RECENT URINARY MARKERS IN CHRONIC KIDNEY DISEASE

Abstract

Kidney disease has serious complications whether acute or chronic. CKD cases are in focus due to an unparalleled increase in cases to an unexpected level because of metabolic diseases like diabetes mellitus (DM-II). Other causes of CKD include hypertension (HTN), chronic urinary tract infections, cystic kidney disease and glomerulonephritis. The burden of CKD will rise as the potentiating factors like HTN, DM-2 and obesity are increasing in Asian countries. Recent biomarkers are being tested and used in early and better diagnosis of CKD. These markers are usually present mostly in both serum and urine. Key markers, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) (TIMP-2/IGFBP7) are discussed in detail, shedding light on their sensitivity and specificity. The combination of recentmarkers may be found effective for early and accurate diagnosis. This chapter explores the latest developments in urinary biomarkers, providing a comprehensive overview of their role in assessing CKD progression.As the medical community continues to embrace these advancements, urinary markers emerge as promising tools for enhancing the precision and effectiveness of CKD diagnosis and management.

Authors

Rajesh Kumar
Assistant professor
Department of Biochemistry
Adesh Medical College and Hospital
Shahbad. Haryana, India.

Kiran Dahiya
Professor
Department of Biochemistry
PGIMS
Rohtak, Haryana, India.

Deepika Dalal
Assistant professor,
Department of Biochemistry
PGIMS
Rohtak, Haryana,India.

Neeru Bhaskar
Professor & HOD
Department of Biochemistry
Adesh Medical College and Hospital
Shahbad, Haryana, India.

I. KIDNEY DISEASE

Kidney diseases form an important aspect of non-communicable diseases carrying high morbidity and mortality. Irrespective of this high weightage remark kidney diseases are neglected when it comes to the early diagnosis and treatment. This helps disease to spread further and increase mortality as well as treatment cost to rise manifolds.

Causes of kidney disease include diarrhoea, HIV, Low Birth weight, malaria, preterm birth, lifestyle changes. Kidney disease have its serious complications when it comes to its both type of presentations, either it being acute or it bechronic. Acute kidney injury (AKI) have its deleterious effects as the excretory functions are lost rapidly and serum urea and creatinine rise abruptly which currently are being used in AKI diagnosis (1).

1. Chronic Kidney Disease (CKD)

Time duration for conversion to CKD have been found to have a range of 3.8 years to 12 years depending upon the management of under lying condition (2). Definition of Chronic kidney diseases(CKD) includes GFR<60mL/min/1.73m2 or presence of protein in the urine (3). Biopsy of the renal tissues in CKD cases shows renal sclerosis, tubular atrophy and interstitial fibrosis. CKD is associated with number of complications which affects the treatment protocol, these are decreased hemoglobin content as the erythropoietin levels are decreased in renal damage. Bone health is also adversely affected as the calcium and phosphorus metabolismis affected. Complications ultimately increase chances to premature death to five to ten percent as the CKD progress to end stage renal failure, main cause being cardiovascular event (4).

CKD cases are in focus due to an unparalleled increase in cases to an unexpected levels because of metabolic diseases like diabetes mellitus (DM-II). Other causes of CKD includes hypertension (HTN), chronic urinary tract infections (UTI's), cystic kidney disease and glomerulonephritis (5).

In certain tropical countries like Sri Lanka, India, Nicaragua, Costa Rica and central American states outbreaks of CKD were seen where no evidence of the etiology could be find. Here risk factor could be related to environmental pollutants, prolonged dehydration, smoking, drinking and chewing betel (6).

In a study it was seen that around 23% of the cystic kidney disease patients progressed to end stage renal disease (ESRD) per year whereas this stage conversion rate to ESRD was about 12% in diabetic nephropathy patients. But important point of consideration was that the risk of death in diabetic nephropathy cases was about two fold more than the cystic kidney disease (7).

DM-II being one of the most common cause in today's scenario needs to be extensively studied so that chronic kidney disease can be attended as early as possible because of the effects it can pose to patient and the healthcare burden to the society.

Some data suggests that DM-II accounts for around 50% for end stage renal disease in developed countries (8). Diabetic nephropathy is one of the most important cause of death in

Insulin dependent diabetes mellitus (IDDM) patients. Risk of Renal mortality in diabetics increased by two folds after age of 45 year (9).

2. Globalprevalence of CKD

Chronic kidney disease (CKD) has emerged as one of the leading public non communicable disease worldwide. The overall global estimated presence of CKD is around 13.4% (11.7–15.1%), and patients who reaches end-stage kidney disease (ESKD) needing renal replacement therapy is somewhere between 4.902 to 7.083 million (10).

In India the renal transplant data suggests that around eighteen to twenty thousand patients require renal replacement every year (11).

As per global burden of disease study 2010 the list of total number of death worldwide had numbered CKD at 18th place, which was huge ascent in the list from 27th place in 1990 (12).

In Asia the prevalence of CKD is 14% and in India the prevalence of CKD is around 16% and proteinuria is around 2.2%. The incidence of CKD is found to be as high as 27% in adults with hypertension and 31% in adults with diabetes. In overweight and obese patient the incidence is found to be 14% in Asian countries (13).

The burden of CKD will rise as the potentiating factors like HTN, DM-2 and obesity are increasing in Asian countries. Also burden of death due to risk factor like cardiac event are upto before the age of 65 years. Some regions in Asia carry risk of developing CKD without any known factor, labelled as CKDu. Endemic regions of south Asian region carry risk of about 8% for CKDu (13).

Non-communicable diseases (such as heart disease, diabetes, or kidney disease) have replaced communicable diseases (such as influence, malaria, or AIDs) as the most common causes of premature death worldwide. An estimated 80% of this burden occurs in low- or middle-income countries, and 25% is in people younger than 60 years (14).

3. CKDstaging and Markers

Once the cause sets in to damage the nephrons in the renal tissue, adaptation mechanisms starts to compensate for the loss. Eventually the damage in renal tissue supersedes the compensatory mechanism and GFR starts to decline. Underlying pathophysiology for injury involves tubule interstitial hypoxia, oxidative injury and inflammation in a cyclic manner. So we need markers to assess renal dysfunction according to the damage caused during the progression of CKD and early diagnosis to minimize the mortality and morbidity (15).

To find the better markers we need to understand the progression criteria of the chronic kidney disease. Diagnosis of chronic kidney disease based on Kidney disease:Improvingglobaloutcomes(KDIGO)andKidneydiseaseoutcomequality initiative (KDOQI) criteria suggests that stage I includes kidney damage with increased or normal GFR mentioned as GFR>= 90, stage 2 includes kidney damage with mild decrease in GFR and

GFR of 60-89, stage 3 includes moderate decrease in GFR up to 30-59, stage 4 includes severe decrease in GFR to a level of 15-29and stage 5 if patient have GFR less than<15 to be labeled as kidney failure and to be treated by dialysis (16).

Yet the renal biopsy is necessary for diagnosis of CKD, it comes with risk of bleeding which can be minor to life threatening one. So we definitely need different Markers to diagnose CKD, these includes serum markers and urinary markers (17).

Currently used some of the serum markers include serum urea, serum creatinine and eGFR. Others are urinary markers. One of the most important urinary marker used these days is urinary albumin excretion. Presence of albumin is considered to be one of the earliest manifestation of Diabetic nephropathy, but renal impairment start seven before the albumin starts to   appear in the urine.

Even in minute amounts it predicts increased morbidity and mortality due to renal complications and CVS diseases. Microvascular complications in CKD patients leads to albumin loss more than 300 mg/day and decreases glomerular filtration rate, major cause being DM- II among various causes. Low GFR of range <60ml/min/1.73m2 established independent risk factor for Cardiac event and death (18).

This is established by studies that diagnosing kidney disease before protein start to appear in the urine, can help to use interventions which can reverse or prevent the onset of nephropathy. Option constraints are there once the proteinuria sets in to slow the nephropathy stage conversion (19).

Some studies also indicate that diabetic nephropathy can also progress even when urinary albumins are not fluctuating. Some other factors like increase body weight, bad food habit and infections also affect albumin levels (20).

On the other hand e- GFR, which is one of the best available index to calculate the kidney function, but it can evaluate functional changes of the kidney, exact structural alterations cannot be assessed. So we do need to have more markers which can overcome these short comings of available markers, urinary markers in particular where no needle prick is required and better patient compliance is there (21).

4. Recent Markers Advancement in Diagnosis and Prognosis of CKD

Recent biomarkers are being tested and used in early and better diagnosis of CKD. These markers are usually present mostly in both serum and urine. Some of these recent markers are cystatin-C, L-FABP, KIM-1, NGAL, uromodulin(UMOD) (22).

As the collection of blood sample is a painful procedure and can be a cause that patient might avoid proper follow up during the treatment. So urine markers can play an important role in early diagnosis and prognosis for CKD patients.

Urinary markers of recent origin includes cystatin-C, KIM-1, NGAL, L-FABP, NAG osteopontin (OPN), retinol binding protein-4 (RBP-4) ACE-2, Angiotensinogen and alpha-1 microglobulin. These markers are used to assess different structural renal damage in CKD patients. Other recent urinary markers include 8-OHdG, transferrin, Type IV-collagen and

cystatin-C which helps to find glomerular damage and oxidative stress (23).

Cystatin-C is a new marker which is stable, no effect of muscle mass, also not affected by re absorption or secretion in the kidney, also not affected by muscle mass, age or diet. This fact increases its usefulness in terms of sensitivity in these patients. It is raised in prediabetic nephropathy and early diabetic nephropathy, which makes it better marker to assess the damage in early CKD to minimize the damage by starting effective therapy during early times. Limitations being costly due to high cost of immunoassay and is not widely available (24).

Any damage to tubules plays an important role in progression and poor prognosis of renal nephropathy. And markers reflecting tubular injury helps to find the extent of kidney damage in CKD patients. Important recent markers to find out tubular damage are urinary Liver-type fatty acid binding protein (L-FABP), urinary neutrophil gelatinase-associated Lipocalin (NGAL), Urinary kidney injury molecule (KIM-1) and N-acetyl-beta-glucosaminidase (NAG) (25).

L-FABP is a protein found in abundance in cytoplasm of proximal renal tubules and liver cells with a weight of 14000kDa. Other tissues expressing L-FABP are intestine, muscles and heart, brain and epidermis. It is seen in association with long chain fatty acids. Presence of L-FABP in urine is found to have role in early diagnosis as well as prognosis of CKD with high sensitivity and specificity (26).

Excretion of L-FABP starts in urine in case in case of tubular injury even before presence albumin in the urine. Various factors found to increase and up regulate the synthesis of L-FABP in kidney includes stress factors like increased blood glucose levels, hypertension, increased protein loss and various toxins (26).

So injury at the proximal tubular region activates the genes related to production of L-FABP and increased levels in the urine, ultimately they parallels the extent of injury in the tubule interstitial cells (26).

L-FABP helps to estimate the extent of injury and also helps to understand the conversion of acute to chronic state of kidney injury. It has been seen that L-FABP appears to be more sensitive than presence of protein in the urine to measure CKD progression.ItisalsoseentobeassociatedwithdeclineinGFRinpatientswhoare not yet showing proteinuria. L-FABPisalsoseentoparallelcardiacmarkersindiabeticpatientsatCKDstage1 and 2. Which ultimately can be useful in predicting outcome of the progression and planning the therapy accordingly (27).

The above mentioned facts not only increase L-FABP's effectiveness in CKD related with diabetic nephropathy, also L-FABP is an effective marker to diagnose acute kidney injury and a good marker for renal injury prognosis (27).

KIM -1 is seen in apical membrane of proximal tubules and is seen to rises nephropathyadvancedstages.TreatmentwithRASblockingagentsdecreaseKIM- 1 in the urine which correlates with decreased blood pressure and decrease in urinary albumin loss (28).

KIM-1 is an integral protein found to be raised with tubular injury and shows signs to be a good early marker in tubular damage. Also being found in higher amount in diabetic patients and complementing other markers like serum creatinine, urea, and BUN also increases its usefulness in these patient's diagnosis and progression of nephropathy (28).

It has been observed that glomerular injury in renal nephropathy may be following tubular injury. And as it is noted KIM-1 being an early marker for tubular injury

It can surely be helpful in controlling further damage and nephropathy stage conversion in these patients. KIM-1 along with NGAL depicts ongoing injury so theextentofinjurycanbeaccuratelymeasuredwhereascystatin-Calsoreflectsthe previous or old injury. KIM-1 levels in some instances when found to be high were coinciding with faster decrease in GFR, thus enhancing mortality, which establish KIM-1 as prognostic marker as well (29).

Treatment with Irbesartan in diabetic nephropathy patients showed in KIM-1 level regression along with microalbuminuria improvement which indicates role of KIM-I in monitoring efficacy of treatment in such patients (30).

NGALcarriesironinitsstructureandissecretedbyneutrophilswhenactivated duringtheinfections.Alsopresentintubularepithelialcellsofkidneysois released at the time of tubular injury. NGAL is a highly sensitive marker having more accuracy for acute kidney injury. Also high amount of NGAL rises in relation with decreased GFR in nephropathy patients (31).

NGAL have been studied to be negatively correlated with e-GFR and have been found to have positive correlation with other important markers of nephropathylike proteinuria, serum creatinine and urinary albumin creatinine ratio. These studies hint that urinary NGAL may have bole in clinical usage with other diagnostic and prognostic markers for Nephropathy (32).

And some important observations suggested that NGAL is closely correlated with duration of hyperglycemia in diabetes, correlated with glycated hemoglobin and interleukin-18 (Pro-inflammatory marker) (33).
Some studies suggested that NGAL may have role in renal adaptation to hyperglycemia so its measurement becomes even more useful in these patients.

Presence of NGAL in raised amount with micro albumin urea nearly stages of nephropathy suggest its role in early diagnosis of Nephropathy onset. NGAL have been found to be moderately correlated with five stages of CKD for predicting progression to ESRD and risk of death (34).

NAG belongs to glycosidase family and is present in lysosomes of renal tubules. Having molecular weight of 130,000 Da. It does not cross glomerulus so any presence of NAG in the urine will suggest proximal renal tubular damage (35).

NAG levels are effective to diagnose kidney injury as its levels remain high as long as sustained toxin insult continues and levels return to baseline once the injury incidence are

over. False positive results are relatively very few with NAG evaluations. NAG when used in conjunction with other urinary markers, predicts the extent and progression of CKD very effectively (36).

A strong association has been noted in CKD progression in patients with chronic heart failure in respect to NAG and KIM-1 levels but not in NGAL levels. In some other instances NGAL was found to be more strongly related to advance CKD progression Than KIM-1 and NAG. Out of these NGAL was the main predictor of final stage conversion to ESRD and death (37).

Overall benefit of recent urinary markers not only includes better patient compliance but also overcome the shortcomings of routine markers of CKD. For instance the creatinine have a significant blind area in diagnosis of renal injury and serum urea is affected by diet and detection of albuminuria may be delayed, as the considerable extent of injury have also been occurred.

So combination of recent markers may be found effective for early and accurate diagnose the renal damage, which form the base of better treatment planning. This effect will ultimately improve disease outcome with delayed stage progression, decreased cardiovascular events and decreased dialysis burden. Patient treatment cost will improve once the CKD it diagnosed early and thus patient can have better prognosis with less disability adjusted life years.

REFERENCES

[1] Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, Stevens PE, Caskey FJ, Farmer CK, Fuentes AF, Fukagawa M. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney international. 2021 Sep 1;100(3):516-26.

[2] Gerber C, Cai X, Lee J, Craven T, Scialla J, Souma N, Srivastava A, Mehta R, Paluch A, Hodakowski A, Frazier R. Incidence and progression of chronic kidney disease in black and white individuals with type 2 diabetes. Clinical journal of the American Society of Nephrology: CJASN. 2018 Jun 6;13(6):884.

[3] Murphree DD, Thelen SM. Chronic kidney disease in primary care. The Journal of the American Board of Family Medicine. 2010 Jul 1;23(4):542-50.

[4] Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. The lancet. 2017 Mar 25;389(10075):1238-52.

[5] Noble R, Taal MW. Epidemiology and causes of chronic kidney disease. Medicine. 2019 Sep 1;47(9):562-6.

[6] Weaver VM, Fadrowski JJ, Jaar BG. Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy?. BMC nephrology. 2015 Dec;16(1):1-8.

[7] Haynes R, Staplin N, Emberson J, Herrington WG, Tomson C, Agodoa L, Tesar V, Levin A, Lewis D, Reith C, Baigent C. Evaluating the contribution of the cause of kidney disease to prognosis in CKD: results from the Study of Heart and Renal Protection (SHARP). American journal of kidney diseases. 2014 Jul 1;64(1):40-8.

[8] Ghaderian SB, Hayati F, Shayanpour S, Mousavi SS. Diabetes and end-stage renal disease; a review article on new concepts. Journal of renal injury prevention. 2015;4(2):28.

[9] Zargar AH, Wani AI, Masoodi SR, Laway BA, Bashir MI. Mortality in diabetes mellitus—data from a developing region of the world. Diabetes research and clinical practice. 1999 Jan 1;43(1):67-74.

[10] Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Renal fibrosis: mechanisms and therapies. 2019:3-15.

[11] Agarwal SK, Srivastava RK. Chronic kidney disease in India: challenges and solutions. Nephron clinical practice. 2009 Mar 1;111(3):c197-203.

[12] Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives.

Lancet. Jul 20 2013;382(9888):260-272.

[13] Shrestha N, Gautam S, Mishra SR, Virani SS, Dhungana RR. Burden of chronic kidney disease in the general population and high-risk groups in South Asia: A systematic review and meta-analysis. PLoS One. 2021 Oct 14;16(10):e0258494.

[14] Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. Dec 2011;80(12):1258-1270.

[15] López-Novoa JM, Rodríguez-Peña AB, Ortiz A, Martínez-Salgado C, López Hernández FJ. Etiopathology of chronic tubular, glomerular and renovascular nephropathies: clinical implications. Journal of translational medicine. 2011 Dec;9:1-26.

[16] Eckardt KU, Berns JS, Rocco MV, Kasiske BL. Definition and classification of CKD: the debate should be about patient prognosis—a position statement from KDOQI and KDIGO. American journal of kidney diseases. 2009 Jun 1;53(6):915-20.

[17] Brachemi S, Bollée G. Renal biopsy practice: What is the gold standard?. World journal of nephrology. 2014 Nov 11;3(4):287.

[18] Sandilands EA, Dhaun N, Dear JW, Webb DJ. Measurement of renal function in patients with chronic kidney disease. British journal of clinical pharmacology. 2013 Oct;76(4):504-15.

[19] Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. Journal of the American Society of Nephrology: JASN. 2009 May;20(5):1069.

[20] MacIsaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. Current opinion in nephrology and hypertension. 2011 May 1;20(3):246-57.

[21] Ferguson MA, Waikar SS. Established and emerging markers of kidney function. Clinical chemistry. 2012 Apr 1;58(4):680-9.

[22] Mizdrak M, Kumrić M, Kurir TT, Božić J. Emerging biomarkers for early detection of chronic kidney disease. Journal of personalized medicine. 2022 Mar 31;12(4):548.

[23] Tesch GH. Serum and urine biomarkers of kidney disease: A pathophysiological perspective. Nephrology. 2010 Sep;15(6):609-16.

[24] Menon V, Shlipak MG, Wang X, Coresh J, Greene T, Stevens L, Kusek JW, Beck GJ, Collins AJ, Levey AS, Sarnak MJ. Cystatin C as a risk factor for outcomes in chronic kidney disease. Annals of internal medicine. 2007 Jul 3;147(1):19-27.

[25] Caplin B, Nit sch D. Urinary biomarkers of tubular injury in chronic kidney disease. Kidney international. 2017 Jan 1;91(1):21-3.

[26] Xu Y, Xie Y, Shao X, Ni Z, Mou S. L-FABP: A novel biomarker of kidney disease. Clinicachimicaacta. 2015 May 20;445:85-90.

[27] Kamijo-Ikemori A, Sugaya T, Kimura K. L-type fatty acid binding protein (L-FABP) and kidney disease. Rinshobyori. The Japanese Journal of Clinical Pathology. 2014 Feb 1;62(2):163-70.

[28] Huo W, Zhang K, Nie Z, Li Q, Jin F. Kidney injury molecule-1 (KIM-1): a novel kidney-specific injury molecule playing potential double-edged functions in kidney injury. Transplantation Reviews. 2010 Jul 1;24(3):143-6.

[29] Seibert FS, Sitz M, Passfall J, Haesner M, Laschinski P, Buhl M, Bauer F, Babel N, Pagonas N, Westhoff TH. Prognostic value of urinary calprotectin, NGAL and KIM-1 in chronic kidney disease. Kidney and Blood Pressure Research. 2018 Oct 5;43(4):1255-62.

[30] Nielsen SE, Rossing K, Hess G, Zdunek D, Jensen BR, Parving HH, Rossing P. The effect of RAAS blockade on markers of renal tubular damage in diabetic nephropathy: u-NGAL, u-KIM1 and u-LFABP. Scandinavian Journal of Clinical and Laboratory Investigation. 2012 Apr 1;72(2):137-42.

[31] Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. American journal of kidney diseases. 2009 Dec 1;54(6):1012-24.

[32] Bolignano D, Donato V, Coppolino G, Campo S, Buemi A, Lacquaniti A, Buemi M. Neutrophil gelatinase–associated lipocalin (NGAL) as a marker of kidney damage. American journal of kidney diseases. 2008 Sep 1;52(3):595-605.

[33] Nielsen SE, Schjoedt KJ, Astrup AS, Tarnow L, Lajer M, Hansen PR, Parving HH, Rossing P. Neutrophil Gelatinase- Associated Lipocalin(NGAL) and Kidney Injury Molecule 1 (KIM1) in patients with diabetic nephropathy: a cross- sectional study and the effects of lisinopril. Diabetic Medicine. 2010 Oct;27(10):1144-50.

[34] Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, Fazio MR, Nicocia G, Buemi M. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clinical

journal of the American Society of Nephrology: CJASN. 2009 Feb;4(2):337.

[35] Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney international. 2008 Apr 1;73(7):863-9.

[36] Waikar SS, Bonventre JV. Biomarkers for the diagnosis of acute kidney injury. Nephron Clinical Practice. 2008 Sep 18;109(4):c192-7.

[37] Jungbauer CG, Uecer E, Stadler S, Birner C, Buchner S, Maier LS, Luchner A. N- acteyl- ss- D- glucosaminidase and kidney injury molecule- 1: new predictors for long- term progression of chronic kidney disease in patients with heart failure. Nephrology. 2016 Jun;21(6):490-8.