



Original Article

Relationship Between CD44 and Glomerular Filtration Rate in Chronic Kidney Disease

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ABSTRACT

Background: Chronic kidney disease (CKD) is very important to have biomarker that can be detected in time before kidney function is impaired, because it is only detected at very late stages. CD44 is a potential biomarker for kidney injury, involved in inflammation and fibrosis.

Methods: This cross-sectional study included 137 participants: The concentration of CD44 urine was measured by enzyme-linked immunosorbent assay (ELISA), and proteomic analysis was performed by mass spectrometry. For assessment, estimated glomerular filtration rate (eGFR) and 24-hour proteinuria have been monitored, while accounting for clinical and laboratory parameters. The correlation between kidney function and CD44 levels was determined using Spearman's rank correlation.

Results: The level of CD44 in urine, as detected by ELISA, was higher in healthy controls than in CKD patients ($p = 0.007$). In addition, a positive correlation was observed between CD44 levels and eGFR (Spearman's $\rho = 0.2808$, $p = 0.0052$), indicating that higher CD44 levels are associated with kidney function. Proteomic analysis confirmed these results, showing a significant relationship between CD44 expression and kidney function parameters.

Conclusion: The research results demonstrate that CD44 levels in urine differ significantly between healthy individuals and CKD patients, suggesting that CD44 may be a candidate biomarker associated with kidney function. Further investigation in large-scale studies is required to confirm its clinical applicability.

Keywords: Chronic Kidney Disease (CKD); CD44; Egfr; Proteinuria; Albuminuria; ELISA

Introduction

Given the increasing prevalence of CKD, early and timely detection and management are crucial to prevent further progression, however, the disease is asymptomatic in the early stages. At the time of diagnosis, the CKD stage has already progressed to stages 3 or 4 leading to a greater number of patients requiring renal replacement therapy (RRT). Even though nowadays in most countries RRT is well developed, and it can prolong the patient's life and become a bridge to kidney transplantation, it affects the patient's quality of life and causes socioeconomic burden (1). Hereby, for effective prevention, there is a need for a novel biomarker capable of identifying kidney deterioration at an earlier stage, when patients way leave predisposing risk factors but have not yet developed a clear clinical presentation. Traditionally used biomarkers, such as estimated glomerular filtration rate (GFR) based on serum creatinine levels and proteinuria or albuminuria, are sensitive for identifying high risk of progression and death. However, there are limitations to these biomarkers, especially in the early stages of CKD, which prevent monitoring or detection of early signs of kidney injury (2-4). Even though serum creatinine and albuminuria remain essential in clinical practice, there is a demand for complementary approaches. One possible biomarker is the CD44 protein. CD44 is a surface glycoprotein widely expressed in various cell types, from epithelial cells to leukocytes (5-6). Due to alternative splicing, various isoforms of this protein tailor the molecule's function, ligand binding properties and localisation to serve the specific needs of the cell type and tissue environment and pathophysiological conditions (6-8). CD44 standard (CD44s) isoform is considered the most abundant and shortest form, and it plays a role in cell-cell and cell-

matrix signaling, which is important for proliferation, adhesion, migration, and wound scarring (9). There are variant isoforms (CD44v) that are expressed in a tissue-specific and disease-specific manner, such as inflammation, injury, and fibrosis (8, 10-11). In normal kidneys, CD44 expression was reported to be minimal (12-15). Several studies showed that there was a link between increased CD44 expression and progressive renal diseases. Glomerular and interstitial expression patterns of CD44 have been assessed in various nephropathies. CD44 was overexpressed in parietal epithelial cells and mesangial cells in patients with focal segmental glomerulosclerosis (FSGS) and IgA nephropathy in comparison to groups with minimal change disease (MCD) and membranous nephropathy (MN) (15-21). Moreover, in individuals with IgA nephropathy the severity of glomerular and tubulointerstitial injury and proteinuria exhibited a strong correlation with the level of CD44 expression (22). In patients with FSGS, the development of renal fibrosis was found to be associated with high CD44 expression in the glomeruli and interstitium as well as elevated levels of urinary complement components (10). A recent pilot study investigated the correlation of urinary CD44 levels with 24-hour proteinuria and eGFR (23). Importantly, a negative relationship emerged with proteinuria, revealing lower CD44 levels in the urine of CKD patients and higher concentrations in healthy individuals. This finding is consistent with existing studies on IgA nephropathy, acute kidney transplant rejection, and diabetic nephropathy (24-25). To validate previous results further, we investigate the correlation between CD44 concentration in urine with eGFR and CKD stage by evaluating CD44 urine concentrations in healthy and CKD participants using the ELISA technique.

Methods

Patients and Study Settings: This cross-sectional study enrolled early-stage CKD patients with varying levels of proteinuria. Approval was obtained from the local research committee of the Nazarbayev University Institutional Research Ethics Committee (NU-IREC 208/06122019) on 25 February 2020. The inclusion criteria required participation to be aged between 18 and 65 years and to have early CKD (stage 1-3 by KDIGO 2012 guidelines) (26). The diagnosis of CKD was established by the treating nephrologists based on the patients' clinical history and available medical records. In the present cross-sectional study, eGFR, 24-hour urinary protein excretion, and urinary microalbumin were assessed at a single study time point. Therefore, chronicity (≥ 3 months) was not

independently confirmed by repeated measurements within the study protocol. The exclusion criteria were pregnancy and coexisting conditions such as cancer, infections, and other acute 82 conditions that could interfere with research accuracy. All participants were provided informed consent before enrollment. Overall, 137 participants were recruited at "National Scientific Medical Center" from March 2020 to December 2021. There were 88 patients in the CKD/case group and 49 in the healthy control group.

Laboratory Tests and Data Collection: Blood and urine samples were collected for complete blood count, basic metabolic panel, including serum creatinine, urea, uric acid, total protein, albumin, liver function tests, and 24-hour urinalysis. Laboratory tests

were performed using a colorimetric method on a Cobas Integra 400 Plus analyzer (Oststeinbek, Germany). The estimated GFR was calculated based on the CKD-EPI equation. The participants' medical history were obtained from electronic medical records. For the proteomics analysis the 24-hour urine samples were stored at -80°C . Protein extraction was performed using the acetone precipitation method (27).

Enzyme-linked Immunosorbent Assay (ELISA): Human sCD44std levels were qualified using sCD44std ELISA kit (catalog numbers: BMS209-2 and BMS209-2TEN, Invitrogen). An ELISA sandwich method was used according to the manufacturer's instructions. Stock solutions were prepared following the standard protocol. Microwell plates were precoated with anti-human sCD44std antibodies. Samples (20 pL) were added in duplicate to the microwells, where they could bind to the corresponding antibodies. Subsequently, anti-human CD44 antibodies conjugated with 50 pL of horseradish peroxidase (HRP) were added followed by a 3-hour incubation at room temperature. After an incubation period, the washing step was performed (3 times) to remove any unbound HRP-conjugated antibodies. Straight after the washing step, the substrate of the HRP enzyme was added, and color development was allowed to proceed. The reaction was stopped by adding a stop solution. Then, to quantify the concentration of bound enzyme-linked antibodies with CD44 protein, the microplate reader

was set to 450 and 540 nm and run through a microwell reader at a wavelength of 450 nm. After obtaining the absorbance rates, the standard curve was constructed to identify the concentration of samples containing CD44 protein.

Urine Dipstick Analysis: Urine dipstick testing was performed for all 137 participants. The urinary microalbumin to creatinine ratio (MALB) was measured. According to the results, the median (IQR) CKD MALB in patients was 150 (150-150) mg/L and it was 150 (30-150) mg/L for healthy participants. The albumin to creatinine ratio was significantly higher in CKD patients compared with healthy participants ($p = 0.001$).

Statistical Methods: The statistical analysis was performed using Stata/MP version 17.0 (StataCorp, College Station, TX, USA). Regarding numerical variables the mean and standard deviation (SD) were used for normal distribution and the interquartile range (IQR) for non-normally distributed data. Between-group comparisons were conducted using the two-sided t-test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. To assess correlations between the protein properties and eGFR, associations were evaluated using Spearman's rank correlation test between the 24-hour protein excretion and the emPAI of 32 urinary proteins. All data included both healthy controls and CKD patients.

Results

The General Information of the Study

Participants: A total of participants were included in the study, comprising 49 healthy controls and 88 patients with early-stage CKD. Table 1 summarizes other parameters such as age, eGFR, and gender. As

expected, the eGFR was significantly lower than for the control group. Moreover, laboratory results demonstrated abnormalities in the CKD consistent with kidney dysfunction, including hypoproteinemia, hyperlipidemia, and proteinuria.

Table 1. Baseline clinical and laboratory characteristics of study participants

	Control (n=49)	CKD (n=88)	P-value
Demographics			
Age (years), mean (SD)	31.7 (± 7.9)	38.5 (± 12.3)	0.48
Female, n (%)	34 (69.4)	38 (43.2)	0.003
Male, n (%)	15 (30.6)	50 (56.8)	
Kidney Function eGFR			
(mL/min/1.73 m ²)	112.4 (105.1–115.4)	83.9 (56.9–114.2)	<0.001
Creatinine ($\mu\text{mol/L}$)	60.9 (55.3–71.8)	94.3 (63.8–135.6)	<0.001
Serum uric acid ($\mu\text{mol/L}$), mean (SD)	306.3 (± 92.6)	385 (± 118.1)	0.0002
Biochemical Parameters			
Alpha-amylase (pkat/L)	1.0 (0.9–1.3)	1.4 (1.1–1.8)	<0.001
Direct bilirubin ($\mu\text{mol/L}$)	3.5 (2.7–4.8)	2.8 (1.6–4.2)	0.0021

Protein Fractions			
Albumin (%), mean (SD)	67.7 (± 2.8)	58.5 (± 11.2)	<0.001
Alpha1-globulin (%), mean (SD)	1.9 (± 0.3)	2.6 (± 0.8)	<0.001
Alpha2-globulin (%)	8.3 (7.7–8.8)	11.4 (9.5–16.3)	<0.001
Beta1-globulin(%),mean (SD)	6.2 (± 0.7)	7.8 (± 2.0)	<0.001
Beta2-globulin (%)	3.4 (3.1–3.8)	4.7 (3.8–5.7)	<0.001
Gamma-globulin (%)	11.6 (10.5–13.5)	11.0 (8.9–13.8)	0.0947
Complete Blood Count WBC ($10^9/L$)	5.9 (5.2–6.5)	7.3 (5.7–9.0)	<0.001
RBC ($10^{12}/L$), mean (SD)	4.7 (± 0.5)	4.5 (± 0.7)	0.0744
HGB (g/L), mean (SD)	136.4 (± 18.1)	132.4 (± 22.4)	0.2989
HCT(%), mean (SD)	40.7 (± 4.5)	39.7 (± 6.0)	0.2905
PLT ($10^9/L$), mean (SD)	241.9 (± 58.1)	284.4 (± 70.4)	0.0006
24-hour Urine Analysis			
Proteinuria (g/day)	0.10 (0.07–0.15)	1.72 (0.65–3.94)	<0.001
Erythrocytes (per field)	0.12 (0.12–0.60)	1.3 (0.23–9.4)	<0.001

Note. Normally distributed data are presented as mean $\pm$ SD, and non-normally distributed data are presented as median (IQR). CKD = chronic kidney disease group; eGFR = estimated glomerular filtration rate; WBC = white blood cell count; RBC = a red blood cell count; HGB= hemoglobin; HCT= hematocrit; PLT = platelet count.

The table shows protein fractions of the total serum protein of participants. Serum albumin levels were markedly decreased compared with the control group, whereas the levels of globulin proteins were increased in the patient group except for globulin gamma. Also, the level of white blood cells was increased in the CKD group, the same applies for platelets. Other values are similar for both groups. Data from the 24-hour urine analysis demonstrated a marked increase in total protein excretion and the number of erythrocytes per high-power field in the CKD group compared with healthy participants. The table 1 shows a higher level of creatinine in the CKD group than for the control. The same trend applies to the level of serum uric acid, where the diseased group has a higher value than the control group. In contrast, direct bilirubin concentrations were lower in the diseased group compared with the healthy group. Serum alpha-

amylase levels were higher in the CKD group. Although these values differed between groups, they largely remained within the normal reference range.

Concentration of CD44 in healthy and diseased patients: In a pilot study, investigated urinary proteomics and its relationship with proteinuria in early-stage CKD and healthy individuals using mass spectrometry-based proteomics analysis (23). In the study, protein abundance was quantified using emPAI. According to the emPAI results, CD44 showed a negative correlation with 24h proteinuria levels. To validate these findings, sCD44std levels were measured using a human ELISA kit. Table 2 demonstrates the result of the ELISA method, confirming the increased concentration of CD44 in healthy controls compared to patients with CKD.

Table 2. Definition of CD44 in urine HLPC and ELISA

Parameter	Control (n = 49)	CKD (n = 88)	P-value
CD44 (ng/mL) (ELISA)	195.3 (97.2–335.1)	114.2 (63.9–201.6)	0.007
CD44_HUMAN (emPAI), mean (SD)	0.10 ($\pm$ 0.03)	0.06 ($\pm$ 0.04)	<0.0001

Note. emPAI = exponentially modified protein abundance index.

Table 3 shows the extent to which CD44 measured by ELISA correlates with eGFR. According to

Spearman's rho coefficient, the correlation was moderately weak but statistically significant.

Table 3. Correlations of CD44 ELISA and eGFR

Proteome / Protein Name	N of Obs	Spearman's Rho	P-value
CD44 / CD44 antigen	98	0.2808	0.0052

Note. Spearman's rho was used to assess the correlation between urinary CD44 measured by ELISA and eGFR.

Table 4 shows the correlation between CD44 protein abundance and eGFR. CD44 antigen demonstrated a moderate positive correlation with

eGFR, which was statistically significant (Spearman's rho = 0.3619, p = 0.0012).

Table 4. Correlation between CD44 emPAI and eGFR

Protein Name	N of Obs	Spearman's Rho	P-value
CD44 antigen	78	0.3619	0.0012

Note. Spearman's rho was used to assess the correlation between urinary CD44 abundance measured by emPAI and eGFR.

Discussion

CKD remains a major challenge to the global healthcare system with increasing incidence and prevalence. The disease burden also negatively imposes economic strain (28). The rapid rise in CKD cases is largely attributable to delayed diagnosis and insufficient implementation of effective primary prevention at early stages (28). Therefore, it is critical to identify biomarkers that can serve as indicators of early signs of kidney damage when conventional biomarkers are unable to reflect renal tissue injury. The divergence in urine protein profiles between CKD patients and healthy individuals suggests the presence of diverse biological pathways and altered cellular pathways in

the disease state (3, 29). Identifying the underlying pathogenic alterations and their associated protein signatures using proteomic analysis provides crucial information for biomarker discovery, thereby facilitating CKD early detection. CD44 is a transmembrane glycoprotein that plays an important role in kidney pathology. Experimental studies have shown that CD44 expression is restricted in normal renal tissue but is increased during renal injury in the tubular and endothelial compartments, contributing to inflammatory and fibrotic cascades in the kidney (12, 23). Kidney biopsy findings in patients with IgA nephropathy revealed a strong correlation of CD44

expression and the severity of glomerular and tubulointerstitial damage and proteinuria (22). Our urinary proteomics results and ELISA study demonstrated decreased urinary levels of CD44 in patients with CKD compared with healthy controls. Membrane proteins such as CD44 are enzymatically cleaved by proteases and may be shed in early injury, resulting in urine excretion (30-33). However, with the development of fibrosis in advanced stages of CKD, increased CD44 expression may remain tightly anchored to the damaged tissue limiting its release into the urine (34). Thus, our findings suggest that CD44 protein has inverse patterns in renal tissue and urine in CKD. The severity of renal fibrosis is a critical prognostic factor in CKD. Inflammation, release of chemokines and proteinuria contribute to a shift from normal extracellular matrix (ECM) turnover to hypertrophy causing extensive damage. Hyaluronic acid is an important part of the extracellular matrix and is associated with organ fibrosis (13, 35). CD44 is the primary hyaluronan receptor on the cell surface and has been strongly implicated in renal fibrosis (30, 36-37). In our study, CD44 levels measured by HPLC-MS and ELISA methods significantly positively correlated with eGFR levels. Thus, these results support previous reports that increased urine CD44 levels may reflect high or normal eGFR, suggesting preserved kidney function (38). Interestingly, however, this positive association with kidney function was reversed in a recent follow-up cohort study, in which CD44 showed a negative association (38). Thus, its role in tubular injury and fibrosis warrants further investigation. CKD progression is driven by proteinuria, which exerts toxic effects on proximal tubular epithelial cells, leading to tubular atrophy and interstitial fibrosis (39). The tubular compartment is metabolically active and reabsorbs the excess protein. When this system is overwhelmed under pathological conditions, it causes lysosomal stress and the release of reactive oxygen species. This leads to an inflammatory response and tubular apoptosis, activating the complement system and amplification of inflammatory cascades. Injured tubules through TGF- β /SMAD signaling induce epithelial-mesenchymal transition and fibroblast activation, ultimately culminating in irreversible tubulointerstitial scarring (40). Increasing evidence reveals that CD44 also plays a vital role in fibrosis through hyaluronan binding (17, 41-42). A study in IgA nephropathy demonstrated an association between proteinuria and CD44 expression in renal tissue.

However, limited data are available regarding a relationship between CKD progression and urinary CD44. Our results showed that emPAI values for CD44 were negatively associated with 24h proteinuria. However, ELISA results showed this association was not confirmed. This can be explained by technical differences between the two platforms. ELISA methods commonly detect a “standard” form of the protein, whereas mass spectrometry can identify various isoforms, making this technique more sensitive even for low-abundance proteins (43). High levels of proteinuria may also mask proteins by binding a particular protein to albumin or hyaluronan (44-45). This may hinder antibody accessibility to specific epitopes, thereby interfering with ELISA-based detection. This study is the first research aimed at CD44 excretion in urine. Further research is needed to evaluate CD44 levels in both urine and serum among healthy individuals and patients with CKD in order to better understand its association with disease progression. These findings suggest a potential role of CD44 as a biomarker in early-stage CKD. Further studies using standardized methodologies and larger cohorts are required to validate its clinical relevance.

Laboratory Data: According to the KDIGO classification, the G2 category corresponds to an eGFR of 60–89 mL/min/1.73 m². In our study, the median eGFR in the CKD group was 83.9 (56.9–114.2) mL/min/1.73 m². CKD diagnosis was established by the treating nephrologists based on the patients’ clinical history and available medical records, rather than on a single eGFR measurement alone. Elevated serum creatinine levels further characterize renal dysfunction. Additionally, serum uric acid levels were higher in the CKD group than in healthy controls, as shown in Table 1.

Limitations of the Data: This study has several limitations. Firstly, all patients were in the early stages of CKD (median eGFR 83.9 mL/min/1.73 m²). Secondly, the sample size was relatively small (healthy: 49; diseased: 88). 24-hour urine protein analysis has limitations, including challenges with accurate 24-hour urine collection and inaccuracies due to occasional partial urine collection. Additionally, the individual-level source data required to reconstruct the exact distribution of participants across G1, G2, and G3 and albuminuria categories A1–A3 were not available for the present analysis. Therefore, these category-specific distributions could not be reported.

Conclusion

In conclusion, this study revealed distinct quantitative and qualitative differences in the urinary

proteome between healthy individuals and CKD patients, as well as a relationship between proteomics

and kidney function parameters. These findings suggest that CD44 may contribute to renal fibrogenesis and may represent a candidate biomarker associated

with kidney function. Further large-scale studies are warranted to assess urinary CD44 levels in broader patient populations and to validate its clinical utility.

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