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Review

# Blood and urine biomarkers in chronic kidney disease: An update

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ABSTRACT

*Introduction:* Chronic kidney disease (CKD) is a silent disease. Most CKD patients are unaware of their condition during the early stages of the disease which poses a challenge for healthcare professionals to institute treatment or start prevention. The trouble with the diagnosis of CKD is that in most parts of the world, it is still diagnosed based on measurements of serum creatinine and corresponding calculations of eGFR. There are controversies with the current staging system, especially in the methodology to diagnose and prognosticate CKD.
*Objective:* The aim of this review is to examine studies that focused on the different types of samples which may serve as a good and promising biomarker for early diagnosis of CKD or to detect rapidly declining renal function among CKD patient.
*Method:* The review of international literature was made on paper and electronic databases Nature, PubMed, Springer Link and Science Direct. The Scopus index was used to verify the scientific relevance of the papers. Publications were selected based on the inclusion and exclusion criteria.
*Result:* 63 publications were found to be compatible with the study objectives. Several biomarkers of interest with different sample types were taken for comparison.
*Conclusion:* Biomarkers from urine samples yield more significant outcome as compare to biomarkers from blood samples. But, validation and confirmation with a different type of study designed on a larger population is needed. More comparison studies on different types of samples are needed to further illuminate which biomarker is the better tool for the diagnosis and prognosis of CKD.

## 1. Background

Chronic kidney disease (CKD) is defined as gradual loss of kidney function for 3 or more months as characterized by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) or GFR < 60 ml/min per 1.73 $m^2$. By using this definition, the global prevalence of CKD (stages 1–5) has been consistent between the ranges of 3–18% [1–6]. Chronic kidney disease is associated with catastrophic health expenditure in low and middle income countries [7] and is a significant contributor to the overall healthcare spending in the United States [8,9], Asia [7,10], Eastern Europe and Latin America [11–14]. Thus, a condition of this scale demands a definitive action in areas of screening, prevention and treatment. Chronic kidney disease (CKD), being a silent disease means most CKD patients are unaware of their condition during the early stages of the disease which poses a challenge for healthcare professionals to institute treatment or start prevention. The trouble with the diagnosis of CKD is that in most parts of the world, it is still diagnosed based on measurements of serum creatinine and corresponding calculations of eGFR. There are controversies with the current staging system, especially in the methodology to diagnose and prognosticate CKD, appropriateness of the thresholds or cut-offs for CKD and diagnosing CKD without any consideration of etiologies [15].

## 2. Limitation of invasive method, GFR measurement and existing biomarkers

In several circumstances, renal biopsy is needed to show definitive evidence of CKD, by looking at the anatomy changes. Several studies have reported that the usage of renal biopsy to confirm diagnosis has its own risk and complications, which include bleeding [88.6%], hypotension [15.9%], local pain and renal loss [FSGS, 31.9% in pead]

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[16,17]. Some renal biopsies may not even achieve its intended aim, by which 12% will give unclear diagnosis, 11% are non-diagnostic and 1.5% are failed attempts [18].

In clinical practice, glomerular filtration rate (GFR) is considered to be the gold standard to determine CKD and measurement of kidney function [19]. GFR can be assessed through plasma clearance of a filtration marker in urine and blood. But it requires an external marker with specific physiological characteristics [20].

Several methods have been established to determine the diagnosis and classification of CKD, but these methods cannot be used for early CKD detection.

1. **Creatinine:** It is one the factors in most eGFR equations, but accuracy are limited by conditions such as serum creatinine measurement variability [21]. A study from Coresh J et al., has reported that the variation of GFR estimation can occur when different type of assay is used to measure the creatinine [22], leading to calls to standardize creatinine measurement in 2006 [23].
2. **Cystatin C:** Cystatin C is more stable with less variability compared to creatinine, but usage is mostly limited in research settings. A report by Shlipak et al., demonstrated that Cystatin C is a better predictor for adverse cardiovascular and non-cardiovascular outcomes as compared to serum creatinine [24]. Cystatin C is also not influenced by muscle mass [25].
3. **Blood Urea Nitrogen (BUN):** High BUN may be related to the decreasing of GFR. However, the production of urea is not stable and influenced by high protein diet, muscle trauma, bleeding, and steroid consumption. Low protein diet and liver failure can decrease BUN level thus affecting GFR measurement [26].
4. **Albuminuria (microalbuminuria):** Increased AER (albumin excretion rate) is significantly related to kidney injury and is featured prominently in the most recent guideline. Studies have reported that ACR > 30 mg/g is a marker of kidney damage and has been validated as a risk factor for CKD, cardiovascular and all-cause mortality [27]. The 2012 KDIGO guidelines included the linear association of albuminuria with the progression of CKD, ESRD and all-cause mortality. But while this biomarker has been used in prediction in AKI and late stages of CKD, it is still not validated for early stages of CKD.

Therefore, the purpose of this Narrative Review is to answer the following research questions:

(a) Which type of sample (blood/urine) will serve as a good and promising biomarker for early diagnosis of CKD?
(b) Which type of sample (blood/urine) will serve as a good and promising biomarker for detecting rapid decline in renal function among CKD patients?

## 3. Research methods

The methodological approach adopted in this paper consists of a narrative review, which is an interpretive-qualitative form of research, that when included some features of systemic methodology [28], can allow synthetization of literature findings with regards to a specific theme and improve our knowledge on the topic [29]. Specifically, our methodological research was inspired by the four steps provided by Egger et al. [30] as shown in Table 1.

### 3.1. Primary studies selection

Primary Studies (articles examined in this paper) are traceable through e-journal databases: ScienceDirect, SpringerLink, PubMed, and Nature, and Scopus index was used to verify the scientific relevance of the papers. Keywords used to search the studies are: 'CKD' (Chronic Kidney disease), 'urine biomarker', 'blood biomarkers', 'renal decline and "CKD progression biomarker". Studies published between January 2015 and January 2019 are included. In the next sub-section, inclusion and exclusion criteria of the studies being used will be discussed.

The data extrapolated from these revised studies were collocated in table format and carried out in the form of a narrative review. Table 1 shows the summary of the methodology used in the review. The flow diagram of the narrative review is shown in Fig. 1.

### 3.2. Inclusion criteria

Articles (primary studies) used in this narrative review include:

a. Studies generated from "CKD/(Chronic Kidney disease)", "urine biomarker", "blood biomarkers", "renal decline", "CKD biomarkers" and "CKD progression biomarkers" keyword,
b. The studies used are not distinguished based on the methodological approach, so this narrative review is also based on the results of quantitative research, not only qualitative ones,
c. Monthly reports or annual reports on CKD that include hemodialysis, transplant and biopsies from sub-units of the Ministry of Health or related formal institutions,
d. Periodic bulletins containing CKD topics, published by formal health institutions or professional institutions,
e. Follow-up > 6 months

### 3.3. Exclusion criteria

Research which not used in this narrative review are:

a. Studies related to biomarkers in AKI (Acute Kidney Injury),
b. Studies related to CKD in children (patient < 18 years old)
c. Studies on the topic of CKD or CKD biomarkers written in foreign languages other than English.
d. Review paper
e. Animal studies
f. Non-follow up studies < 6 months
g. Pediatric studies
h. Dialysis studies
i. Conferences
j. Abstract only
k. Cancer related studies
l. Medication related studies
m. Transplant studies

## 4. Result

A total of 63 studies CKD related to biomarkers and progression of biomarkers in CKD had been identified. They met the criteria for inclusion in this review and found suitable to answer the research questions (Table 2).

## 5. Emerging biomarkers of interest

Over 63 publications were selected based on inclusion and exclusion criteria from 2015 to 2019 publications. There were 48 type of biomarkers being identified with different types of samples. Only several types of biomarkers of interest in this study showed good potential as an early biomarker in CKD progression and diagnosis (Fig. 2).

1. **ADMA (Asymmetric Dimethylarginine):**

ADMA is an analogue of L-arginine which is naturally occurring in human circulation. From our overview, increased ADMA plasma level during follow-up was associated with progression of CKD, and the correlations between ADMA and GFR changes were direct. Furthermore, high ADMA levels were associated with the progression of

**Table 1**
Summary of methodology.

| Step | General activities | Specific activities |
|---|---|---|
| 1 | Formation of a working group | 2 nephrologist and 1 research expert:<br>1. One as a methodological operator<br>2. Two as clinical operators<br>3. One as a research operator |
| 2 | Formulation of the review questions | Evaluation of newly developed biomarkers, limitation of conventional diagnosis and comparison between blood and urine sample as biomarkers. |
| 3 | Identification of relevant studies on ScienceDirect, SpringerLink, PubMed, and Nature. | 1. Identification of the keywords of interest, grouped in inverted commas ("…") and used separately or combined<br>2. Use of Boolean operators, in order to establish a logical relationship among concepts<br>3. Research modalities: advanced search<br>4. Limits: papers published in the last 5 years; languages: English; type of paper: peer-review<br>5. Manual search through the reference lists of articles, using the Scopus index to verify the scientific relevance of papers |
| 4 | Analysis and presentation of the outcomes | The data extrapolated from revised studies were tabulated and presented in the form of a narrative review. |

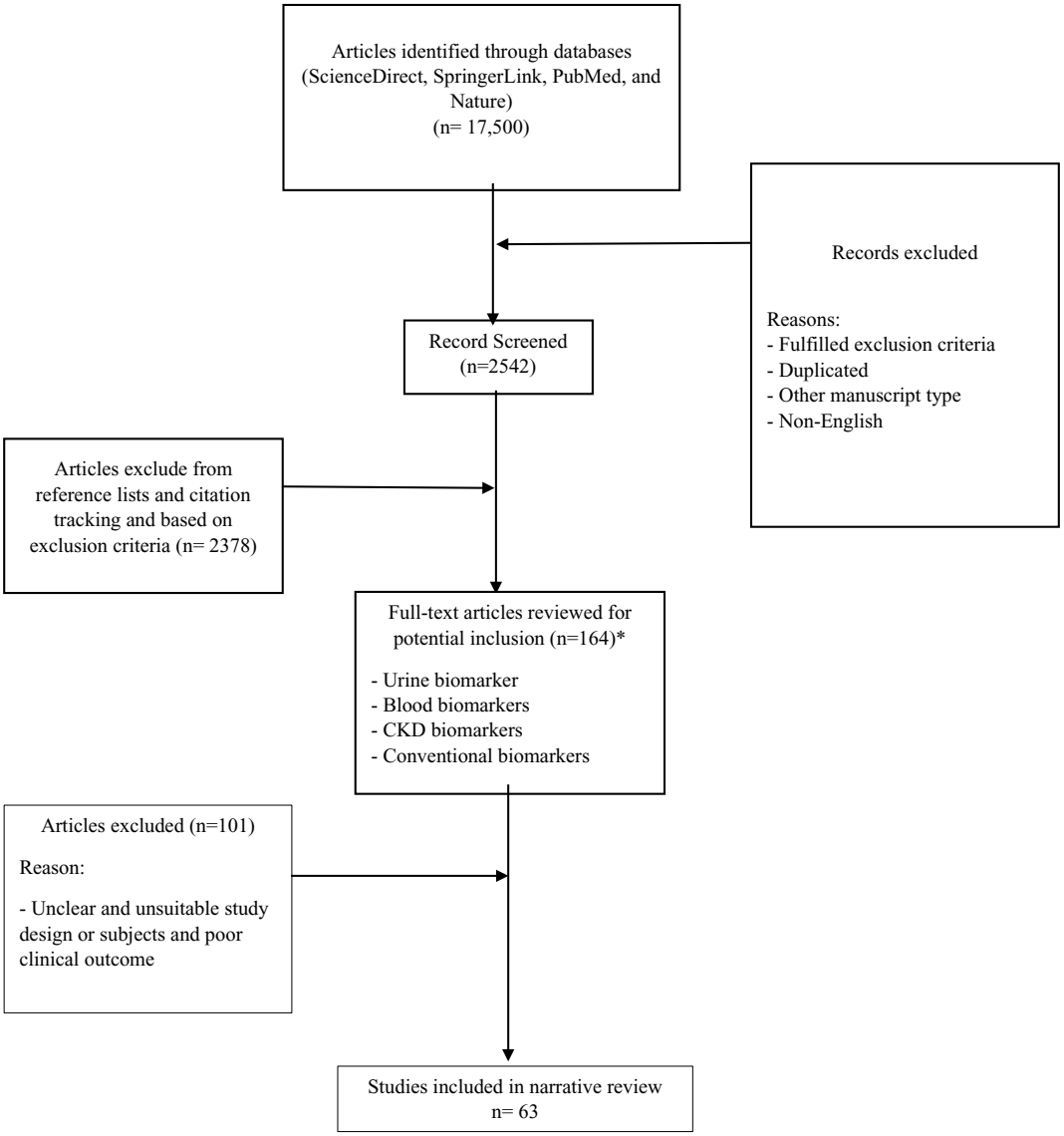


**Fig. 1.** Flow chart of the narrative review.

**Table 2**
Articles included in the narrative review based on inclusion and exclusion criteria.

| No | Author (year) | Disease related | Biomarker | Sample type | Compare | Renal outcome |
|---|---|---|---|---|---|---|
| 1 | Zhang et al., 2018 [31] | CKD only | KIM-1, MCP-1 | Urine sample | eGFR | Higher concentrations of urinary albumin, KIM-1, and MCP-1 at baseline, are significantly associated with CKD incidence. |
| 2 | Pontillo et al., 2017 [32] | CKD and Diabetes | CKD273 | Urine sample | eGFR | Study patients with high baseline of CKD273 were found to have a reduction in eGFR level at median follow up of 5 years. |
| 3 | Triches et al., 2018 [33] | Hypertension, Diabetes and CKD | Plasma ADMA | Blood sample | eGFR and protein | 1. High ADMA levels were associated with progression of albuminuria in hypertensive patients, with and without type 2 diabetes.<br>2. Increases in ADMA plasma level are associated with progression of CKD. |
| 4 | Wu et al., 2015 [34] | Diabetic Nephropathies/ DKD | Serum suPAR | Blood sample | eGFR | 1. Serum suPAR level was significantly elevated and highest in DN. It is progressively higher in later DN stages.<br>2. suPAR level was negatively related to eGFR and positively related to the amount of proteinuria |
| 5 | Chanra et al., 2018 [35] | Glomerulonephritis | UEGF and MCP-1 | Urine and Biopsies | eGFR and Creatinine Ratio | 1. Urine EGF and EGF/MCP-1 levels were significantly higher in Creatinine Ratio.<br>2. High EGF (EGF > 75 ng/mgCr) was a significant predictor for Creatinine Ratio by multivariate analysis.<br>3. EGF correlated inversely with proteinuria and positively with eGFR at 24 months. |
| 6 | Qiu et al., 2018 [36] | Diabetes | **Genomic study:** Cytosine methylation | Blood sample | eGFR and ACR | 1. Methylation levels at 77 sites (DNA) showed significant association with eGFR decline.<br>2. Cg25799291 and Cg22253401 improved the prediction of eGFR decline in addition to baseline eGFR and ACR. |
| 7 | Flaviu Bob et al., 2018 [37] | DKD | s-Klotho and KIM-1 (blood), UACR (Urine) | Blood and Urine sample | eGFR and UACR | 1. Strong, statistically significant correlation of s-Klotho and KIM-1 with the rate of reduction of eGFR/year.<br>2. Strong correlations of UACR with rate of reduction of eGFR/year |
| 8 | Nowak et al., 2017 [38] | Diabetes | **1.Circulating markers (blood):**<br>-TNFR1, KIM-1, and FGF23.<br>**2. Urinary markers:**<br>- albumin, KIM-1, NGAL and MCP-1 | Blood and Urine sample | eGFR | 1. Univariate - all plasma and urinary markers were significantly associated with risk of early renal decline.<br>2. Multivariate - TNFR1, KIM-1, ACR, and EGF/MCP-1 ratio could be a multi-marker prognostic test of detecting early renal decline. |
| 9 | Satirapoj et al., 2018 [39] | DKD | UMCP-1, UACR, UEGF and UEGF/MCP-1 ratio. | Urine sample | eGFR | 1. Univariate- UMCP-1, UEGF, and UEGF/MCP-1 were associated with rapid decline of GFR.<br>2. Multivariate analysis- UACR, systolic blood pressure, and UMCP-1 or UEGF/MCP-1 were independently associated with rapid GFR decline. |
| 10 | Saulnier et al., 2018 [40] | Diabetes | **Urine metabolomic:** Urine Aconitic, glycolic acids and 2-ethyl 3-OH propionate | Urine sample | eGFR and Biopsies | 1. Urine aconitic and glycolic acids correlated positively with glomerular filtration surface density and total filtration surface per glomerulus<br>2. 2-ethyl 3-OH propionate correlated positively with the percentage of fenestrated endothelium. |
| 11 | Liu et al., 2015 [41] | CKD | Plasma levels of resistin, tumor necrosis factor-α receptor 2 (TNF-R2) | Blood sample | eGFR | Elevated levels of resistin and TNF-R2 were independently associated with a greater risk of kidney function decline. |
| 12 | Carlsson et al., 2016 [42] | Diabetes | Soluble tumor necrosis factor receptors 1 and 2 (sTNFR1 and sTNFR2) | Blood sample | eGFR and ACR | 1. Higher circulating sTNFR1 and sTNFR2 were associated with diabetic kidney disease.<br>2. It also predicted incident cardiovascular disease and mortality independently of microalbuminuria and kidney function, even in those without kidney disease. |
| 13 | Ortiz et al., 2018 [43] | CKD | CKD273 | Urine sample | eGFR | Urinary peptidomics CKD273 subclassifiers outperformed albuminuria and CKD273 classifier in predicting the risk of rapid CKD progression in individuals with eGFR > 60 ml/min/1.73 $m^2$. |
| 14 | Rasmussen et al., 2017 [44] | CKD | Urinary endotrophin: creatinine ratio (ECR) | Urine sample | eGFR | 1. Urinary endotrophin: creatinine ratio (ECR) were independently associated with one-year disease progression after adjustment for traditional risk factors.<br>2. ECR was associated with development of end-stage renal disease (ESRD). |
| 15 | Zhang e al., 2018 [45] | FSGS | **Genomic study:** Urinary miR-196a | Urine sample | | |

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**Table 2** (*continued*)

| No | Author (year) | Disease related | Biomarker | Sample type | Compare | Renal outcome |
|---|---|---|---|---|---|---|
| | | | | | eGFR and Proteinuria | 1. Urinary miR-196a is an independent risk factor for FSGS progression after adjusting for age, sex, proteinuria and eGFR.<br>2. Prediction accuracy of ESRD was significantly improved by combining urinary miR-196a with other indicators including eGFR and proteinuria. |
| 16 | Kimura et al., 2016 [46] | CKD | **Chiral Amino Acids**: D-Ser and D-Asn | Blood sample | eGFR | D-Ser and D-Asn were significantly associated with the progression of CKD. |
| 17 | Nam et al., 2018 [47] | Anemia and CKD | serum FGF23 | Blood sample | eGFR | High serum FGF23 levels were associated with an increased risk for anemia in patients with non-dialysis CKD. |
| 18 | Tuegel et al., 2018 [48] | CVD and CKD | Growth differentiation factor 15 (GDF-15), galectin 3 (Gal-3), and soluble ST2 (sST2) | Blood | eGFR | Higher GDF-15, Gal-3, and sST2 concentrations were significantly associated with mortality in CKD patient with CVD. |
| 19 | Alam et al., 2019 [49] | CKD | sST2 and galectin-3 | Blood sample | eGFR | 1. Higher concentrations of galectin-3 may be associated with progression of CKD.<br>2. Every doubling of galectin-3 was significantly associated with a 38% increased risk of progression to eGFR $< 15$ ml/min per 1.73 m2 or ESRD. |
| 20 | Dubin et al., 2018 [50] | CKD | uNGAL and uKIM-1 | Urine sample | eGFR | 1. High levels of uNGAL were associated with increased risk of ESRD and death.<br>2. Higher levels of uKIM-1 were associated with increased risk of ESRD and death. |
| 21 | Zhang et al., 2017 [51] | CKD | **Urine proteomic:** Urinary mucin-1 | Urine sample | eGFR | Urinary mucin-1 subunit α was associated with renal dysfunction. |
| 22 | Lu et al.,2016 [52] | Diabetic nephropathy | Urine AQP5/creatinine | Urine sample | eGFR | Urine AQP5/creatinine is significantly higher in diabetic nephropathy stage V. |
| 23 | Ju et al., 2015 [53] | CKD | uEGF | Urine sample | eGFR and Biopsies | uEGF showed significant correlation with intrarenal EGF mRNA, interstitial fibrosis/tubular atrophy, eGFR, and rate of eGFR loss. |
| 24 | Messchendorp et al., 2018 [54] | ADPKD | β2MG and MCP-1 | Urine sample | eGFR | Urinary β2MG and MCP-1 excretion were both associated with GFR decline in ADPKD. |
| 25 | Looker et al., 2015 [55] | CKD | Fibroblast Growth Factor-21, The Symmetric To Asymmetric Dimethylarginine Ratio, B2-Microglobulin, C16-Acylcarnitine, And Kidney Injury Molecule-1 | Blood sample | eGFR | 1. 30 biomarkers showed significant associations with rapid progression of renal decline.<br>2. 14 biomarkers showed to have an increased the area under the ROC curve. |
| 26 | Afshinnia et al., 2016 [56] | CKD | **Lipidomic study:** Phosphatidic Acid 44:4 And Monoacylglycerol 16:0 | Blood sample | eGFR and uPCR | Phosphatidic acid 44:4 and monoacylglycerol 16:0 were shown to be significantly higher in CKD progression. |
| 27 | Chauhan et al., 2018 [57] | CKD | Plasma Endostatin | Blood sample | eGFR | Plasma endostatin were strongly associated with kidney outcomes in type 2 diabetics with preserved eGFR and improved risk discrimination over traditional predictors. |
| 28 | Feng et al., 2018 [58] | IgA Nephropathies | CCL2 and Exosome excretion | Urine sample | eGFR and Biopsies | 1. Exosome excretion was increased markedly in IgAN patients and correlated with levels of proteinuria and tubular injury.<br>2. Exosomal chemokine CCL2 were highly expressed in IgAN patients and it correlated with tubulointerstitial inflammation and C3 deposition.<br>3. High CCL2 levels at the time of renal biopsy were associated with subsequent deterioration in renal function. |
| 29 | Kim et al., 2015 [59] | Diabetic Nephropathy | NAPCR (Nonalbumin Protein-to-Creatinine Ratio) | Urine sample | eGFR | NAPCR showed a significant association with annual eGFR decline in diabetic nephropathy. |
| 30 | Hwang et al., 2017 [60] | Diabetic Nephropathies | NGAL and KIM-1 | Blood sample | eGFR and uPCR | 1. Positive correlations were observed between tubular expressions of NGAL and KIM-1, and GFR decline<br>2. Based on multivariate analysis, the association between tubular expressions of KIM-1 and GFR decline slopes was dependent on uPCR. And, tubular expressions of NGAL were independently associated with GFR decline. |
| 31 | Park et al., 2017 [61] | CKD and CVD | TNFR1 | Blood sample | eGFR | Levels of TNFR1 were associated with kidney function decline and rapid loss in kidney function. |
| 32 | Wang et al., 2016 [62] | CKD | **Genomic study:** Urinary COL1A1 mRNA | Urine sample | eGFR and biopsies | |

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**Table 2** (*continued*)

| No | Author (year) | Disease related | Biomarker | Sample type | Compare | Renal outcome |
|---|---|---|---|---|---|---|
| | | | | | | 1. Urinary COL1A1 mRNA level were elevated in nephrotic patients, and it correlated with proteinuria, histological scarring, and inversely with renal function.<br>2. It also correlated with eGFR decline that predicted renal function loss during follow-up. |
| 33 | Kim et al., 2016 [63] | Diabetic Nephropathy | Plasma α-klotho | Blood sample | eGFR | Plasma α-klotho was significantly associated with the decline of eGFR in type 2 diabetic nephropathy. |
| 34 | Nowak et al., 2016 [64] | T1DM (Diabetes) | KIM-1 and TNFR1 | Blood sample | eGFR | Increase of plasma KIM-1 was strongly associated with risk of early progressive renal decline. |
| 35 | Pavkov et al., 2015 [65] | T2DM (Diabetes) | TNFR1 and TNFR2 | Blood sample | eGFR | Increase of serum concentrations of TNFR1 or TNFR2 were associated with increased risk of ESRD in type 2 diabetes. |
| 36 | Rebholz et al., 2017 [66] | CKD with CVD | Plasma Galectin-3 | Blood sample | eGFR | Increase of plasma galectin-3 levels were associated with elevated risk of developing incident CKD, particularly among those with hypertension. |
| 37 | Nadkarni et al., 2018 [67] | CKD | TNFR1, TNFR2, and KIM1 | Blood sample | eGFR | Plasma concentrations of TNFR1, TNFR2, and KIM1 are independently associated with renal outcome. |
| 38 | Wei et al., 2018 [68] | CKD | Genomic study: Urinary mtDNA | Urine sample | eGFR | Every increase in urinary mtDNA by 100 copy/μL confers a 25.0% increase in risk of doubling of serum creatinine or need of dialysis. |
| 39 | Siwy et al., 2019 [69] | CKD | CKD273 | Urine sample | eGFR | There is a significant correlation between CKD273 with eGFR decline. |
| 40 | Wu et al., 2018 [70] | DKD | uEGF/MCP-1 | Urine sample | eGFR | 1. Urinary EGF/MCP-1 was negatively associated with the occurrence of DKD.<br>2. UEGF/MCP-1 had a better ability to predict the composite endpoint and correlated more closely with kidney function decline in advanced DKD. |
| 41 | Żyłk et al., 2018 [71] | T2DM (Diabetes) | Serum and urine NGAL and KIM-1/creatinine ratio | Blood and Urine | eGFR and uACR | 1. Serum and urine NGAL correlated with eGFR changes.<br>2. Increase of urine NGAL, KIM-1/creatinine ratio, were significantly associated with the increase in uACR. |
| 42 | Messchendorp et al., 2018 [72] | ADPKD | b2MG and MCP-1 | Urine sample | eGFR | β2MG and MCP-1 were associated with annual change in eGFR. |
| 43 | Pejchinovski et al., 2016 [73] | ADPKD | **Peptidomic study:** Matrix Metalloproteinases And Cathepsins | Urine sample | eGFR | 1. Matrix metalloproteinases and cathepsins predicted relevant clinical outcomes in ADPKD patients<br>2. It suggested altered proteolytic pathways was involved in disease progression. |
| 44 | Scholten et al., 2016 [74] | CKD with CVD | Urinary HGF | Urine sample | eGFR | 1. Increase urinary HGF was associated with incident CVD and all-cause mortality<br>2. Higher adiponectin was associated with CVD and deterioration in renal function. |
| 45 | Chonchol et al., 2017 [75] | ADPKD | sFGF-23 | Blood sample | eGFR | 1. Higher serum fibroblast growth factor 23 concentration was associated with kidney function decline,<br>2. Fibroblast growth factor 23 did not substantially improved prediction of rapid kidney function decline. |
| 46 | Hayek et al., 2015 [76] | CKD with CVD | suPAR | Blood sample | eGFR | 1. A higher suPAR level at baseline was independently associated with a greater decline in the eGFR during follow-up with annual change in the eGFR of $-0.9$ ml per minute per 1.73 $m^2$ |
| 47 | Bjornstad et al., 2018 [77] | T1DM | SUMOD (Serum Uromodulin) | Blood sample | eGFR | Higher baseline SUMOD level predicted Coronary Arteries Calcification progression (CAC), elevated of albumin excretion incident, rapid eGFR decline and GFR impairment. |
| 48 | Zewinger et al., 2018 [78] | IgA Nephropathies | Urinary DKK3 | Urine sample | eGFR and biopsies | High urinary DKK3 levels identified patients at high risk for eGFR decline with short term eGFR decline. |
| 48 | Tin et al., 2018 [79] | CKD and HPT | **Metabolomic study:** 6-bromotryptophan | Blood sample | eGFR | Lower levels of 6-bromotryptophan were associated with CKD progression. |
| 50 | Frimodt-Møller et al., 2018 [80] | T2DM (Diabetes) | GDF-15 and FGF-23 | Blood sample | eGFR | 1. Higher GDF-15 and FGF-23 in patients with T2DM and microalbuminuria, were independently associated with all-cause mortality. |

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**Table 2** (*continued*)

| No | Author (year) | Disease related | Biomarker | Sample type | Compare | Renal outcome |
|---|---|---|---|---|---|---|
| | | | | | | 2. Higher GDF-15 improved risk prediction of decline in kidney function. |
| 51 | Liu et al., 2017 [81] | T2DM (DKD) | Plasma Leucine-Rich α-2-Glycoprotein 1 | Blood sample | eGFR | 1. Both participants with albuminuria and CKD progression had higher plasma LRG1 levels at baseline<br>2. The association of LRG1 with microalbuminuria to macro-albuminuria progression was stronger in eGFR than its association with normo-albuminuria to microalbuminuria.<br>3. LRG1 independently predicted CKD progression. |
| 52 | Carlsson et al., 2017 [82] | CKD | TNF-related apoptosis-inducing ligand receptor 2, CD40L receptor, TNF receptor 1, placenta growth factor, thrombomodulin, urokinase plasminogen activator surface receptor, growth/differentiation factor 15, macrophage colony-stimulating factor 1, fatty acid-binding protein, cathepsin D, resistin, kallikrein 11, C−C motif chemokine 3, proteinase-activated receptor 1, cathepsin L, chitinase 3-like protein 1, TNF receptor 2, fibroblast growth factor 23, monocyte chemotactic protein 1, and kallikrein 6 | Blood sample | eGFR | 1. 28 plasma proteins were significantly associated with eGFR decline per year. |
| 53 | Khatir et al., 2017 [83] | CKD | Urine L-FABP/C | Urine sample | eGFR | Urine L-FABP/C is permanently elevated in CKD patients, but only associated with GFR decline in those without albuminuria. |
| 54 | Kim et al., 2017 [84] | Diabetic Nephropathy | | | | 1. NAPCR showed a significant association with the annual eGFR decline in early stage diabetic nephropathy.<br>2. The NAPCR predicted a higher probability of developing CKD of stage 3 or greater in early stage diabetic nephropathy. |
| 55 | Pontillo et al., 2017 [85] | CKD | CKD273 and UAE | Urine sample | eGFR | 1. The urinary proteome CKD273-based classifier performed significantly better than UAE in detecting CKD progression in early stages.<br>2. But, UAE performed better in patients with late-stage CKD.<br>3. No significant difference in performance was found between CKD273 and UAE in patients with moderately reduced renal function. |
| 56 | Yoshitomi et al., 2016 [86] | CKD | Serum BNP | Blood sample | eGFR | Higher BNP levels were associated with adverse renal outcomes. |
| 57 | Devetzis et al., 2015 [87] | Diabetic Nephropathy | Serum CAF (C-Terminal Fragment of Agrin) | Blood sample | eGFR | High serum CAF levels predicted eGFR decline at 12 months follow-up. |
| 58 | Jungbauer et al., 2016 [88] | CKD with CVD | KIM-1 and NAG | Blood sample | eGFR | 1. KIM-1 and NAG were significant predictors for CKD progression. |
| 59 | Øvrehus et al., 2015 [89] | CKD | Proteomic study: Urinary protemic (collagen types I-III, uromodulin) | Urine sample | eGFR | Reduced excretion of collagen types I-III, uromodulin, and other indicators of interstitial inflammation, fibrosis and tubular dysfunction were associated with CKD diagnosis and rapid progression. |
| 60 | Lim et al., 2015 [90] | CKD | Plasma NGAL | Blood sample | eGFR | Plasma NGAL in participants with eGFR of $< 60$ ml/min/1.73 $m^2$ significantly improved the accuracy in predicting the 10-year risk of renal disease events. |
| 61 | Bansal et al., 2015 [91] | CKD with CVD | N-terminal pro-B-type natriuretic peptide and troponin T | Blood sample | eGFR | Elevated N-terminal pro-B-type natriuretic peptide and troponin T are associated with rapid decline of kidney function and incident CKD. |
| 62 | Rebholz et al., 2015 [92] | CKD | fibroblast growth factor-23 | Blood sample | eGFR | Higher baseline fibroblast growth factor-23 levels were associated with increased risk of incident. |
| 63 | Colombo et al., 2019 [93] | Diabetes | KIM-1 and β2-M | Blood sample | eGFR | 1. Kidney injury molecule 1 (KIM-1) and β2-microglobulin (β2M) showed the most consistent effects for progression of CKD.<br>2. Serum KIM-1 and B2M independently improve prediction of renal decline in type 2 diabetes. |

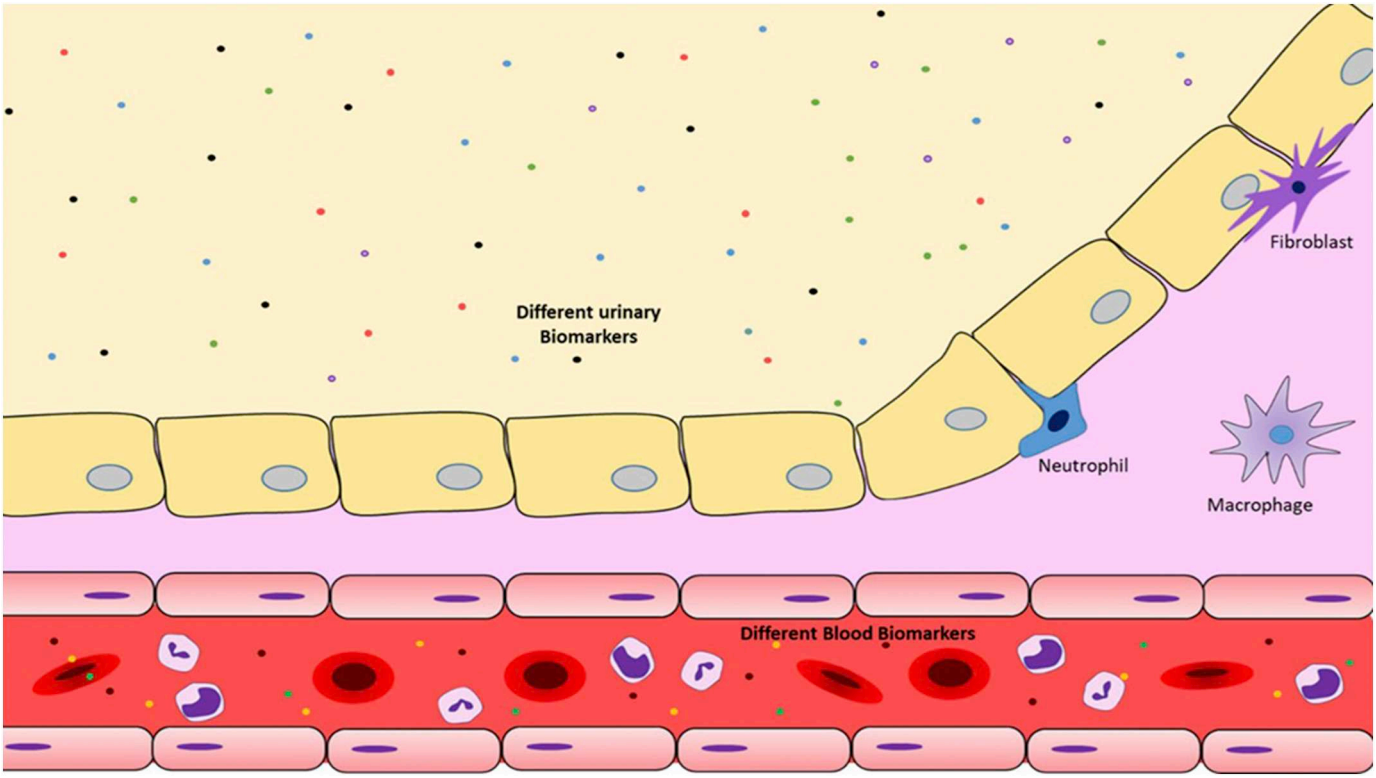


**Fig. 2.** Figure above explaining on expression and stimulation in different type of biomarker that can be found in the blood or urine only. But, some or a few types of biomarker can be found in both.

albuminuria in hypertensive patients, with and without type 2 diabetes [32]. Some studies have reported that SDMA in both serum and urine give better result as compared to ADMA in which SDMA may have a correlation with kidney dysfunction and decline (eGFR and creatinine clearance) [94]. Still, further follow up studies are needed for verification and validation.

2. **suPAR (Soluble Urokinase-Type Plasminogen Activator Receptor):**

suPAR is the circulating form of a glycosyl-phosphatidylinositol–anchored three-domain membrane protein that is expressed on a variety of cells [95–97]. This type of biomarker is readily detected in plasma, serum, urine, and other bodily fluids [98]. Based on our overview, higher level of plasma suPAR is associated with a greater decline in the eGFR during follow-up with the annual change in eGFR of −0.9 ml per minute per 1.73 m2 and independently associated with incident chronic kidney disease and an accelerated decline in the eGFR [76]. Moreover, a study by Wu and his friends has demonstrated that serum suPAR was significantly elevated higher in DN and was progressively increasing with later stages of DN [34].

3. **EGF (Epidermal Growth Factor):**

EGF is a peptide growth factor produced by the renal tubules offering protection from kidney damage [99]. Based on reviews that have been made in this study, high of urinary EGF was associated with rapid decline of eGFR and creatinine ratio [35,39]. Furthermore, Ju and his friend had demonstrated in their study that urinary EGF can be utilized as an independent risk predictor in CKD progression [53]. Further analysis and validation are needed to determine the effectiveness of this biomarker in prognosticating CKD.

4. **Klotho:**

Klotho is a protein composed of a large extracellular and a small intracellular domain, important in the encoding of a single-pass transmembrane co-receptor protein. It is mainly expressed in the kidney and is involved in the anti-aging process [100]. Klotho is identifiable in the blood, urine and cerebrospinal fluid [101]. Based on our overview, klotho, especially soluble klotho has a strong correlation with the rate of eGFR reduction over 1 year [37]. Moreover, previous studies have demonstrated that plasma klotho (Plasma α-klotho) was significantly associated with the rate of eGFR decline in diabetic nephropathy [63]. Further validation is needed through follow up studies to confirm whether this biomarker is suitable to be used as prognostic and early diagnostic tool for CKD.

5. **TNF-R (Tumor Necrosis Factor- Receptor):**

TNF is initially expressed as a type II transmembrane protein. A second soluble form of TNF originates from transmembrane TNF by proteolytic processing. Both forms of TNF bind to two receptors of the TNF receptor superfamily (TNFRSF), TNFR1 and TNFR2 [102]. Many studies have identified this type of biomarker to be a good biomarker especially TNFR1 which gives a good outcome and is independently associated with renal decline and function [38,42,61,64,65,67,and]. Suggested to be a good biomarker in early diagnostic tools and prognostic in CKD progression associated with diabetes.

6. **Galectin-3:**

Galectin-3 is a β-galactoside−binding lectin expressed ubiquitously and thought to be involved in inflammation and fibrosis of both the heart and kidney [103–105]. Based on our overview about this biomarker, several studies showed a significant association of galectin-3

with the progression of CKD when followed up for > 6 months [49,66]. Moreover, Alam and her friends have stated that every doubling of galectin-3 level was associated with 38% high risk of CKD eGFR < 15 ml/min per 1.73 m2 or ESRD [49]. Thus, this can be one of the good biomarkers for early detection of CKD.

7. **DKK-3 (Dickkopf-3):**

DKK3 is a stress-induced, renal tubular epithelia–derived, secreted glycoprotein that induces tubule-interstitial fibrosis through its action on the canonical Wnt/β-catenin signaling pathway. This leads to the decrease of interstitial matrix accumulation and reduced tubular atrophy. [106]. Our review has found that this DKK-3 is highly significant, independently associated with renal decline in patients with CKD as compared to controls when compared to eGFR and albumin alone [78]. Same study also found that it can only be used as a biomarker for early detection of CKD but not in later stages (ESRD). Further analysis and validation are needed to confirm the validity of this biomarker as a CKD prognosticator.

8. **GDF-15 (Growth Differentiation Factor 15):**

GDF-15 is a member of the transforming growth factor β cytokine family that is widely distributed in mammalian tissues (including the kidney) and it shown to play multiple roles in various pathologies, for example CVD inflammation, cancer, obesity, and kidney disease [107,108]. Few studies have identified that high level of GDF-15 is independently associated with kidney decline especially in CKD mortality [48,80]. Further investigation is needed to confirm the effectiveness of this biomarker as compared with other biomarkers.

9. **CKD273**

CKD273 is a urinary peptide that enhances proteolytic fragments especially collagen α-1 (I) chain [109]. This overview identifies a few studies indicating a significant association and correlation with eGFR decline [32,43,69,85,and]. Moreover, this biomarker can predict the risk of rapid decline of CKD progression and gives a better performance as compared to UAE. Therefore, this biomarker is suggested to be a good biomarker for CKD progression especially when there is rapid CKD decline.

## 6. Discussion

Our review highlights the need for better biomarkers in order to enable nephrologists to focus on CKD patients that have complex and unique pathophysiological mechanisms. Proteinuria, serum creatinine, eGFR, CRP, AER/ACR and other traditional markers are insensitive and over-reliance on these results may lead to extensive time lapses of which successful interventions could be applied. Some of the reviewed biomarkers have showed great promise but further validation is required in a larger, more diverse population before translation into clinical practice. Of those reviewed, ADMA, suPAR, EGF, Klotho, TNF-R, Galectin-3, DKK-3, DGF-5 and CKD273 demonstrated the greatest potential as biomarkers of CKD progression as well as a biomarkers for kidney function and cardiovascular risk. The comparison of type of samples either blood or urine is still under investigation and validation. However, the overview of this study has shown that urine biomarkers give a better outcome on predicting rapid decline on renal function as well as a better marker for CKD diagnosis as compared to blood biomarkers.

Nevertheless, it is unlikely that a single marker will satisfy the requirement of predicting CKD progression as it is almost impossible to reflect the complexities of all the underlying pathophysiological processes involved. It is more likely that a focused panel of biomarkers will be most rewarding for specially targeted CKD segment. Other than that, testing biomarkers prospectively in a large, divergent population over extended follow-up periods, and validating them against hard outcome measures such as the development of ESRD and mortality is required before translation into clinical practice. Although advances in proteomics and metabolomic technologies, sample conditioning and analysis methods have greatly improved productivity and efficiency in biomarker discovery; biomarker verification and validation remain a significant, costly and high-risk undertaking in the commercial development and deployment of novel biomarkers for CKD.

## 7. Conclusion

In conclusion, the search for new relevant biomarkers to better stratify patients with CKD according to the risk of progression, morbidity and mortality is underway. It is important to determine whether the newly identified biomarkers are merely associations or real biomarkers of the underlying pathophysiological processes. Nevertheless, this overview found that even though both urine and blood type sample are promising, urine biomarkers are better compared to blood biomarkers. The lack of data comparing urine biomarkers with blood biomarker necessitates the importance of follow up studies to further validate which biomarker shows the most potential in predicting rapid decline in renal function.

## Appendix A

### *A.1. Abbreviations*

eGFR: estimation Glomerular Filtration
AKI: Acute Kidney Injury
KIM-1: Kidney Injury Molecule-1
ADMA: Asymmetric dimethylarginine
suPAR: Soluble Urokinase-Type Plasminogen Activator Receptor
UEGF: Urinary Epidermal Growth Factor
UACR: Urinary Creatinine Ratio
TNFR1: Tumor Necrosis Factor Receptor 1
TNFR2: Tumor Necrosis Factor Receptor 2
NGAL: Neutrophil Gelatinase-Associated Lipocalin
FGF-23: Fibroblast Growth Factor 23
ECR: Endotrophin: Creatinine Ratio
DKD: Diabetic Kidney Disease
FSGS: Focal Segmented Glomerular Syndrome
CVD: Cardiovascular Disease
ADPKD: Autosomal Dominant Polycystic Kidney Disease
T2DM: Type 2 Diabetes Mellitus
T1DM: Type 1 Diabetes Mellitus
mtDNA: mitochondrial DNA
sFGF: serum Fibroblast Growth Factor
DKK-3: Dickkopf-3
SUMOD: Serum Uromodulin
HPT: Hypertension
L-FABP: Liver-Type Fatty Acid Binding Protein
NAG: N-Acetyl Glucosaminidase
B2-M: Beta-2 Microglobulin

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