

Asprosin Levels in Adults with Type 2 Diabetes Mellitus and Diabetic Kidney Disease: A Systematic Review and Meta-Analysis

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Purpose: Diabetic kidney disease (DKD) significantly affects health and healthcare costs due to chronic kidney disease complications. Given asprosin's potential as a biomarker for disease progression, we conducted the first systematic review and meta-analysis on its relationship with DKD in adults with type 2 diabetes mellitus (T2DM).

Methods: PubMed, Embase, Cochrane, and Web of Science were systematically searched. Standard mean differences (SMD) with 95% confidence intervals (CI) and Fisher's Z transformation were used to examine the relationship between asprosin and DKD. The risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS) and its version for cross-sectional studies. Heterogeneity ($I^2 > 50\%$) was analyzed with a random-effects model.

Results: Six studies ($n = 1340$) were included. Meta-analysis results indicated that T2DM patients with DKD (micro/macrolalbuminuria) had significantly higher circulating asprosin levels than normoalbuminuric T2DM patients (SMD: 1.5, 95% CI: 0.69–2.32, $p = 0.0003$). Meta-analysis of correlation revealed a positive association of asprosin with urinary albumin excretion ratio (UACR) (Fisher's Z = 0.4; 95% CI: 0.240–0.554, $p < 0.001$) and body mass index (BMI) (Fisher's Z = 0.17; 95% CI: 0.036–0.301, $p = 0.013$), and a negative association with estimated glomerular filtration rate (eGFR) (Fisher's Z = -0.35 ; 95% CI: -0.471 to -0.239 , $p < 0.001$).

Conclusion: Asprosin is elevated in T2DM patients with pre-DKD (early stage DKD) and DKD and correlates with key markers of disease severity. Additional research is required to better understand the pathophysiological mechanisms of asprosin and its role in DKD.

Keywords: asprosin, diabetic kidney disease, diabetes mellitus, adipokine, eGFR, albuminuria

Introduction

Diabetes mellitus, particularly type 2 (T2DM), is the leading global cause of chronic kidney disease (CKD) and end-stage renal disease.¹ Over 25% of individuals with diabetes are estimated to have CKD, with approximately 40% developing it during their lifetime.² This prevalence has risen alongside increasing diabetes cases. Diabetic kidney disease (DKD) refers to CKD caused specifically by diabetes, though its true incidence is challenging to determine due to limited biopsy data. Globally, DKD has shown a steady increase in incidence, mortality, and disability-adjusted life years over recent decades, imposing a substantial economic burden.^{3–6}

In patients aged 45–64 with both CKD and T2DM, average annual healthcare costs have been reported at \$35,649, rising significantly with disease progression. Advanced CKD requires costly interventions such as dialysis and kidney transplantation, further escalating expenditures.⁷ Additionally, managing CKD-related complications, including myocardial infarction and heart failure, contributes significantly to healthcare costs.⁸

Albuminuria and estimated glomerular filtration rate (eGFR) are the most frequently used markers of DKD.^{9,10} However, both have notable limitations, particularly in individuals with non-albuminuric DKD or reduced muscle mass.^{11–13} To enhance early detection and improve prediction of DKD, extensive research over the past decade has focused on identifying novel biomarkers. These emerging biomarkers hold promise not only for refining risk stratification in DKD patients but also for deepening our understanding of its complex pathophysiology and guiding the development of new therapeutic strategies.^{10,14,15}

Adipokines, hormones primarily secreted by white adipose tissue, have recently been identified as key regulators of organ function and contributors to the pathophysiology of DKD through inflammatory mechanisms.¹⁶ Among these, asprosin, a C-terminal cleavage product of profibrillin (FBN1) secreted by white adipocytes, has gained attention for its roles in glucose metabolism and inflammation (Figure 1).¹⁷ Research on asprosin has focused on its involvement in T2DM and diabetic nephropathy, a common manifestation of DKD.¹⁸ Meta-analyses have demonstrated elevated circulating asprosin levels in patients with T2DM,^{19–21} metabolic syndrome,²¹ and polycystic ovary syndrome (PCOS).²² Furthermore, asprosin levels rise progressively with DKD severity, being higher in pre-DKD (early stage DKD) and DKD groups than in diabetes alone.^{18,23–27} These findings highlight asprosin's potential as a therapeutic target for preventing and managing diabetes-related complications.

Asprosin's role in DKD is further supported by its correlation with metabolic and inflammatory markers, including body mass index (BMI),^{18,23–26,28} urinary albumin excretion ratio (UACR),^{23–27} low-density lipoprotein cholesterol (LDL-C),^{25,26,28} and creatinine (Cr)^{18,23–26,28} while inversely correlating with eGFR.^{18,23–27} These findings suggest that asprosin contributes to DKD pathogenesis by modulating glucose and lipid metabolism and driving inflammation, exacerbating renal damage. Elevated asprosin levels have also been linked to microvascular and macrovascular complications, underscoring its potential as a biomarker for monitoring DKD progression and complications, offering new opportunities for early detection and intervention.²⁹

In consideration of the impact of DKD on the health of individuals and health system costs, especially due to the complications of CKD, and the clinical potential of asprosin as a biomarker of disease progression, we decided to perform a first systematic review and meta-analysis of studies that have analyzed the relationship of asprosin and DKD in adults with T2DM.

Methods

Registration and Reporting

This systematic review and meta-analyses were performed and reported in line with the recommendations from the Cochrane Collaboration³⁰ and with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.³¹ The systematic review protocol was previously registered in PROSPERO [CRD42024589910].

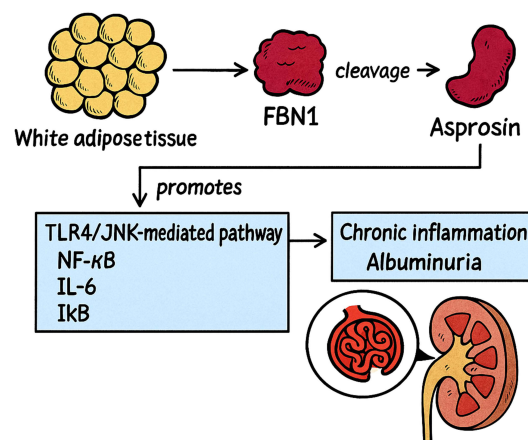


Figure 1 Graphical conceptual model of the relationship between asprosin and DKD.

Abbreviations: FBN, Fibrillin-1; TLR-4, Toll-like receptor 4; JNK, c-Jun N-terminal kinase; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; IL-6, Interleukin-6; IκB, Inhibitor of kappa B. The figure was edited using GIMP image-editing software.

Eligibility Criteria

Inclusion in the meta-analyses was restricted to studies that met the following eligibility criteria: (1) Observational studies (cross-sectional, cohort, and case-control); in (2) adult patients (aged ≥ 18 years or older) with T2DM that (3) measured asprosin levels. In addition, studies were included only if they reported any of the outcomes of interest, as reported afterward. We excluded: (1) duplicated articles; (2) conference abstracts; (3) scoping reviews; (4) systematic reviews; (5) narrative reviews; (6) case reports; (7) studies with participants younger than 18 years old; (8) patients with T1DM; (9) in vitro or laboratory animal studies.

Search Strategy and Data Extraction

We systematically searched PubMed, Embase, Cochrane, and Web of Science up to August 13, 2024. We used the following search terms: asprosin AND (T2DM OR “type 2 diabetes” OR “Type 2 Diabetes Mellitus” OR “insulin resistance” OR nephropathy OR “renal function” OR “diabetic kidney disease”). We did not limit our search by date or language. The references from all included studies were also searched manually for any additional studies. Following the databases search, the articles were uploaded into Rayyan,³² a program for data management. Screening by title and abstract was independently performed by two authors (J. R. and S. K.) using the established selection criteria. After this first screening, the full text of each article was carefully examined by three authors (J. R., S. K. and S. M.), and all potential discrepancies were solved by consensus. Three authors (J. R., S. K. and S. M.) independently extracted the data following the predefined search criteria and quality assessment.

Endpoints

The main outcome was asprosin levels. We compared asprosin levels between three groups: patients with T2DM and DKD, patients with T2DM and pre-DKD, and T2DM patients without DKD. Meta-analysis of correlation was performed to further investigate the relationship between asprosin and UACR, BMI, eGFR, and LDL-C.

Quality Assessment

We evaluated the risk of bias using the Newcastle-Ottawa Scale (NOS)³³ and the Newcastle–Ottawa Scale for Cross-Sectional Studies (NOS-C)³⁴ recommended by the Agency for Healthcare Research and Quality and Methodological Index (AHRQ) for observational and non-randomized studies. The risk of bias was assessed separately by three reviewers (J. R., G. P-J. and S. M.). A rating of < 7 stars indicated a high risk of bias, whereas a rating of ≥ 7 stars indicated a low risk of bias in both scales.

To explore potential sources of heterogeneity, we conducted meta-regression analyses using a random-effects model with restricted maximum likelihood (REML) estimation. Moderator variables were selected a priori based on clinical relevance and availability across studies, including DKD definition criteria, sample type, geographic region, and year of publication. Each moderator was initially assessed in univariable models due to the limited number of included studies.

A minimum of 10 studies is generally recommended for the reliable assessment of publication bias using funnel plots; however, our analysis included only 6 studies, which did not meet this threshold. As a result, funnel plots and Egger tests were not utilized due to the risk of unreliable interpretations arising from insufficient statistical power. Instead, we performed a “leave-one-out” sensitivity analysis to evaluate the robustness of our findings and to identify any potential influence of individual studies on the overall results. This approach ensured a thorough examination of the data despite the limited number of included studies.

Statistical Analysis

The data extracted from the articles were reported as mean $\pm$ standard deviation (SD). However, for studies that reported data as median and interquartile range, we estimated the mean and the standard deviation using the approaches outlined by Luo et al³⁵ and Wan et al.³⁶ To estimate differences in circulating asprosin levels between groups, the standard mean difference (SMD) and corresponding 95% confidence intervals (CI) were calculated in the meta-analyses. For each study, Spearman or Pearson correlation coefficients were recorded, and Fisher’s Z transformation was applied to calculate

a mean transformed correlation weighted by sample size based on the data provided. Means and standard deviations were combined where appropriate following the guidelines outlined in the Cochrane Handbook.³⁷ This approach was applied when merging two reported subgroups into a single group was desirable to ensure accurate and comprehensive data synthesis.

The significance of the overall effects was assessed using the Z test, and forest plots were generated to illustrate effect sizes and their corresponding 95% CI. Heterogeneity was evaluated using Cochran's Q test, the I^2 statistic, and the tau-squared statistic for between-study variance. Substantial heterogeneity was assumed when $I^2 > 50\%$, in which case a random-effects model was applied (DerSimonian and Laird). Additionally, sensitivity analyses were conducted through a leave-one-out approach, where each study was omitted sequentially to evaluate its impact on the pooled results. This analysis tested the robustness of the findings by comparing the sensitivity results to the main analysis outcomes. Statistical analyses were conducted via Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and MedCalc 23.0.9 (MedCalc Software, Ostend, Belgium). Meta-regression analyses were performed using RStudio (version 2024.12.0+467, Boston, USA). The significance p -value was set as 0.05.

Results

Study Selection

The search strategy initially identified 384 results from all databases. Of these, 204 duplicates were eliminated, and 155 articles were excluded by reviewing the title and abstract. Finally, 25 articles underwent full text screening and 6 were included in the qualitative and quantitative synthesis.^{18,23–27} The selection process is illustrated in Figure 2.

Characteristics of the Included Studies

Six studies were included, of which 5 were cross-sectional and 1 was case-control. Altogether, 1340 participants were included, with 765 males and 575 females. Five studies were conducted in China^{23–27} and one study was in Iran.¹⁸ Two studies^{23,24} defined T2DM using the World Health Organisation diagnostic criteria from 1999, three studies^{18,25,27} used the standards of the American Diabetes Association, and one study²⁶ did not specify its criteria. All articles defined stages of DKD based on UACR. Patients with normoalbuminuria ($\text{UACR} < 30 \text{ mg/g}$) are considered T2DM patients without DKD, those with microalbuminuria ($30 \leq \text{UACR} < 300 \text{ mg/g}$) have early or pre-DKD, and patients with macroalbuminuria ($\text{UACR} \geq 300 \text{ mg/g}$) are referred to as having DKD. In all articles, asprosin levels were determined by enzyme-linked immunosorbent assay using serum, except for one manuscript²³ that used plasma. The characteristics of the studies are presented in Table 1.

Risk of Bias and Sensitivity Analysis

Based on the NOS and NOS-C, all studies had a low risk of bias (Supplementary Table 1).

The sensitivity analysis showed that excluding any single study from the analysis did not significantly affect the overall asprosin result. (Supplementary Tables 2–4). However, when comparing T2DM patients with DKD to those with pre-DKD we found that excluding the study by Wang et al²⁶ revealed a significant difference between these two groups (SMD: 0.45, 95% CI: 0.03–0.87, I^2 : 67%, $p = 0.04$, (Supplementary Table 5).

Meta-Regression Analysis

Meta-regression analyses were performed to examine the impact of study-level moderators on asprosin levels across different patient comparisons. Results comparing asprosin levels in T2DM patients with pre-DKD/DKD to those without DKD identified sample type ($p = 0.0044$, $R^2 = 61\%$) and publication year ($p = 0.0316$, $R^2 = 55.7\%$) as significant moderators. Despite this, residual heterogeneity remained high ($I^2 = 96.08\%$ and 95.03% , respectively). Similarly, results comparing T2DM patients with pre-DKD to those without DKD showed sample type ($p = 0.0001$, $R^2 = 83\%$) and publication year ($p = 0.0008$, $R^2 = 83\%$) as significant moderators, but residual heterogeneity stayed elevated ($I^2 = 96.40\%$ and 93.82%). The results are showed in Supplementary Tables 6–9. The persistently high residual heterogeneity suggests that other unmeasured factors may contribute to variability between studies.

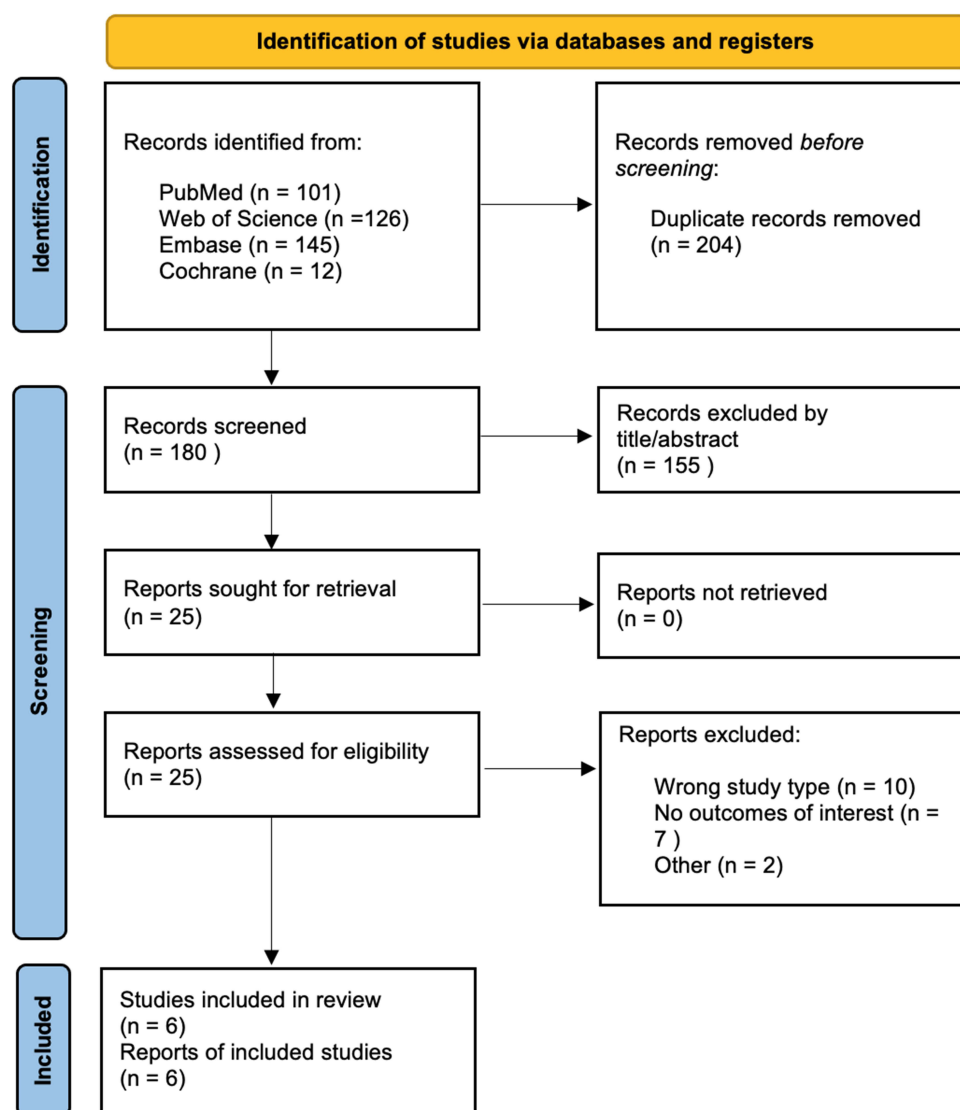


Figure 2 PRISMA flow diagram of study screening and selection.

Asprosin Levels in T2DM Patients

The pooled analysis showed that T2DM patients with pre-DKD or with DKD were associated with higher levels of circulating asprosin compared to T2DM patients without DKD (SMD: 1.5, 95% CI: 0.69–2.32, I^2 : 97%, $p = 0.0003$; [Figure 3](#)).

Moreover, analyses comparing pre-DKD patients vs T2DM patients without DKD (SMD: 2.08, 95% CI: 0.99–3.17, I^2 : 97%, $p = 0.0002$; [Figure 4](#)) and DKD patients vs T2DM patients without DKD (SMD: 3.51, 95% CI: 0.93–6.08, I^2 : 99%, $p = 0.008$; [Figure 5](#)) both showed an association with higher circulating asprosin levels.

We found no difference in circulating asprosin levels when we compared T2DM patients with DKD to those with pre-DKD (SMD: 1.47, 95% CI: –0.04–2.98, I^2 : 98%, $p = 0.06$, [Figure 6](#)). However, excluding the study by Wang et al²⁶ revealed a significant difference between these two groups (SMD: 0.45, 95% CI: 0.03–0.87, I^2 : 67%, $p = 0.04$, [Supplementary Table 5](#)).

Association of Asprosin with eGFR, UACR, BMI, LDL-C

To explore the association between asprosin and eGFR, a meta-analysis of correlations was performed on all 6 studies^{18,23–27} using Fisher's Z transformation to compare the given Spearman or Pearson correlation coefficients.

Table 1 Characteristics of the Included Studies

	Deng, 2020 ²⁵	Goodarzi, 2021 ¹⁸	Wang, 2021 ²⁶	Xu Linxin, 2022 ²⁴	Xu Mingyue, 2024 ²³	Zhang, 2020 ²⁷
Country	China	Iran	China	China	China	China
Study Design	Cross-sectional	Case-control	Cross-sectional	Cross-sectional	Cross-sectional	Case-control
Number of Patients	207	164	284	498	82	105
Male	120	103	152	298	39	53
Female	87	61	132	200	43	52
Sample & Methods	Serum/ELISA	Serum/ELISA	Serum/ELISA	Serum/ELISA	Plasma/ELISA	Serum/ELISA
T2DM patients without DKD						
Number of patients (m/f)	107 (63/44)	54 (32/22)	94 (51/43)	172 (112/60)	22 (8/14)	42 (23/19)
Age (years)	60.15 ± 10.56	61.83 ± 7.78	57.55 ± 11.57	55 ± 13	49.23 ± 13.99	55.98 ± 8.59
Asprosin level	1.59 ± 0.18	6.73 ± 1.67	15.45 ± 1.07	314.2 ± 81.1	44.97 ± 4.55	6.23 ± 0.87
T2DM patients with pre/early-DKD						
Number of patients (m/f)	80 (47/33)	N/A	82 (41/41)	221 (126/95)	20 (10/10)	33 (16/17)
Age	62.96 ± 10.87	N/A	58.39 ± 13.22	60 ± 14	54.35 ± 10.98	56.12 ± 7.44
Asprosin level	2.12 ± 0.27	N/A	17.29 ± 1.17	338.6 ± 89.7	102.34 ± 12.44	7.23 ± 0.94
T2DM patients with DKD						
Number of patients (m/f)	20 (10/10)	N/A	36 (19/17)	105 (60/45)	40 (21/19)	N/A
Age	63.40 ± 10.51	N/A	59.78 ± 11.32	60 ± 13	57.48 ± 15.74	N/A
Asprosin level	2.44 ± 0.52	N/A	22.49 ± 1.02	365.0 ± 88.5	105.13 ± 19.87	N/A

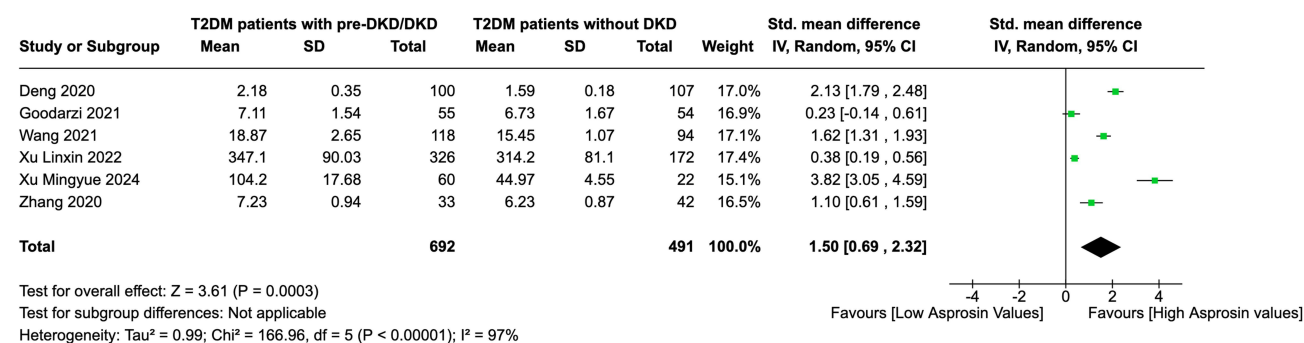
Abbreviations: T2DM, Type 2 Diabetes Mellitus; DKD, Diabetic Kidney Disease; N/A, Not applicable; ELISA, Enzyme-linked immunosorbent assay.

Random effect models were used as significant heterogeneity was observed (eGFR: $I^2 = 75.88\%$, $p = 0.0009$). The results revealed a negative association of asprosin with eGFR, with a Fisher's Z of -0.35 (eGFR: 95% CI: -0.471 to -0.239 , $p < 0.001$, Figure 7 and Supplementary Table 10).

To explore the association between asprosin and UACR, a meta-analysis of correlations was performed on 5 studies.^{23–27} Random effect models were used as significant heterogeneity was observed (UACR: $I^2 = 87.98\%$, $p < 0.0001$). The results revealed a positive association of asprosin with UACR, with a Fisher's Z of 0.4 (UACR: 95% CI: 0.240 to 0.554 , $p < 0.001$, Figure 8 and Supplementary Table 11).

The results from 5 analysed studies^{18,23–26} indicated a positive association of asprosin with BMI. Fisher's Z was 0.17 (95% CI: 0.036 – 0.301 , $p = 0.013$, Figure 9 and Supplementary Table 12).

As for the association between asprosin and LDL-C, data from 5 studies was analysed.^{18,23–26} The results showed no significant association of asprosin with LDL-C, neither negative nor positive correlation. Fisher's Z was 0.01 (95% CI: -0.109 to 0.131 , $p = 0.858$) (Figure 10 and Supplementary Table 13).

**Figure 3** Forest plot showing asprosin levels in T2DM patients with pre-DKD/DKD compared to T2DM patients without DKD.

Abbreviations: T2DM, Type 2 Diabetes Mellitus; DKD, Diabetic Kidney Disease; SD, Standard Deviation; CI, Confidence Interval; IV, Inverse Variance.

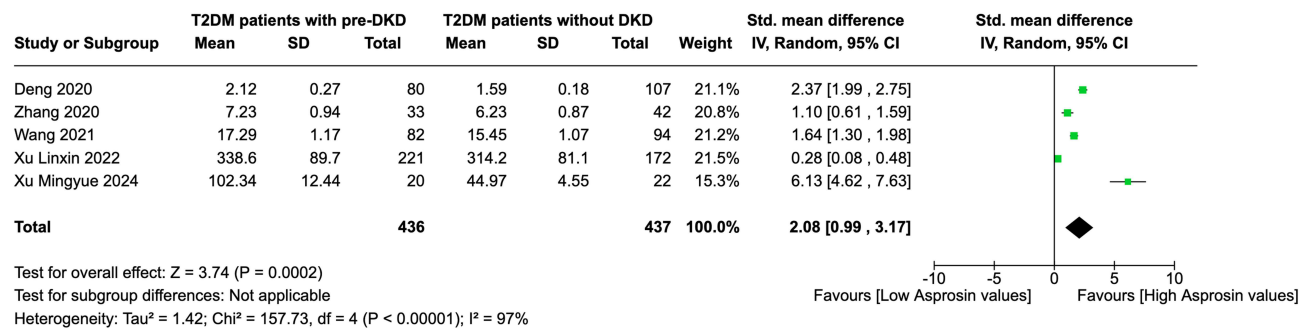


Figure 4 Forest plot showing asprosin levels in T2DM patients with pre-DKD compared to T2DM patients without DKD.

Abbreviations: T2DM, Type 2 Diabetes Mellitus; DKD, Diabetic Kidney Disease; SD, Standard Deviation; CI, Confidence Interval; IV, Inverse Variance.

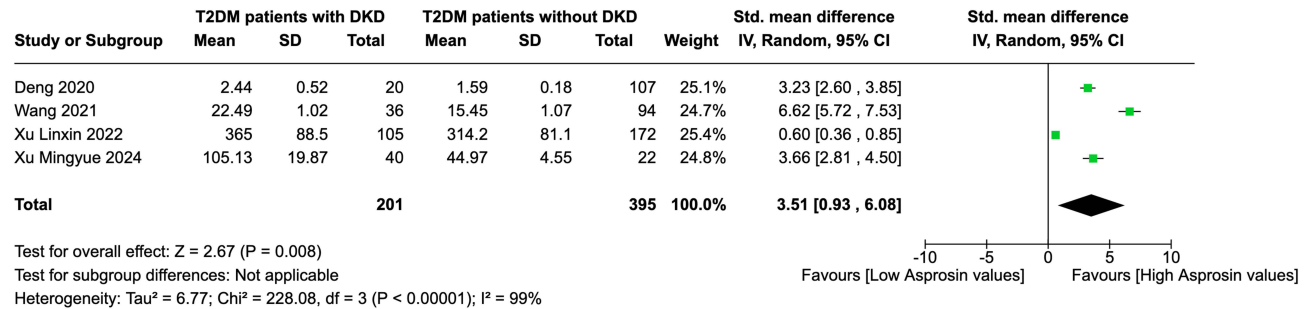


Figure 5 Forest plot showing asprosin levels in T2DM patients with DKD compared to T2DM patients without DKD.

Abbreviations: T2DM, Type 2 Diabetes Mellitus; DKD, Diabetic Kidney Disease; SD, Standard Deviation; CI, Confidence Interval; IV, Inverse Variance.

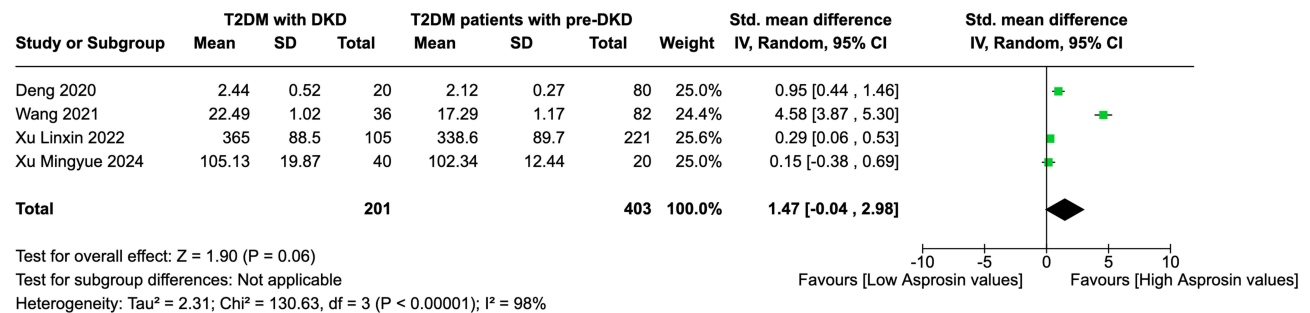


Figure 6 Forest plot showing asprosin levels in T2DM patients with pre-DKD compared to T2DM patients with DKD.

Abbreviations: T2DM, Type 2 Diabetes Mellitus; DKD, Diabetic Kidney Disease; SD, Standard Deviation; CI, Confidence Interval; IV, Inverse Variance.

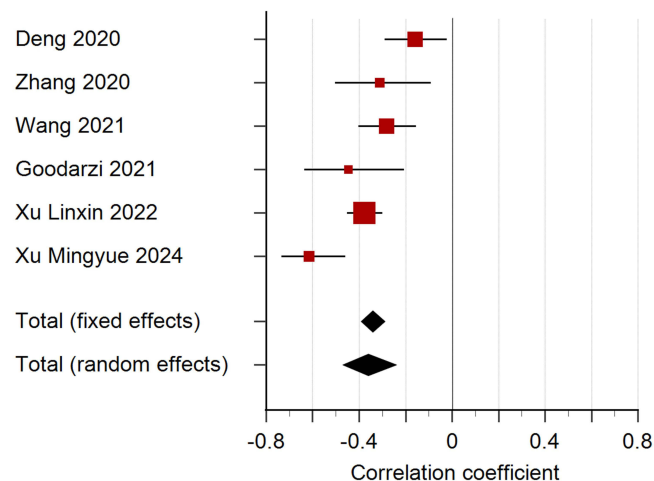


Figure 7 Forest plot of correlation between asprosin and eGFR.

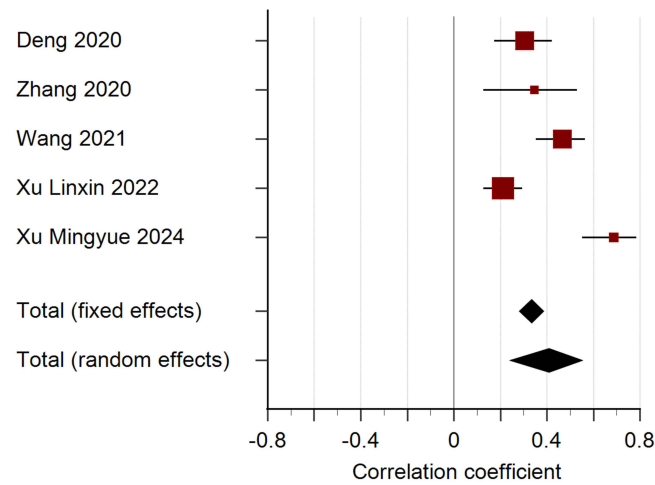


Figure 8 Forest plot of correlation between asprosin and UACR.

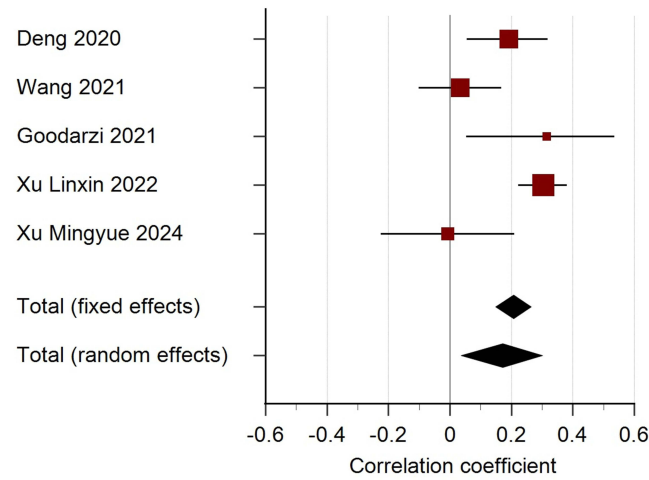


Figure 9 Forest plot of correlation between asprosin and BMI.

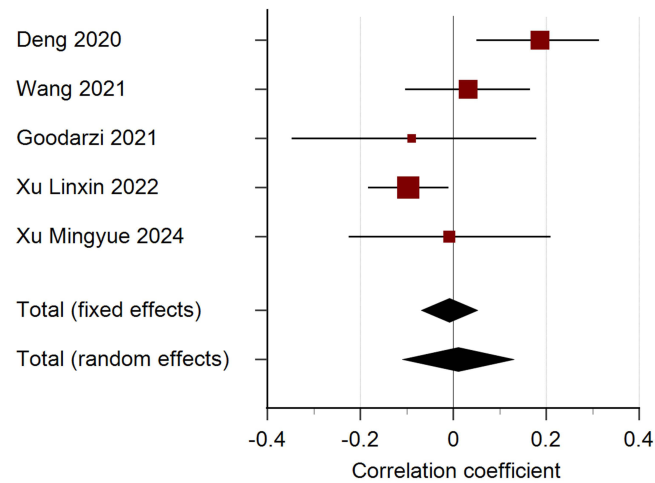


Figure 10 Forest plot of correlation between asprosin and LDL-C.

Discussion

Our study synthesized existing evidence on the relationship between asprosin and DKD. This is the first systematic review and meta-analysis to explore the connection between asprosin and DKD. The findings revealed that asprosin levels are higher in T2DM patients with pre-DKD and DKD compared to T2DM patients without DKD. Further analyses identified significant associations between circulating asprosin levels and eGFR, BMI, and UACR. However, no association was observed between asprosin and LDL-C. Given that DKD significantly affects individual health and healthcare costs, and asprosin shows promise as a biomarker for disease progression, our findings provide evidence supporting further investigation into asprosin as a potential biomarker.

Previous meta-analyses have demonstrated elevated asprosin levels in patients with T2DM,^{19–21} metabolic syndrome,²¹ women with PCOS,²² and children with obesity.³⁸ Several other studies have also showed correlation of asprosin with various metabolic and anthropometric characteristics in patients with impaired glucose tolerance.^{39–45} A study by Liang et al showed that asprosin was correlated with obesity in community-based T2DM patients and hypothesized that serum asprosin could be used as a risk predictor of T2DM.⁴⁶ A recent meta-analysis by Zeng et al revealed a significant difference in asprosin levels between diabetic patients without complications and those with complications. Individuals affected with complications such as diabetic nephropathy, diabetic peripheral neuropathy and diabetic retinopathy exhibited elevated asprosin levels in comparison to those not afflicted with complications.²⁰ Our meta-analysis of correlation showed a significant negative association between asprosin and eGFR as well as a positive association with BMI and UACR. The association between blood-circulating asprosin and UACR could permit early identification of renal disturbances in patients without symptoms or in the early onset stage of kidney dysfunction. Moreover, the correlation between high asprosin levels and BMI could point to the importance of the lipidic tissue as a regulator for metabolism and its impact on organic balance as a whole. These results are compatible with previous studies that compared asprosin values in saliva and blood related to BMI.^{47,48}

While the exact pathophysiological mechanisms of this adipokine remain under investigation, current studies highlight its role in glucose metabolism and inflammation.^{49,50} Asprosin is a protein secreted from white adipose tissue, consisting of 140 amino acid residues derived from the C-terminal fragment of profibrillin.¹⁷ It is released into the bloodstream and targets the liver, where it promotes glucose production by activating the OR4M1 receptor, a type of olfactory G-protein-coupled receptor.⁵¹ Additionally, asprosin crosses the blood-brain barrier to influence the hypothalamus, stimulating appetite by activating AgRP neurons and suppressing POMC neurons. However, the receptor involved in this neural mechanism remains unknown.⁵¹ Beyond its effects on glucose metabolism and appetite, asprosin also plays a critical role in the health of pancreatic β -cells. Fatty acids such as palmitate, elevated during obesity, enhance asprosin production in β -cells, leading to inflammation marked by NF κ B activation and the release of pro-inflammatory cytokines like TNF and MCP-1, impairing insulin secretion and reducing cell viability. Furthermore, asprosin activates the TLR4/JNK pathway, intensifying inflammation and inducing β -cell apoptosis.⁵² Such inflammation is also observed in T2DM patients.^{53,54} Asprosin also disrupts autophagy in β -cells by downregulating the AMPK pathway and upregulating mTOR activity, resulting in decreased levels of autophagy-related proteins (LC3-II/LC3-I, beclin 1) and increased apoptosis markers. Activation of the AMPK pathway, however, can partially restore autophagy and mitigate the harmful effects caused by asprosin, further highlighting its significant role in β -cell dysfunction.⁵⁵ The AMPK and mTOR signaling pathways are also key regulators in the progression of DKD, as they help preserve the function of podocytes and tubular epithelial cells. Excessive mTOR activation combined with reduced AMPK activity disrupts lipid metabolism, promotes cellular damage, and heightens the risk of kidney injury.^{56–58} A study by Mishra et al researching asprosin-neutralizing antibodies yielded promising results. These monoclonal antibodies have demonstrated the potential to lower blood sugar, reduce appetite, and promote weight loss, highlighting asprosin's therapeutic importance.⁵⁹

Traditionally, DKD has been considered a non-inflammatory condition. However, emerging research and growing evidence suggest that DKD is an inflammatory disease characterized by complex interactions among multiple factors.^{10,15,60–68} A recent study showed that one of the key elements linking vascular complications in DKD to hyperglycemia is oxidative stress.⁶⁴ Hyperglycemia increases the levels of crucial proinflammatory cytokines such as IL-6 and TNF α ,^{63,64} and elevates the production of reactive oxygen species (ROS).^{64,66,67} This disrupts the balance between oxidants and antioxidants in the body, triggering the activation of immune cells, the complement system, and

various signaling pathways, all of which contribute to the deterioration of kidney function.^{64,66–69} Macrophages are central players in the inflammation associated with DKD, linking impaired lipid metabolism to inflammation and disease progression.^{58,70} They rely on fatty acid synthesis and aerobic glycolysis,⁷⁰ activate the Toll-like receptor 4 (TLR4) signaling pathway,^{71,72} and promote the production of pro-inflammatory cytokines.^{58,70–72} Other immune cells, including monocytes, neutrophils and T cells, as well as Nlrp-3 inflammasomes, also infiltrate and accumulate in DKD^{10,73,74} Recent studies have investigated the role of neutrophil extracellular traps (NETs) in the progression of DKD and found that NETs contribute to glomerular endothelial cell dysfunction.^{75,76} The study by Ye et al identified elevated IL-33 levels in two NET-related subtypes, suggesting its contribution to intensified inflammation.⁷⁵ Renal intrinsic cells further contribute to the immune response, with different types of renal cells showing varying sensitivity to metabolic stress.^{58,77} Podocytes, which are essential for maintaining the integrity of the glomerular filtration barrier, are especially vulnerable. Elevated activity of fatty acid metabolism enzymes in podocytes results in lipid accumulation, leading to structural damage and disruption of the glomerular filtration barrier.^{58,78,79} Additionally, podocytes showed the highest expression of insulin receptor (IR) and insulin receptor substrate-1 (IRS1) compared to mesangial and endothelial cells, suggesting that they may benefit the most from improved insulin sensitivity in vascular and glomerular tissues, thereby reducing the risk of diabetic nephropathy.⁸⁰ A study by Lay et al found that glycoprotein synthesis in podocytes may play a role in DKD progression, as glycoproteins are essential for forming the glomerular basement membrane, endothelial glycocalyx, and slit diaphragm. The cell-type-specific pathway disruptions observed in DKD, particularly in podocytes, highlight the potential for targeted therapies to address mitochondrial dysfunction and glycoprotein abnormalities.⁸¹

Preventing and managing diabetic nephropathy necessitates early recognition in order to minimize the risk of additional complications and mortality. In current clinical practice, the detection and monitoring of DKD primarily rely on albuminuria and eGFR.^{9,10} However, around 10–30% of DKD patients do not exhibit albuminuria.^{82–84} Additionally, disease progression is not always linear - some patients may not transition from microalbuminuria to macroalbuminuria, and others may even revert to normoalbuminuria.⁸⁵ Some patients may present with early tubulointerstitial damage with absence of proteinuria.^{15,86} Albumin levels can also be affected by unrelated conditions such as liver disease, nephrotic syndrome, or dehydration, limiting its specificity.⁸⁷ eGFR, while widely used, also has limitations. One major issue is the variability introduced by different equations used to calculate it.⁸⁸ For instance, a study by Moazzeni et al demonstrated higher incidence rates of CKD when using the Modification of Diet in Renal Disease (MDRD) equation compared to the CKD Epidemiology Collaboration (CKD-EPI) equation.⁸⁹ Furthermore, creatinine-based eGFR may not accurately reflect kidney function in individuals with low muscle mass.¹³ Although cystatin C was introduced to address this limitation, it is also affected by factors such as fat mass and systemic inflammation.⁹⁰ Due to the complex pathophysiology of DKD, future advancements in detection and monitoring of disease progression will potentially rely on identifying novel biomarkers, such as asprosin, and integrating them with existing markers to enhance diagnostic accuracy and guide clinical decision-making.

This study has several key strengths. A thorough search of multiple databases was conducted to ensure a comprehensive literature review. All included studies demonstrated a low risk of bias based on the NOS and NOS-C. To the best of our knowledge, this is the first study to aggregate the existing evidence on asprosin levels in individuals with T2DM and DKD. This was accomplished through an in-depth and meticulous systematic review and meta-analysis of the available data. Our study also synthesizes the diverse pathophysiological mechanisms underlying DKD, providing a clear, evidence-based foundation to support and guide future research in this critically important field.

However, this study must be interpreted in light of its limitations. First, the findings are based on a small number of observational studies, as this is a relatively new and emerging research area that requires further exploration. The lack of randomization may introduce bias and limits the ability to establish causality. Additionally, multiple outcomes (eGFR, UACR, BMI, LDL-C) were analyzed, which increases the risk of Type I error due to multiple comparisons. Although no formal corrections for multiplicity were applied, the results should be interpreted with caution, emphasizing the overall consistency rather than isolated significant findings. Furthermore, the limited number of studies prevented formal assessment of publication bias through funnel plots or Egger's tests, yet the possibility of such bias remains and should be considered when interpreting the results. Second, all the studies included in this analysis were conducted in Asian countries, with the majority (5 out of 6) taking place in China. This restricts the generalizability of the results to other

populations. Third, DKD was defined solely by albuminuria levels, excluding non-albuminuric DKD patients, which may affect the study's comprehensiveness. Finally, there was considerable heterogeneity across the studies included in the analysis. To reduce heterogeneity and improve the reliability of future results, researchers should aim to develop standardized study protocols, use consistent sample types, and employ the same measurement kits. This is particularly important in biomarker research, where variability often arises from the use of different analytical platforms, making cross-study comparisons challenging.

Conclusion

Asprosin is elevated in T2DM patients with pre-DKD and DKD, and correlates with key markers of disease severity. Incorporating asprosin into routine testing could be a revolutionary step toward identifying patients at risk of renal impairment before overt dysfunction appears, while also enabling better monitoring of disease progression. Furthermore, asprosin's involvement in metabolic and inflammatory pathways suggests it may also represent a promising therapeutic target. Further research, particularly through prospective cohort studies and interventional trials, is essential to validate its predictive value and to explore its potential role in therapeutic strategies for T2DM and DKD.

Data Sharing Statement

All of the data is provided in the published paper and the [supplementary files](#). Further inquiries can be directed to the corresponding authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of 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 report no conflicts of interest in this work.

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