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ORIGINAL RESEARCH

Plasma Asprosin Concentrations are Associated with Progression of Diabetic Kidney Disease

Mingyue Xu*, Chunlin Zhang*, Linlin Zhang, Hua Qu, Yuren Wang

Department of Endocrinology, Translational Research of Diabetes Key Laboratory of Chongqing Education Commission of China, Second Affiliated Hospital of Army Medical University, Chongqing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hua Qu; Yuren Wang, Department of Endocrinology, Translational Research of Diabetes Key Laboratory of Chongqing Education Commission of China, the Second Affiliated Hospital of Army Medical University, Chongqing, 400037, People's Republic of China, Tel +86 2368763255, Fax +86 2368755707, Email quhuahua120@163.com; 346577395@qq.com

Purpose: To explore the expression of asprosin in subjects with pre-DKD and DKD and to analyze its relationship with kidney injury, inflammation, and glucose and lipid metabolism.

Methods: Based on urine albumin:creatinine ratio (UACr), participants were divided into DM, pre-DKD, and DKD groups. Relevant human physiological and biochemical parameters were detected in the three groups.

Results: We found relatively higher levels of asprosin in both pre-DKD and DKD groups than the DM group. Moreover, data from the Nephroseq database support increased gene expression of asprosin in kidney tissue from DKD patients. Further correlation analysis revealed that the plasma asprosin level was positively correlated with age, waist circumference, waist:hip ratio, systolic blood pressure, creatinine, UACr, triglycerides, HDL-c, fasting insulin, HOMA-IR, and the inflammatory marker G3P and negatively associated with eGFR. Multiple logistical regression analysis showed that asprosin concentration was significantly associated with pre-DKD and DKD after adjusting for sex, age, BMI, WHR, and HOMA-IR, while this correlation was lost after controlling for G3P.

Conclusion: Plasma asprosin is associated with kidney injury in diabetic conditions, and this association might be connected through inflammatory response. Further studies are needed to assess the role and mechanism of asprosin in DKD.

Keywords: asprosin, diabetes, diabetic kidney disease, kidney injury

Introduction

With the increasing prevalence of diabetes worldwide, the incidence of chronic complications of diabetes, such as diabetic retinopathy, diabetic kidney disease (DKD), and diabetic neuropathy, is also rising.[1] Among these, DKD has become the leading cause of end-stage renal disease in developed countries,[2,3] and its incidence in type 1 and type 2 diabetes isas high as 30% and 40%, respectively.[1,4] Therefore, understanding the risk factors related to the progression of DKD is critical in the treatment and prevention of DKD.

In previous studies, the increased level of circulating glucose was thought to be the pathogeny of kidney injury under diabetic situations.[5] However, several large-scale clinical trials (ACCORD, VADT, ADVANCE) failed to find a positive outcome after intensive control of glucose.[6] In recent years, adipokines, which are predominantly secreted from adipose tissue, were found to regulate functions of other organs, and were reported to participate in the pathology of DKD via inflammatory response.[7] Asprosin is such a sample. It is a C-terminal cleavage product of profibrillin (FBN1) secreted by white adipocytes, and was found to regulate the gluconeogenesis process in the liver.[8] Our previous studies have shown that plasma asprosin is increased in patients with type 2 diabetes and insulin resistance.[9] Moreover, it also has been reported to be associated with several inflammatory parameters, such as IL6 and MCP1.[10,11] Considering the double roles of asprosin in glucose metabolism and inflammation, we suspected that it may take part in the pathological processes of DKD. To answer this question, we

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conducted a cross-sectional study to evaluate plasma levels of asprosin in DM, pre-DKD, and DKD populations and to analyze their correlations with kidney function and injury.

Methods

Study Subjects

Our study recruited a total of 82 subjects. They were divided into three groups in based on urine albumin:creatinine (Cr) ratio (UACr): diabetic subjects without kidney disease (DM, n=22), early-stage DKD (pre-DKD, n=20), and DKD (n=40). Inclusion criteria were age >18 years, diabetes diagnosed on the basis of diagnostic criteria of the WHO (1999), and with pre-DKD (UACr ≥30 but <300 mg/g or DKD (UACr) ≥300 mg/g. Exclusion criteria were history of smoking and drinking, acute complications of DM, such as diabetic ketoacidosis, chronic kidney disease caused by other diseases, such as nephritis, presence of liver disease, coronary heart disease, or cerebrovascular disease, on systemic corticosteroid treatment, and pregnant or lactating. A review of human experimentation was approved by the Ethics Committee of Xinqiao Hospital, Third Military Medical University (Institutional Review Board-approved protocol 2016–056-01). This study complied with the Helsinki Declaration, and informed consent was signed by each participant.

Clinical Evaluations and Sample Collection

Clinical parameters were evaluated according to our previous work.[9,12] In detail, a fixed trained professional used the same measuring equipment to evaluate weight, height, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) in all subjects. Body mass index (BMI) is calculated as the ratio of body weight to height squared. Waist:hip ratio (WHR) is calculated as the ratio of WC to hip HC. Peripheral venous blood was drawn in the morning following fasting the previous night. Fasting duration was >8 hours. The supernatant was put into a new EP tube after centrifugation (1500 *g*, 15 minutes, 4°C) and stored (100 μL/tube). Repeated freezing and thawing was avoided in subsequent use, and it was stored in a refrigerator at –80°C. Morning urine was collected and stored (50 μL/tube). The storage method was the same as that for serum. Frozen samples were used within 3 months.

Biochemical Assessment

Levels of microalbuminuria and creatinine (Cr) in urine samples were determined by commercial kit (Nanjing Jiancheng Bio, Jiangsu, China), and the ratios of microalbuminuria to Cr were calculated. The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate estimated glomerular filtration rate (eGFR).[13] Lipid panel assays were assessed using an enzymatic method (Beckman CX7 biochemical autoanalyzer, Brea, CA). Glycosylated hemoglobin (HbA_{1c}) were measured by gas chromatography–mass spectrometry. The concentrations of fasting plasma glucose and fasting serum insulin (FIns) were assessed by the glucose oxidase method and human-specific insulin radioimmunoassay (Ins-RIA), respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting plasma glucose (mmol/L) × FIns (μU/mL)/22.5.[14]

Plasma Asprosin and Glyceraldehyde-3-Phosphate Concentration Determination

The concentrations of asprosin in the samples were determined using a commercial double-antibody sandwich ELISA kit according to the manufacturer's instructions (EIAab, Wuhan, China). The detection range of this kit is 3.9–250 ng/mL. Initial trials were conducted to ensure that the measured value was within this range. Intra- and interassay coefficients of variation were 10% and 12%, respectively. The assay exhibited no significant cross-reactivity or interference. For glyceraldehyde-3-phosphate (G3P), commercial assay kits were purchased from Abnova (Taiwan, China), and its concentration was determined by colorimetry. The calibration range was 0.04–0.2 μmol/mL. Optical density was measured with spectrophotometry at 450 nm, and all measures were duplicated and repeated for duplicate differences >10%. The concentrations of asprosin and G3P in each sample were calculated using standard curves.

Mice

Male C57BL/6, BKS-db/db and BKS-db/m mice were purchased from GemPharmatech. Type 1 diabetes in mice was induced by streptozotocin (Stz) in accordance with our previous approach.[15] The animal experiments were approved by the Laboratory Animal Welfare and Ethics Committee of the Army Medical University (AMUWEC20235154). This study abided by laboratory animal welfare guidelibes (GB/T 35892–2018, ICS: 65.020.30).

Quantitative Real-Time PCR

Quantitative real-time PCR was conducted as previously described.[16] The primer sequences were: asprosin, 5′-TGA GAGTCCGAGCCGCTAGT-3′ (forward) and 5′-CTGTCCGGCTGTCCTGATGC-3′ (reverse); GAPDH, 5′-TGAACG GGAAGCTCACTG-3′ (forward) and 5′-TCCACCACCCTGTTGCTG-3′ (reverse).

Statistical Analyses

All statistical analyses were conducted using SPSS 20.0 (IBM Corp, NY, USA). Kolmogorov–Smirnov tests were conducted to assess normality of data distribution. Variables with skewed distributions were converted to normal distributions logarithmically before further analysis. Multiple comparisons were estimated by one-way ANOVA, with Tukey's honest significant difference (HSD) test. Variable correlations were tested using Pearson's correlation coefficient (adjusted for age). Associations between asprosin and pre-DKD and DKD were analyzed using multivariate logistic regression analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Asprosin Higher in Circulation and Kidney Tissue from DKD Patients

Table 1 shows the clinical characteristics of participants in the three groups. There were no significant differences in terms of sex ratio, WC, WHR, BMI, LDL-c, or HOMA-β among the three groups. The DKD group showed greater age, SBP, Cr, TC, TG, HbA_{1c}, FIns, HOMA-IR, IL6, and TNFα, but lower eGFR and HDL-c than the DM group. As for the pre-DKD group, patients had higher levels of Cr, FIns, IL6, and TNFα, but lower levels of eGFR than the DM group. Notably, asprosin levels were significantly higher in both the pre-DKD (102.34±12.44 ng/mL, $P<0.001$) and DKD (105.13±19.87 ng/mL, $P<0.001$) groups than the DM (44.97±4.55 ng/mL) group (Figure 1A). Moreover, concentrations of G3P and mitochondrial glycerol 3-phosphate dehydrogenase (mGPDH), the substrate of a newly recognized inflammation driver, were significantly higher in both pre-DKD and DKD patients (Figure 1B).

To further explore the role of asprosin in DKD, we searched the Nephroseq database, an online transcriptomic dataset for kidney disease. As mentioned before, asprosin is encoded by the gene *FBN1* as part of the protein profibrillin and is released from the C-terminus of the latter by specific proteolysis. *FBN1* mRNA expression was significantly higher in the kidney tissue of DKD patients than healthy controls (fold change 1.87, $P<0.001$; Supplementary Figure 1A). This finding was consistent with our observations in plasma, and suggests a potential association between asprosin and the progression of DKD.

Asprosin Higher in Kidney Tissue from DKD Mice

Except for white adipose tissue, asprosin is expressed in other tissue types, including pancreas, liver, and kidney.[11,17] In an initial expression survey of kidneys, we observed higher levels of asprosin in glomeruli than in tubulointerstitial tissue (Figure 2A). Next, we explored the expression pattern of asprosin in kidney tissue from DKD mice. Both Stz-induced diabetic (Figure 2B) and db/db mice (Figure 2C) showed significantly increased asprosin expression. These results suggested that kidney-generated asprosin might participate in the pathology of DKD, excluding circulating asprosin.

Asprosin Significantly Associated with Progression of DKD

To further assess the relationship between asprosin and renal function impairment in DKD, we conducted Pearson's correlation coefficient tests. As shown in Table 2, plasma asprosin was significantly positively associated with age, Wc, WHR, SBP, Cr (Figure 3A), UACr (Figure 3B), TG, FIns, HOMA-IR, and G3P and negatively correlated with eGFR (Figure 3C) and HDL-c.

Table 1 Clinical and Laboratory Characteristics of Study Participants

	DM	Pre-DKD	DKD
Sex (M/F)	22 (8/14)	20 (10/10)	40 (21/19)
Age (years)	49.23±13.99	54.35±10.98	57.48±15.74[a]
BMI (kg/m^2)	23.36±3.32	25.65±2.75	23.84±4.82
WC (cm)	83.30±10.06	91.68±6.39	108.23±94.65
HC (cm)	95.32±6.84	98.75±4.39	101.02±10.44[a]
WHR	0.87±0.06	0.92±0.06	1.09±1.07
SBP (mmHg)	122.60±16.07	134.80±16.99	139.75±23.87[b]
DBP (mmHg)	79.35±11	86±9.51	83.45±14.27
Cr (μmol/L)	56.85±10.51	102.35±6.16[b]	140.70±69.87[bd]
UACr (mg/mmol)	14.10±7.88	61.40±12.48[a]	396.15±96.14[bd]
eGFR (mL/min/1.73 m^2)	110.67±10.52	76.07±3.70[b]	51.84±17.21[bd]
TC (mmol/L)	4.87±1.02	4.56±0.97	5.23±1.02[c]
TG (mmol/L)	1.28±0.60	1.57±0.65	3.65±3.35[bd]
HDL-c (mmol/L)	1.50±0.55	1.27±0.26	1.19±0.35[b]
LDL-c (mmol/L)	2.86±0.99	2.74±0.75	2.93±0.91
HbA_{1c} (%), mmol/mol	7.7±0.3/61	7.0±1.6/53	8.5±2.1/69[d]
FPG (mmol/L)	8.11±0.37	8.32±1.52	8.55±3.03[bc]
FIns (mU/L)	11.92±5.21	13.35±3.19[b]	15.95±4.47[bc]
HOMA-IR	4.30±0.95	5.04±2.08	6.06±2.72[b]
IL6 (pg/mL)	2.08±0.26	2.29±0.30[a]	2.70±0.28[bd]
TNFα (pg/mL)	8.96±0.75	10.78±1.46[a]	11.89±2.30[b]

Notes: Data presented as means ± SD. [a]$P<0.05$ compared with DM; [b]$P<0.01$ compared with DM; [c]$P<0.05$ compared with pre-DKD; [d]$P<0.01$ compared with pre-DKD.

Abbreviations: DM, diabetic mellitus; pre-DKD, early stage of diabetic kidney disease; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist:hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; UACr, urinary albumin: creatinine ratio; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-c, high-density-lipoprotein cholesterol; LDL-c, low-density-lipoprotein cholesterol; FPG, fasting plasma glucose; FIns, fasting serum insulin; HOMA-IR, Homeostasis Model Assessment for insulin resistance.

After adjustment for age, plasma asprosin remained significantly positively related to WHR, Cr, UACr, FIns, HOMA-IR, and G3P and negatively related to eGFR (Table 2). These results indicated that circulating asprosin was not only associated with renal function markers but also with metabolic and inflammatory parameters in our population. Again, we queried the Nephroseq

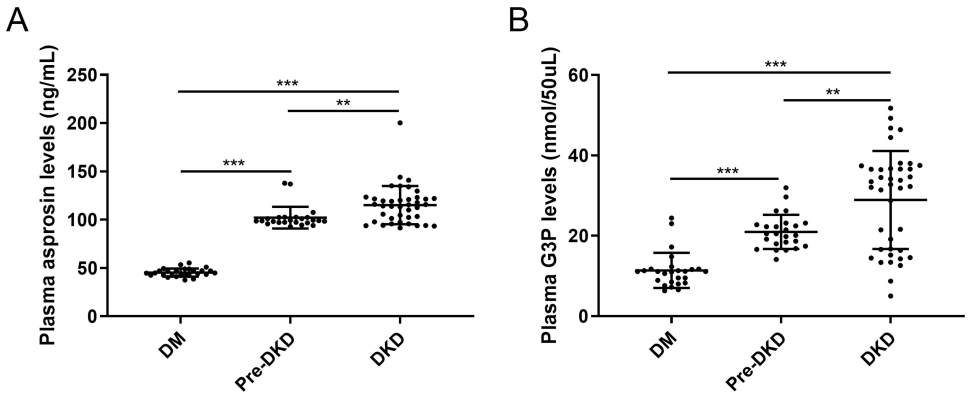

Figure 1 Scatterplots of plasma asprosin and glyceraldehyde-3-phosphate (G3P) concentrations in healthy, pre-DKD, and DKD patients. Asprosin (**A**) and G3P (**B**) concentrations in human plasma samples from indicated group. Each data point represents a plasma sample, the horizontal middle line in each data set represents the mean, and the limits of the vertical lines represent the SD. One-way ANOVA with Tukey's post hoc test was performed for multiple comparisons. ***$P<0.001$, **$P<0.01$.

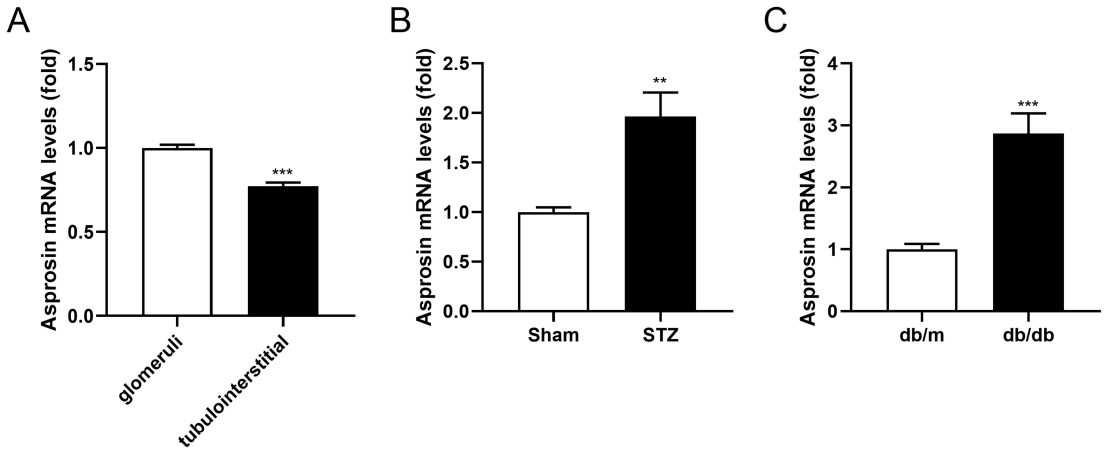

Figure 2 Expression of asprosin in kidney tissue from DKD mouse models. (**A**) mRNA expression of asprosin in glomeruli and tubulointerstitial tissue. mRNA expression of asprosin in kidney from Stz-induced diabetic (**B**) and db/db mice (**C**). Data shown as means and SD, n=6 mice per group. ***P<0.001, **P<0.01.

database, and consistently, the gene expression of asprosin was significantly negatively correlated with eGFR and positively correlated with Cr in kidney tissue from DKD patients (Supplementary Figure 1B). These findings further confirmed a significant association between asprosin and the progression of DKD.

Table 2 Spearman Correlation Coefficients of Variables Associated with Circulating Concentration

	Plasma asprosin		Plasma asprosin (age-adjusted)	
	R	***P***	***R***	***P***
Age	0.234	0.034	—	—
Sex	−0.190	0.087	−0.199	0.148
BMI	−0.007	0.948	0.127	0.360
WC	0.365	0.001	0.203	0.141
HC	0.187	0.093	0.012	0.932
WHR	0.347	0.001	0.329	0.015
SBP	0.278	0.012	0.112	0.421
DBP	0.152	0.179	0.110	0.431
Cr	0.597	<0.001	0.751	<0.001
UACr	0.686	<0.001	0.502	<0.001
eGFR	−0.615	<0.001	−0.759	<0.001
TC	0.074	0.509	−0.043	0.758
TG	0.305	0.005	0.119	0.390
HDL-c	−0.293	0.008	−0.035	0.799
LDL-c	−0.008	0.944	0.011	0.939
HbA_{1c}	0.094	0.408	0.136	0.326
FPG	0.121	0.279	0.014	0.917
FIns	0.490	<0.001	0.505	<0.001
HOMA-IR	0.447	<0.001	0.511	<0.001
G3P	0.663	<0.001	0.524	<0.001

Abbreviations: BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; UACr, urinary albumin:Cr ratio, eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-c, high-density-lipoprotein cholesterol; LDL-c, low-density-lipoprotein cholesterol; FPG, fasting plasma glucose; FIns, fasting serum insulin; HOMA-IR, homeostasis model assessment for insulin resistance; G3P, glyceraldehyde-3-phosphate.

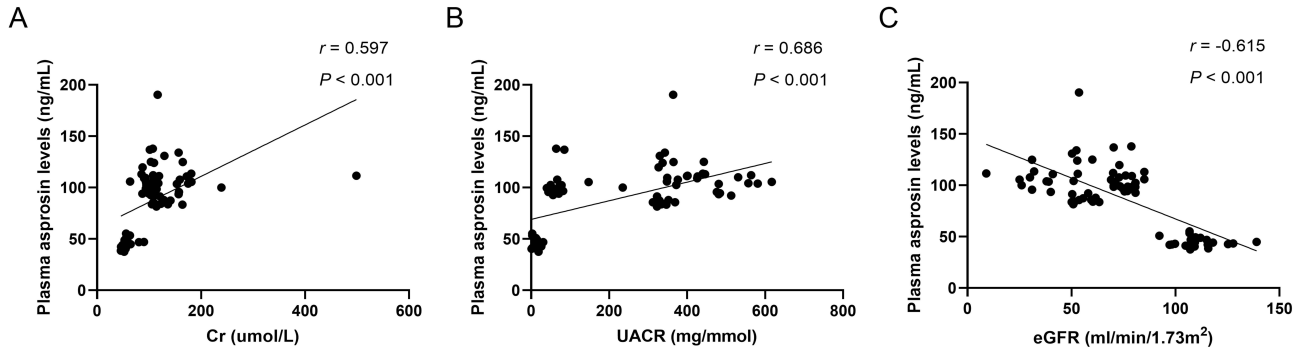

Figure 3 Scatterplots showing correlations of plasma asprosin levels with Cr, UACr, and eGFR in all subjects. (**A**) Correlation of plasma asprosin levels with Cr. (**B**) Correlation of plasma asprosin levels with UACr. (**C**) Correlation of plasma asprosin levels with eGFR.
Abbreviations: Cr, creatinine; UACr, urinary albumin:Cr ratio; eGFR, estimated glomerular filtration rate.

Next, we assessed potential intermediate factors within this association by multiple logistical regression analysis. Our results indicated that plasma asprosin level was significantly associated with pre-DKD and DKD after adjusting for sex, age, BMI, WHR, and HOMA-IR (ORs 1.733 and 3.867, 95% CIs 1.105–3.054 and 1.542–8.234, both $P<0.01$), while these correlations were lost after controlling for the inflammatory marker G3P (ORs 1.005 and 1.298, 95% CIs 0.823–1.394 and 0.654–2.574, both $P>0.05$). These results indicated that asprosin might affect the progression of DKD via inflammatory response.

Discussion

DKD is one of the most common and severe diabetic chronic complications, and its pathology and thus therapeutic strategy remain unclear. This study combined results from human subjects, the Nephroseq database, and animal models, revealing that a newly found adipokine, asprosin, was significantly increased not only in the circulation but also in kidney tissue from DKD patients and mouse models. Furthermore, we also found that its expression was closely related to renal function, the progression of DKD, obesity, insulin resistance, and inflammatory response. Inflammation might be a mediator of the relationship between asprosin and DKD.

Asprosin, secreted from white adipose tissue, is a protein comprising 140 amino-acid residues and is produced by a C-terminal fragment of profibrillin, which is encoded by the *FBN1* gene. Previous studies showed that it is recruited to the liver, activates the G protein–cAMP–PKA pathway, and regulates hepatic glucose generation and insulin resistance.[8] An earlier study of ours found that it was deeply associated with newly diagnosed type 2 diabetes via insulin resistance.[9] As we know, insulin resistance is not only a risk factor for diabetes itself but also for diabetic complications, including DKD. In podocytes of glomeruli, all the key molecules of insulin-signaling pathways have been detected, such as IR, IRS1, and PI3K–Akt, and among these, podocytes showed the highest expression of IR and IRS1 compared with mesangial and endothelial cells in primary culture.[18] Defects in any site of this signaling may result in insulin resistance. For example, podocyte-specific deletion of IR in mice induces a disease state reminiscent of DKD without hyperglycemia.[19] Inhibition of the PI3K–Akt pathway or increased activation of cGMP-dependent protein kinase G type Iα via TRPC6 might increase the permeability of podocyte monolayers to albumin, contributing to injury to podocytes and progression of DKD. Further research suggests that improving insulin sensitivity in vascular and glomerular tissue may decrease the risk of diabetic nephropathy.[20–22] In the current study, although asprosin concentrations were still significantly associated with insulin resistance, the latter was not an effector of the relationship between asprosin and DKD, which indicated that asprosin's contribution to the progression of DKD might not be through insulin resistance.

In exploring the mechanisms of DKD, studies have usually classified DKD as a noninflammatory glomerular disease. However, more and more studies suggest that DKD is an inflammatory process and that immune cells may be involved. Hyperglycemia can increase IL6 and TNFα, which promote the development of DKD.[23–26] In the circulating and kidney tissue of DKD patients, abundant inflammatory mediators are increased, such as IL6, TNFα, and CCL2.[27,28] Recently, mGPDH was reported to be an inflammatory response driver, boosting glucose oxidation to produce acetyl coenzyme A, the latter leading to

histone acetylation and induction of genes encoding inflammatory mediators.[29] In our observations, we found significant increases in concentration of IL6, TNFα, and the mGPDH substrate G3Pin both pre-DKD and DKD patients, which is consistent with the increase inflammatory response in DKD. Moreover, we found a strong and positive correlation between asprosin and G3P, and the latter might mediate the association of asprosin and DKD based on our regression analysis. In fact, several studies have shown that asprosin regulates certain inflammatory responses. In primary human pancreatic β cells and the mouse pancreatic β-cell line MIN6, asprosin was found to induce inflammation and cellular dysfunction via the TLR4–JNK signal-transduction pathway,[11] and in mouse skeletal muscle cells, asprosin was reported to promote inflammation through PKCδ activation, augmenting ER stress.[10] All these findings indicate that asprosin might participate in the progression of DKD via regulation of inflammatory response, but further preclinical and clinical studies are needed to confirm this finding.

Our research has some limitations that need to be addressed. First, due to the cross-sectional design, we cannot identify a causal relationship between plasma asprosin levels and DKD. Second, based on our regression analysis and previous animal studies that demonstrated a regulatory role of asprosin in inflammatory response, we speculate that the inflammation might mediate asprosin-related DKD progression. However, we cannot rule out the possibility that they were just parallel phenotypes, and more studies are required to shed light on this association. Third, there may have been some selection bias because of the relatively small sample, especially in the DM and pre-DKD groups. Finally, medication administration and/or catabolism, which may influence the plasma level of asprosin, were not assessed.

Conclusion

In summary, our study combined data from a DKD population, the Nephroseq database, and animal models, and found significantly increased levels of asprosin in both plasma and kidney tissue. This might be closely related to renal function, the progression of DKD, glucolipid metabolism, and inflammation. Further preclinical and clinical studies are needed to demonstrate the role of asprosin in the pathology and therapy of DKD.

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Author Contributions

All authors made a significant contribution to the work reported, whether in conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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