differences were found between hemodialysis patients with and without MS in terms of age, HD duration, antihypertensive drugs, albumin, transaminase, urea nitrogen, creatinine, calcium, phosphorus, and cholesterol. All but one patient had hypertension (Table 1 for more details).

The patients with MS exhibited significantly higher serum asprosin levels than patients without MS [502.2 ± 153.3 ng/ml, $n = 51$ vs. 371.5 ± 144.9 ng/ml, $n = 83$, $p < 0.001$] (Figure 1). The ROC curve for MS prediction is displayed in Figure 2. The AUC for the serum asprosin level was 0.725 (95% confidence interval: 0.639, 0.811). The optimum cutoff value was 369.85 ng/mL, with a sensitivity and specificity of 82.4 and 51.8%, respectively.

Univariate logistic regression analysis revealed that the factors associated with metabolic syndrome included sex, BMI, diabetes, triglycerides, HDL cholesterol, LDL cholesterol, and asprosin (Supplemental Table 1). Multivariate logistic regression analysis of the variables significantly associated with metabolic syndrome revealed that asprosin was independently and significantly associated in a positive manner

Table 1. Clinical and biochemical characteristics of the patients.

	All patients ($n=134$)	MS ($n=51$)	No MS ($n=83$)	p
Characteristics				
Male, *n* (%)	79 (59%)	23 (45.1%)	56 (67.5%)	0.011*
Age (years)	57.24 ± 15.09	59.9 (52,69)	55.0 (42.0,71.0)	0.144
Waist circumference	83.52 ± 13.08	95.9 ± 9.8	75.9 ± 8.1	0.001*
BMI	21.30 (19.2,24.8)	25.4 ± 3.6	20.0 ± 2.5	0.001*
Diabetes, *n* (%)	44 (32.8%)	27 (52.9%)	17 (20.5%)	0.001*
Systolic pressure(mmHg)	141.51 ± 17.55	141.49 ± 17.60	141.52 ± 17.62	0.993
Diastolic pressure(mmHg)	78.66 ± 11.79	75.69 ± 11.38	80.49 ± 11.73	0.021*
Dialysis duration (months)	54.50 (26.7, 98.25)	50.0 (23.0, 108.0)	60.0 (34.0, 96.0)	0.506
Etiology				
Chronic nephritis, *n* (%)	67 (50%)	20 (39.2%)	47 (56.6%)	0.050
Diabetic nephropathy, *n* (%)	30 (22.4%)	19 (37.3%)	11 (13.4%)	0.001*
Hypertension kidney disease, (%)	29 (21.6%)	8 (15.7%)	21 (25.3%)	0.189
Others, *n* (%)	8 (6%)	4 (7.8%)	4 (4.8%)	0.473
Medicine				
Calcium channel blocker, *n* (%)	98 (73.1%)	36 (70.6%)	62 (74.7%)	0.602
α, β Blocker, *n* (%)	80 (59.7%)	28 (54.9%)	52 (62.7%)	0.375
Angiotensin receptor blocker, *n* (%)	24 (17.9%)	9 (17.6%)	15 (18.1%)	0.950
Statin, *n* (%)[#]	8 (6%)	9 (11.8%)	2 (2.4%)	0.065
Laboratory data				
Alb (g/L)	39.34 ± 2.28	39.4 ± 2.3	39.3 ± 2.3	0.734
Alt (U/L)	9.00 (6.00, 14.00)	9.0 (6.0, 13.0)	9.0 (5.0, 15.0)	0.914
Ast (U/L)	13.00 (10.00, 16.25)	13.0 (10.0, 16.0)	12.0 (10.0, 17.0)	0.951
BUN (mmol/L)	21.66 ± 4.59	22.0 ± 4.6	21.5 ± 4.6	0.530
Creatinine (umol/L)	919.07 ± 202.34	907.9 ± 169.7	926.0 ± 220.7	0.617
Ca^{2+} (mmol/L)	2.38 ± 0.21	2.40 ± 0.23	2.36 ± 0.20	0.321
P (mmol/L)	1.84 ± 0.47	1.82 ± 0.43	1.86 ± 0.50	0.692
Cholesterol (mmol/L)	3.90 ± 0.90	4.07 ± 1.10	3.79 ± 0.75	0.116
Triglyceride(mmol/L)	0.98 (0.71, 1.33)	1.37 (1.02, 2.19)	0.79 (0.65, 1.08)	0.001*
LDL cholesterol (mmol/L)	2.31 (1.86, 2.73)	2.43 (2.00, 3.13)	2.21 (1.75, 2.56)	0.014*
HDL cholesterol (mmol/L)	1.07 (0.91, 1.26)	0.93 ± 0.21	1.20 ± 0.32	0.001*
iPTH (pg/ml)[$]	333.1 (205.3, 546.9)	400.9 (263.8, 598.3)	268.6 (176.4, 515.5)	0.015*
Asprosin (ng/ml)	421.26 ± 160.75	502.2 ± 153.3	371.5 ± 144.9	0.001*

Continuous variables are presented as mean ± SD or median with interquartile range. Categorical variables are presented as percentile. MS: metabolic syndrome; BMI: body mass index; Alb: albumin; Alt: alanine aminotransferase; Ast: aspartate aminotransferase; BUN: blood urea nitrogen; LDL: low density lipoprotein; HDL: high density lipoprotein; iPTH: intact parathyroid hormone. *$p<0.05$ Was considered statistically significant. [#]Means continuity correction Chi-Square test was used. [$]Means two data in MS and four data in no MS are missing.

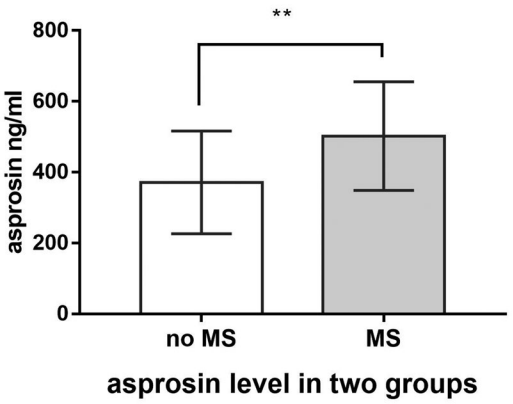

Figure 1. Fasting serum asprosin levels are significantly higher in patients with MS than in those without MS (502.2 ± 153.3 ng/ml, $n=51$ vs. 371.5 ± 144.9 ng/ml, $n=83$, $p<0.001$). **Means $p<0.001$.

with metabolic syndrome (OR = 1.008, $p<0.010$) after adjustment for sex, BMI, diabetes mellitus, triglycerides, LDL cholesterol, and HDL cholesterol (Supplemental Table 2).

Simple linear regression analysis of asprosin with each diagnostic criterion of MS showed that waist circumference ($p<0.001$) and triglycerides ($p<0.050$) were associated with asprosin. Diabetes ($p=0.063$) was also associated with asprosin, although the association did not reach statistical significance (Supplementary Table 3). There were significant differences between asprosin levels in patients with different numbers of metabolic syndrome criteria (one-way ANOVA, $p<0.001$), and there was a tendency for an increase in asprosin levels as the number of diagnostic criteria of MS increased (Spearman rank correlation test, p for trend < 0.001) (Figure 3).

Discussion

The results of our study showed that 38.1% of hemodialysis patients were diagnosed with metabolic syndrome. The fasting asprosin levels were higher in the MS group than in the non-MS group and were independently and significantly positively associated with MS in these HD patients. The fasting asprosin level increased as the number of metabolic syndrome criteria increased, which could be used as a diagnostic indicator for metabolic syndrome in hemodialysis patients.

Metabolic syndrome is a group of risk factors that are closely related to cardiovascular diseases, namely, abdominal obesity, dyslipidemia, hypertension, insulin resistance, and proinflammatory status [15]. The prevalence of metabolic syndrome in patients with CKD stages 3–5 was as high as 64.7% [16]. In hemodialysis patients, the prevalence

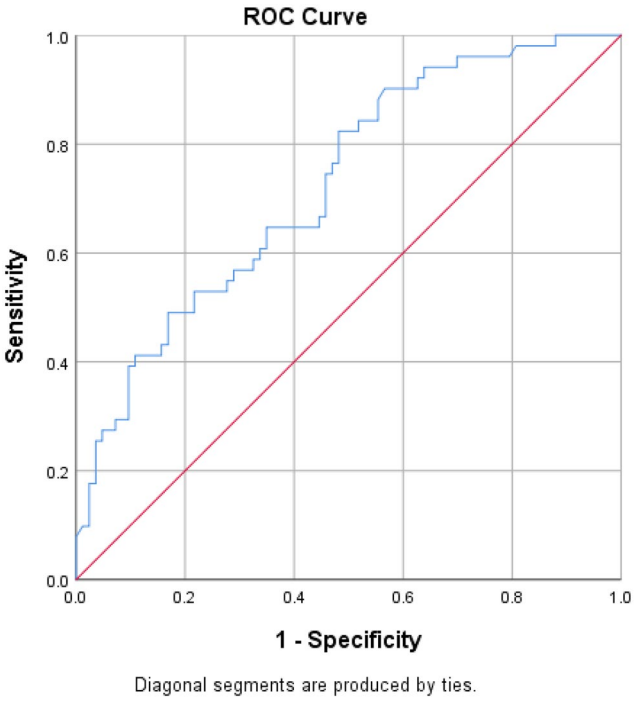

Figure 2. ROC curve of asprosin for MS. AUC = 0.725 (95% CI: 0.639, 0.811). Cutoff value: 369.85 ng/mL.

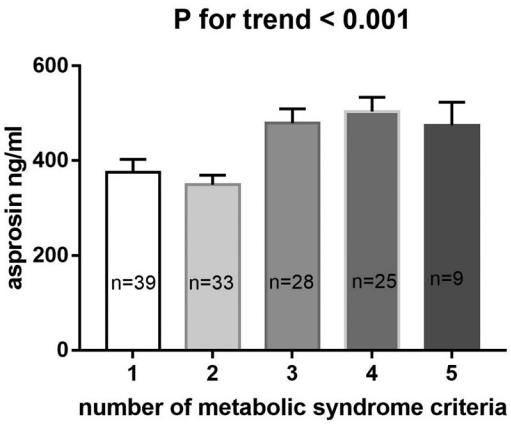

Figure 3. Fasting serum asprosin levels in 134 hemodialysis patients with different numbers of metabolic syndrome criteria. Data were analyzed by Spearman's rank correlation test.

of MS was higher in the first year of dialysis (56.25%) and gradually decreased to 44.8% at 2–5 years and 29.7% after 5 years [3]. One study showed that 38.2% of patients on hemodialysis had MS, and these particular patients were older, mostly females, and presented with a higher BMI, WC, prevalence of T2D and hypertension, as well as a shorter HD duration [17]. These results are consistent with our findings. MS is common in hemodialysis patients admitted to hospitals who are at risk of developing complications such as cardiovascular diseases [18]. Hemodialysis patients with MS reported nearly twice as high a risk of all-cause mortality and a 2.5 times higher risk of cardiovascular mortality than those without MS [19]. MS can serve as an important and independent predictor of mortality in hemodialysis patients.

As a fasting-induced protein hormone that regulates hepatic glucose release and a 140-amino-acid-long protein that is the C-terminal cleavage product of profibrillin (encoded by FBN1), asprosin is secreted by white fat, is transported primarily to the liver and binds olfactory receptor OLFR734 [6]. It activates protein kinase A in the liver, resulting in a rapid release of glucose into the circulation. Circulating asprosin can cross the blood–brain barrier to directly activate appetitive-promoting AgRP + neurons, leading to body weight gain [7]. Asprosin exhibits circadian oscillations, with fasting increasing circulating asprosin and its levels sharply decreasing at the onset of feeding [20]. Some studies have found that circulating asprosin levels were significantly higher in obese mice, adults and children than in controls [6,7,21,22]. Plasma asprosin levels were elevated in insulin-resistant mice and human patients [21]. Serum asprosin levels are increased in type 2 diabetes [11,12,23]. The patients with MS had higher serum levels of asprosin, which were positively associated with body mass index, waist circumference, triglycerides, fasting blood glucose, 2-h blood glucose, fasting insulin, insulin resistance homeostasis model assessment (HOMA-IR) index, interleukin-6 and monocyte chemoattractant-1 and negatively correlated with HDL cholesterol. Asprosin was independently and positively correlated with the occurrence of MS and insulin resistance (IR) [24]. It was a new biomarker of metabolic syndrome in general population [25]. Additionally, one study reported that asprosin predicted the severity of coronary artery lesions in unstable angina, thus becoming a marker of the severity of unstable angina and acute coronary syndrome [26]. In patients with diabetic nephropathy, the asprosin concentration was higher than that in controls [27,28]. Our study found that fasting asprosin levels were higher in the MS group than in the non-MS group and that the level of asprosin was an independent influencer of metabolic syndrome in hemodialysis patients. ROC curve analysis revealed that serum asprosin might be a useful marker for the prediction of MS in hemodialysis patients. Some factors can affect fasting asprosin levels, such as eating, acute anaerobic exercise. As the eGFR was decreased, the serum asprosin was increased [29]. It has not been studied whether asprosin is cleared by the hemodialysis process. There are still some questions about factors that affect the fasting serum asprosin. Therefore, more studies are required.

Obesity, glucose metabolism dysfunction and dyslipidemia are pathological states of MS. Obesity is often complicated by chronic low-grade inflammation and insulin resistance (IR). Asprosin promotes glucose production in the liver by activating the cAMP second messenger system, which is also involved in the inflammatory response [20]. In MS patients, serum asprosin levels were positively correlated with interleukin-6 and monocyte chemotaxis protein-1 (MCP-1), which are markers of chronic low-grade inflammation [25]. Conversely, an *in vitro* experiment showed that siRNA-mediated asprosin suppression improved NF-kB phosphorylation and

TNF-α and MCP-1 release in palmitate-treated pancreatic cells. However, a clinical study suggested that serum asprosin levels in diabetic patients were not significantly associated with high-sensitivity C-reactive protein (hs-CRP), an acute inflammatory marker. Further studies are needed to clarify the precise role of asprosin in metabolic inflammation. Some studies have found that asprosin impaired insulin sensitivity and secretion through PKCδ-activated endoplasmic reticulum stress and TLR4/JNK-mediated inflammatory pathways [30,31]. However, genetic defects and specific antibodies against asprosin improved insulin sensitivity [7]. These results suggested that the activity of asprosin may partly contribute to insulin resistance, leading to glucose metabolism dysfunction. Some observational studies have shown that serum asprosin levels are significantly correlated with glucose-lipid metabolism in type 2 diabetes [24], polycystic ovary syndrome [32], and MS [25]. The present study found that the patients with MS had significantly higher triglycerides and low-density lipoprotein contents and a lower high-density lipoprotein content than those without MS. These findings raise the hypothesis that asprosin may provide a molecular association between lipid metabolism and MS. Future studies on the causal effects of asprosin on lipid metabolism are warranted.

There are some limitations in our study. First, as a cross-sectional observational study, we were unable to determine the causality of the relationships. Second, this study was performed in one hospital, the sample size was small, and more patients in multiple centers are needed for further analysis. Third, The related inflammation indicators, such as hs-CRP, IL-6, were not assessed. The association of inflammation, asprosin and MS in hemodialysis patients were not reflected in this study. Fourth, we only examined the asprosin levels in a cross-section, making it necessary to further monitor intra-individual trends of the asprosin level during long-term HD and to investigate the relationship between asprosin levels and cardiovascular events and even death in HD patients.

Conclusion

Fasting serum asprosin is higher in HD patients with MS than in those without MS. It is independently and significantly associated in a positive manner with metabolic syndrome in hemodialysis patients. The asprosin levels increase as the number of MS diagnostic criteria increases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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