Clinica Chimica Acta 555 (2024) 117798

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Urinary biomarkers in kidney disease

Esra Canki [a], Esther Kho [b], Joost G.J. Hoenderop [a,*]

[a] Department of Medical BioSciences, Radboudumc, Nijmegen, The Netherlands
[b] imec within OnePlanet Research Center, Wageningen, The Netherlands

ARTICLE INFO

Keywords:
AKI
Biomarkers
CKD
Creatinine
Urinary

ABSTRACT

Background: Chronic kidney disease (CKD) affects many people worldwide and early diagnosis is essential for successful treatment and improved outcome. Unfortunately, current methods are insufficient especially for early disease detection. However, advances in the analytical methods for urinary biomarkers may provide a unique opportunity for diagnosis and management of CKD. This review explores evolving technology and highlights the importance of early marker detection in these patients.

Approach: A search strategy was set up using the terms CKD, biomarkers, and urine. The search included 53 studies comprising 37 biomarkers. The value of these biomarkers for CKD are based on their ability to diagnose CKD, monitor progression, assess mortality and nephrotoxicity.

Results: KIM-1 was the best marker for diagnosis as it increased with the development of incident CKD. DKK3 increased in patients with declining eGFR, whereas UMOD decreased in those with declining kidney function. Unfortunately, none fulfilled all criteria to adequately assess mortality and nephrotoxicity.

Conclusion: New developments in the field of urinalysis using smart toilets may open several possibilities for urinary biomarkers. This review explored which biomarkers could be used for CKD disease detection and management.

1. Introduction

Chronic kidney disease (CKD) affects around 13.4 % of the population worldwide and these percentages are expected to rise as the rates of CKD risk factors including hypertension, diabetes mellitus, and obesity are steadily increasing[1,2]. CKD carries a high burden on society and the patients' life, due to its high contribution to healthcare costs and high mortality risk[3]. CKD is described as sustained damage to the renal parenchyma, leading to the deterioration of kidney function. Loss of kidney function can result in anemia, concentration problems, and disturbances in mineral homeostasis. Furthermore, the last stage of kidney deterioration leads to end-stage kidney disease (ESKD) and can result in dialysis and renal replacement therapies, such as transplantation[4]. Early diagnosis and monitoring of patients is a necessity as it can slow the progression and start treatment earlier.

Diagnosis of CKD occurs through determination of the glomerular filtration rate (GFR) and the current gold standard to measure the GFR uses an injection of inulin. This method is considered very invasive and expensive[5]. Instead, serum or urinary excretion of creatinine in combination with demographic features is utilized to determine the

Abbreviations: α1M, alpha-1-microglobulin; 2m, beta-2-microglobulin; UMOD, uromodulin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein-1; YKL-40, chitinase-3 like 1; miRNAs, microRNAs; PCR, protein-to-creatinine ratio; ACR, albumin-to-creatinine ratio; RBP, retinol-binding protein; CCR, creatinine clearance; NAG, N-Acetyl-Beta-D-Glucosaminidase; TIMP-2, tissue inhibitor of metalloproteinases 2; uDcR2, urinary decoy receptor 2; BTP, beta-trace protein; CysC, Cystatin C; Alb, albumin; Unon-alb/cr, Urinary non-albumin creatinine ratio; PIIINP, Type III procollagen; PINP, Type I procollagen; uUMOD, urinary uromodulin; L-FABP, liver-type fatty acid-binding protein; uRBC, urinary red blood cells; OPN, osteopontin; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; PODXL1, podocalyxin-like protein 1; DKK3, Dickkopf-3; AAG, alpha-1-acid-glycoprotein; AGT, angiotensin; Cre, creatinine; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; PU, proteinuria; IP-10, chemokine interferon-inducible protein 10; HGF, hepatocyte growth factor; AVP, arginine vasopressin; OC, observational cohort study; IS, intervention study; CC, case cohort study; LA, longitudinal analysis; PA, post-hoc analysis; RCT, randomized controlled trial; PCS, prospective cohort study; CS, cross-sectional; ADPKD, autosomal dominant kidney disease; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; SLE, systemic lupus erythematosus; MGN, membranous nephropathy; T2DM, type 2 diabetes mellitus; RH, resistant hypertension; DM, diabetes mellitus; AKI, acute kidney injury; VC, vascular calcification.

* Corresponding author at: Department of Medical BioSciences, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
E-mail address: joost.hoenderop@radboudumc.nl (J.G.J. Hoenderop).

https://doi.org/10.1016/j.cca.2024.117798
Received 24 November 2023; Received in revised form 22 January 2024; Accepted 22 January 2024
Available online 26 January 2024
0009-8981/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

estimated GFR (eGFR). Yet the accuracy of using creatinine has been questioned, as it is found in food and can be released by the peritubular capillaries causing the overestimation of the eGFR[5]. Moreover, serum creatinine only increases when the kidney parenchyma is 40–50 % damaged, meaning that earlier damage is not detected[6]. For example, healthy values of eGFRs are commonly observed in people with tubulointerstitial fibrosis, which is not well captured by the common techniques in the clinic[7]. Other diagnostics methods, such as albuminuria, are not accurate enough for implementation in the clinical field[8].

Enormous advancements in sensor, display and battery technologies have enabled the development of health monitoring devices, such as smart watches with heart rate monitors[9]. Newer developments in this field have focused on at-home monitoring, including so-called smart toilets[10]. The development of these smart toilets makes monitoring through urinalysis easier and more frequent, which is important as adults in the United States visit their health provider less than four times a year. Increasing the frequency in which patients are sampled could increase the chance of determining renal insufficiency in earlier stages and urinary biomarkers could play a large role in the consistent urinalysis that the smart toilets allow.

Biomarkers can be used as powerful and non-invasive tools to provide insights into diagnostics, prognostics, and progression[11,12]. Biomarkers are a defined characteristic, including proteins, that can be measured as an indicator of normal biological processes[13,14]. This includes measuring tubules' health, which is indicative of the prognosis of kidney injury[15]. In addition, biomarkers could indicate the location of injury enabling more targeted therapies and better insight into pathogenesis[15]. Monitoring and early diagnosis of patients require multiple, repeated measurements, which makes a non-invasive biomarker most suitable[12].

Since recent developments in the urinalysis field using smart toilets have opened up new possibilities for automatic measurements of urinary biomarkers, this review aims to explore known biomarkers in literature that are indicative of CKD. Especially since current methods for determining CKD are not fully accurate. To explore the possibility of each marker to be introduced into a smart toilet for diagnosis, prognosis and disease progression, a set of different criteria and categories are defined. After which, the different biomarkers will be discussed based on their proposed use in literature and based on the different criteria per category. Lastly, the use of these biomarkers in smart toilets will be discussed.

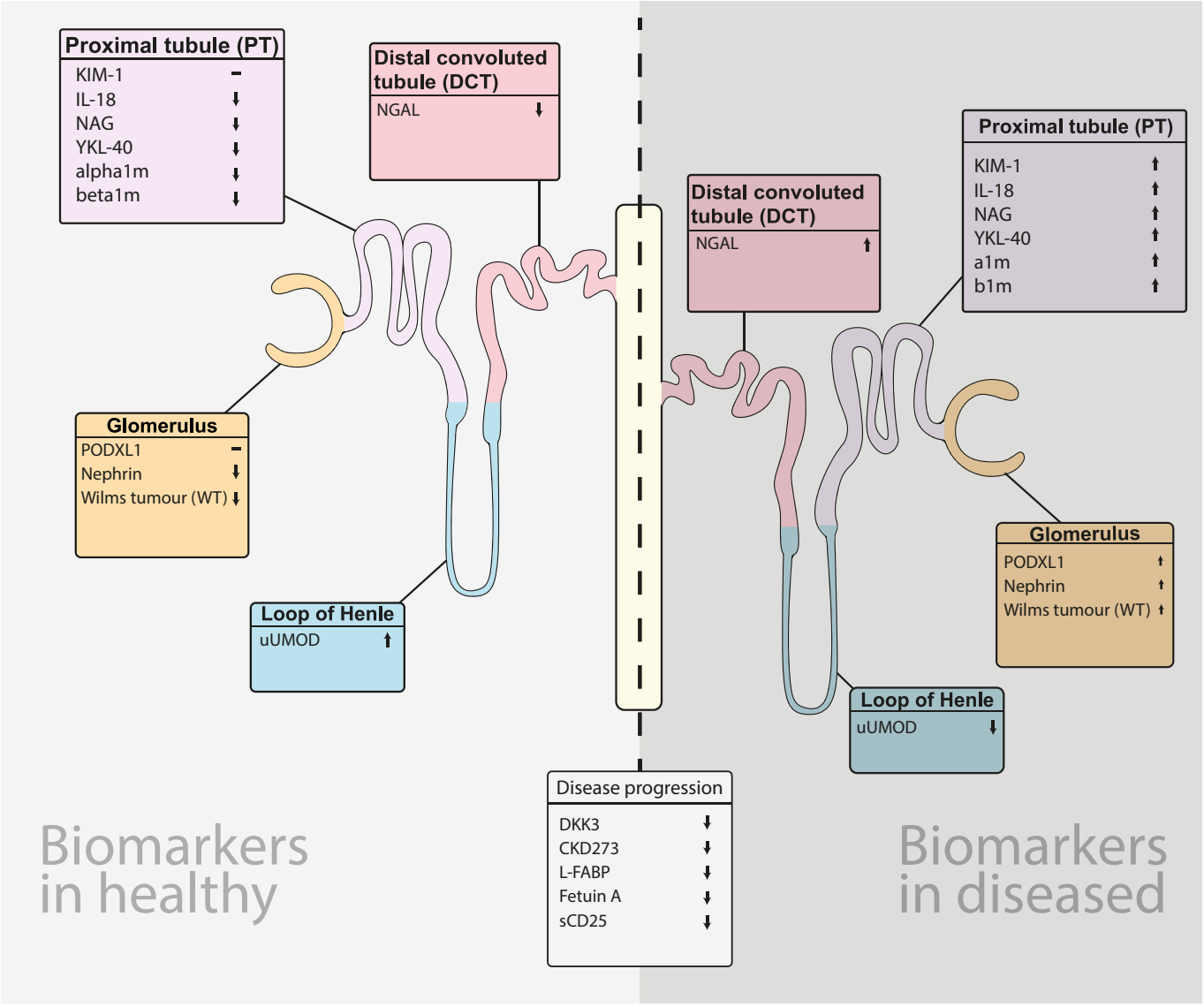

Fig. 1. Biomarkers in different segments of the nephron. The arrows indicate the level of the biomarker compared to the other state (i.e., healthy versus diseased). ↓ indicates a decrease, while ↑ indicates an increase. – denotes that the biomarker is not detected in that state.

2. Approach

Biomarkers hold information on the health of an individual; however, it is necessary to know and determine what information it provides and how to interpret it. Different biomarkers can be indicative of different parts of the nephron and as such, can give information on a certain part of the nephron (Fig. 1). In this review, different biomarkers are described and their suitability for CKD diagnosis, progression, mortality risk and risk of nephrotoxicity. A search was conducted using the terms "urine", "biological marker" and "chronic kidney disease". From this, 53 studies were found, consisting of 37 biomarkers. All articles that were used to discuss the effectivity of the markers can be found in detail in Table 1. To assess the effectivity and usability of the biomarkers for these four categories, a set of criteria has been used that are described in Table 2.

3. Diagnosis

The main challenge of CKD is to diagnose patients early in the disease. This can lead to earlier treatment, which could halt or slow the progression of the disease[67]. A diagnostic biomarker for CKD should be able to detect CKD early in the disease, but also be accurate in diagnosing a patient in any stage of disease. The main biomarkers that were found to be associated with the diagnosis of CKD were KIM-1, α1M, β2M, NGAL and NAG. Each biomarker is explained in the following sections, followed by a summary.

3.1. KIM-1

KIM-1 is a marker for the early nephron, specifically the proximal tubule (PT), where it is shed from damaged cells[59,68]. It is absent in urine when kidneys are healthy[68] and increases with the development of incident CKD[19,65]. It is generally found in the range of picograms in the urine.

The association of KIM-1 with development of incident CKD could make it an ideal candidate to determine kidney injury. However, studies that aim to determine the diagnostic ability of KIM-1 in AKI are inconsistent. Sinkala *et al.* showed that KIM-1 has a receiver operating curve (ROC) and area under the curve (AUC) which is worse than creatinine [51], even though other studies show higher AUCs[25,69]. The discrepancy between the studies of Sinkala *et al.* and Han *et al.* is also seen in the reported sensitivity and specificity of the biomarker. At a cut-off of 3.1 ng/mL Sinkala *et al.* reported a sensitivity of 44.1 and a specificity of 67.6; while, at a cut-off of 2.0 ng/mg Ucr Han *et al.* reported a sensitivity of 65 and a specificity of 42[25,51]. The discrepancies between the studies could be caused by the different populations, as the study by Han *et al.* solely observed the role of KIM-1 in AKI, while Sinkala *et al.* investigated KIM-1 for AKI and CKD. Moreover, the study of Han *et al.* used creatinine to normalize the KIM-1 concentrations, while this is not described in the study of Sinkala *et al.*

Even though there are some inconsistencies between certain studies, KIM-1′s linked expression to damaged kidneys still makes it a promising marker for CKD.

3.2. α1M and β2M

α1M and β2M are two low-molecular weight proteins (LMWP) that are excreted by the kidney. They are markers for the proximal tubule (PT), and they are not reabsorbed by the kidney in case of damaged PT cells (Fig. 2)[21,28]. α1m and β2m concentrations in the urine range between 0.6 ng/ml to 22 mg/L and 78.3 ng/mL to 95 ng/mL, respectively.

Intensive blood pressure lowering (<120 mmHg) has been shown to decrease the risk of major cardiovascular events in comparison with standard blood pressure lowering (<140 mmHg). However, a higher incidence of CKD has been reported in the intensive blood pressure lowering group. To determine kidney injury in these groups, a panel of biomarkers, including α1M and β2M, were used. Conversely, levels of α1M and β2M among others, decreased in the intensive arm compared to standard. This indicates that the changes in eGFR might not be due to damage, and it is hypothesized that the eGFR decline might instead be due to benign changes in blood flow[65]. In addition, β2M is related to changes in eGFR, with levels in CKD patients being associated with faster eGFR decline. However, its levels only markedly increase at the later stages, stage 4 and 5, of the disease[21].

Since β2M increases too late in CKD development, the biomarker is less suitable for early diagnosis of CKD. For α1M, it is unclear in which stage of disease levels start to change. However, since α1M is released in a similar mechanism as β2M, it is likely that this biomarker will also start to increase late in CKD development[21,28].

3.3. NAG

NAG is a marker for the PT, and it is shed by damaged cells in the PT [32]. In the studies found, NAG was measured in different samples including spot urine and 24-hour urine, making it difficult to determine a proper range. NAG is only mildly correlated with the eGFR[58], and its activity can be affected by nephrotoxins which changes its urinary levels [32,59]. This makes NAG less reliable as a marker for CKD. Nevertheless, NAG has been described as a biomarker for AKI[58], generally, AKI will occur suddenly, leading to a steep decrease in kidney function. In CKD, this kidney function decline occurs slowly. Sudden and extreme changes may lead to a stronger release of a biomarker, while a slow effect might lead to low, non-detectable changes.

3.4. NGAL

NGAL is considered a marker for the distal convoluted tubule (DCT) and it is shed from damaged DCT cells[32]. NGAL was measured in different samples including spot and 24-hour urine, making it difficult to determine a range. Laws *et al.* showed that the NGAL concentration in urine increases with a decline in eGFR[32]. In addition, urinary NGAL is better correlated to GFR than serum creatinine, which might translate well in its ability to identify early GFR loss[70]. As a decline in early eGFR could be used as an early indication of CKD, NGAL is an interesting marker for early disease detection.

NGAL does have a high within-subject variation, which could affect the accuracy[19]. The high within-subject variant might prevent easy implementation of the urinary biomarker, since it will be more difficult to determine correct reference ranges.

3.5. Summary

The main biomarkers that were found to be associated with the diagnosis of CKD were KIM-1, α1M, β2M, NAG and NGAL. All these markers are considered tubular markers and, as a result, are more sensitive to tubular insults than glomerular insults[21,28,32,59,68]. They are released by different parts of the nephron and by different mechanisms as shown in respectively Figs. 1 and 2. In addition, all the markers increase when developing a disease. Their initial concentration and its increase with diseases however differs.

Of these biomarkers, KIM-1 is the most promising marker for diagnosing CKD, followed by NGAL. The concentration of KIM-1 and NGAL both increase with development of disease. When using NGAL, however, its high within-subject variation should be considered. This variation is much lower for KIM-1[19].

4. Progression

Patients with CKD can have stable disease for years and suddenly progress to further kidney function loss. Since this occurs suddenly, it is often not recognized in time. It is crucial to identify a biomarker that can

Table 1
Characteristics of the 53 included studies.

First author, year	Biomarker-related findings	Urinary biomarker (s)	Urine sample type	Sample population	Study design	N (male %)	Mean range of biomarker in study population at baseline, not control (unit)
Ascher et al [16]., 2022	Lower levels of UMOD and higher levels of MCP-1 and NGAL, were associated with a risk of adverse kidney events.	α1m, β2m, UMOD, IL-18, KIM-1, NGAL, MCP-1, YKL-40	Spot urine*	CKD	IS	2377 (n.a.)	Not reported
Ben-Dov et al [17]., 2014	Mir-1(4) and Mir-133b(2) played a role in the repression of ADPKD	miRNAs	Spot urine*	ADPKD, CKD	OC	40 (50)	Not reported
Campbell et al[18]., 2012	NGAL poorly correlated with RBPCR or CCR; indicating that they may reflect different types of tubular dysfunction.	PCR, ACR, RBP, NGAL	Spot urine	HIV-positive patients	OC	317 (n. a.)	Protein-creatinine: 82.8 (mg/g creatinine) Albumin-creatinine: 10.3 (mg/g creatinine) RBP: 66.4 (μg/g creatinine) NGAL: 17,993 (ng/g creatinine)
Carter et al [19]., 2016	Urinary biomarkers exhibited a higher CV_i compared to blood biomarkers, creatinine adjustment reduced the within-subject variability.	NAG, α1m, NGAL, KIM-1, Alb, IL-18, TIMP-2	Random urine sample	CKD	OC	80 (n. a.)	NAG: 360 (μg/L) α1m: 22 (mg/L) NGAL: 32 (μg/L) KIM-1: 1.04 (μg/L) Alb: 160.4 (mg/L) IL-18: 39.4 (ng/L) TIMP-2: 2.9 (μg/L)
Chen et al [20]., 2018	uDcR2/cre levels were associated with tubulointerstitial injury.	uDcR2, NAG, ACR	Midstream morning urine samples	CKD, IgA nephropathy, DN, FSGS	OC	72 (n. a.)	NAG: 7.5 (U/Cr) uDcR: 2 67.5 (ng/g Cr) albumin-creatinine: 74.9 (mg/g Cr)
Donadio [21], 2010	uBTP was increased in CKD patients, starting from stage 2.	Creatinine, BTP, Cys, β2M, RBP, Alb.	Fasted morning urine	CKD at any stage	OC	295 (53.6)	Not reported.
Fuhrman et al[22]., 2017	Urinary protein to creatinine ratio, albumin-creatinine ratio and u-non-alb/cr were associated with progressive decline in eGFR or initiation of renal replacement therapy.	PCR, ACR and Unon-alb/cr	Spot urine	Children eGFR 30 – 75 ml/min per 1.73 m^3.	OC	540 (60)	Protein-creatinine: 0.32 (mg/mg creatinine) Albumin-creatinine: 112 (mg/g creatinine) Albumin-protein: 0.44 (mg/mg protein) Nonalbu-creatinine: 167.6 (mg/g creatinine)
Gupta et al [23]., 2014	sCD25 rose in patients experiencing relapse or worsening of disease, it falls in patients with good response.	Urinary sCD25	Spot urine	SLE	OC	119 (7.6)	741.1 (pg/mg creatinine)
Haase-Fielitz et al[24]., 2011	Urine hepcidin levels were higher in patients who did not develop AKI after CPB. Pre-operative levels post-operative were associated with AKI.	Hepcidin	Spot urine	Patients at risk of postoperative AKI	OC	100 (n. a.)	120 ng/mg
Han et al [25]., 2008	KIM-1 levels are increased in patients with AKI, even more than in patients with CKD and normal controls.	KIM-1	Spot urine*	AKI	CS	84 (55)	3.3 ng/mg creatinine
Ix et al[7]., 2017	A1M and MCP-1 levels were associated with risk of allograft failure. PIIINP and PINP were found not to be associated with a risk of allograft failure.	α1m, MCP-1, PIIINP, PINP	Spot urine	Kidney transplant patients	CC	699 (n. a.)	Albumin-creatinine: 24.5 (mg/g creatinine) Further not reported.
Jantos-Siwy et al[26]., 2009	Quantification of urinary peptide levels can occur through a set of peptides that can be detected with low variability. 29 peptides offer a robust method of normalisation, more than using 7 peptides.	7 urinary collagen peptides	24-hour urine, spot urine	DN, macroalbuminuria, MGN, FSGS, vasculitis, IgA nephropathy	CS	80 (77.5)	Not reported.
Jotwani et al [27]., 2020	Lower uUMOD levels and higher β2m levels were associated with eGFR decline; this association was weaker in the treatment arm.	UMOD, β2M, α1m	Spot urine*	Blood pressure > 130 mm Hg and CVD risk	IS	2428 (60)	UMOD: 6.5 (ng/mL) β2M: 95 (ng/mL) α1m: 14 (mg/L)

(*continued on next page*)

Table 1 (*continued*)

First author, year	Biomarker-related findings	Urinary biomarker (s)	Urine sample type	Sample population	Study design	N (male %)	Mean range of biomarker in study population at baseline, not control (unit)
Jotwani et al [28]., 2018	PrEP combined with TDF and FTC caused a rise in α1m and total proteinuria, but not with albuminuria.	α1M, Alb, total proteinuria	Spot urine*	HIV-seronegative men MSM and transgender women	IS	200 (100)	α1m: 0.78 (mg/dL) Albumin-creatinine: 7.6 (mg/g creatinine) Protein-creatinine: 72 (mg/g creatinine)
Jotwani et al [29]., 2019	When indexed for creatinine, YKL-40 was associated with an increased risk of CVD.	IL-18, KIM-1, NGAL, MCP-1, YKL-40	Spot urine*	eGFR $\leq$ 60 ml/min/1.73 m^2	IS	2377 (60)	Not reported.
Kamijo et al [30]., 2005	Urinary L-FABP was more sensitive for CKD progression than urinary protein.	L-FABP	Spot urine*	CKD	CS	48 (75)	L-FABP: 107.4 (μg/g creatinine)
Kamijo et al [31]., 2006	Urinary protein levels were not affected by urinary dysfunction; however, L-FABP did change, indicating that it may be a marker for monitoring progression.	L-FABP, NAG, PCR	Spot urine*	CKD	CS	Study 1: 48 (75) Study 2: 71 (49)	Protein-creatinine: 1.3 (g/g creatinine) NAG: 9.3 (IU/g creatinine) L-FABP: 89.3 (μg/g creatinine)
Laws et al [32]., 2015	There were associations between NGAL and NAG and decreases in eGFR.	NGAL, IL-18, NAG, Alb	Spot urine	$\geq$1.4 mg/dL sCrea	CS	284 (88)	NGAL: 7.5 (μg/g creatinine) IL-18: 9.0 (ng/g creatinine) NAG: 1.32 (U/g creatinine)
Mackay et al [33]., 2018	Urinary RBC did not contribute to any of the risk models. 12-month serum creatinine and proteinuria did.	uRBC	Spot urine, 24-hour urine	LN	OS	944 (n. a.)	Not reported.
Malhotra et al[34]., 2019	Intensive BP lowering lead to declines in eGFR and no changes in 8 urinary biomarkers. B2M and A1M were significantly lower.	β2M, α1M, UMOD, IL-18, KIM-1, NGAL, MCP-1, YKL-40, ACR	Urine collected at months 1, 6, 12 and yearly up until month 60	eGFR 20–59 ml/min/ 1.73 m^2	IS	9361 (64.4)	Albumin-creatinine: 21.9 (mg/g creatinine) β2M: 101.9 (ng/g creatinine) α1M: 10.4 (mg/g creatinine) YKL-40: 442.8 (ng/g creatinine) UMOD: 6366.2 (ng/g creatinine) MCP-1: 152.4 (pg/g creatinine) KIM-1: 673.6 (pg/g creatinine)
Markoska et al[35]., 2018	Downregulation of collagen fragments were associated with progressive disease. Fetuin A is associated with CKD progression.	CKD273, fetuin A, OPN	Spot urine*	eGFR $\geq$ 15 ml/min/1.73 m^2	OS	533 (n. a.)	Not reported.
Miller et al [36]., 2013	Supplementation decreased NGAL, L-FABP, NAG and albuminuria; however, no decrease in creatinine-based eGFR.	KIM-1, NGAL, L-FABP, NAG, Alb	24-hour urine	T2DM	IS	31 (n. a.)	KIM-1: 756 (ng/day) NGAL 16.3 (μg/day) L-FABP: 3.9 (μg/day) NAG: 2.0 (units/day) Albumin: 161 (mg/day)
Nadkarni et al[37]., 2018	Patients who developed incident CKD had an eGFR decrease and a rise in IL-18 and YKL-40.	KIM-1, IL-18, YKL-40, MCP-1	Spot urine	T2DM, HbA1C and 2 risk factors for CVD	IS	529 (n. a.)	KIM-1: 680.6 (pg/mL) IL-18: 22.4 (ng/mL) YKL-40: 223.7 (ng/mL) MCP-1: 133.5 (pg/mL)
Nakamura et al[38]., 2007	Urinary levels of L-FABP and 8-OHdG were higher in IgA patients compared to healthy controls.	L-FABP, 8-OHdG	Spot urine, 24-hour urine	IgA nephropathy	IS	24 (54)	L-FABP: 122.5 (μg/g creatinine) 8-OHdG: 22.6 (ng/mg creatinine)
Nakamura et al[39]., 2006	There was a correlation between L-FABP and urinary protein and creatinine clearance. Pitavastatin was effective in reducing urinary protein and L-FABP levels.	NAG, α1M, L-FABP	Spot urine	Mild CKD	IS	30 (60)	NAG: 7.6 (UI/g creatinine) α1M: 9.5 (mg/g creatinine) L-FABP: 84 (μg/g

(*continued on next page*)

Table 1 (*continued*)

First author, year	Biomarker-related findings	Urinary biomarker (s)	Urine sample type	Sample population	Study design	N (male %)	Mean range of biomarker in study population at baseline, not control (unit)
							creatinine)
Nandula et al [40]., 2021	Treated patients exhibited lower podocyte proteins, indicating a protective effect.	Nephrin, Wilm's Tumor, PODXL1	Spot urine	T2DM	OS	29 (n. a.)	Not reported.
Panagiotou et al[41]., 2020	A decline in uNGAL was observed in patients treated with rhC1INH compared to the placebo. This indicates that rhC1INH interferes with the chronic inflammatory processes.	NGAL	Spot urine	eGFR < 50 ml/min/1.73 m^2, undergoing angiography	IS	80 (n. a.)	19.7 (ng/mL)
Parikh et al [42]., 2019	Plasma YKL-40 and KIM-1 could serve as prognostic biomarkers for AKI.	KIM-1, NGAL, IL-18, UMOD, YKL-40, MCP-1	Urine collected 1–2 h prior to angiography	eGFR < 50 ml/min/1.73 m^2, undergoing angiography	LA	797 (n. a.)	KIM-1: 1804 (pg/mL) NGAL: 37 (pg/mL) IL-18: 21 (pg/mL) MCP-1: 205 (pg/mL) UMOD: 2484 (pg/mL) YKL-40: 90 (pg/mL)
Pontillo et al [43]., 2017	CDK273 predicted decline in GFR and progression in disease.	CKD273	Human Urine Proteome Database/*meta*-analysis	T1DM T2DM, CKD	PA	2087 (53.6)	Not reported.
Prkacin et al [44]., 2013	NGAL was shown to be increased in patients who had AKI in the past.	NGAL	Spot urine*	RH	OS	50 (n. a.)	47.2 (μg/L)
Raphael et al [45]., 2018	UAG with added phosphate and sulphate measurements could act as surrogate of urine ammonium.	Urine ammonium	24-hour urine	Hypertensive CKD	IS	1044 (62)	21 (mEq/d)
Ribitsch et al [46]., 2017	10 patients exhibited a rise in uNGAL, of which only one developed AKI.	NGAL	Midstream	CKD undergoing angiography	IS	617 (53.5)	19 (ng/mL)
Sánchez-Álamo et al [47]., 2021	uDKK3 identified patients at high risk for kidney disease progression.	DKK3	Morning spot urine	CKD	PCS	351 (74.6)	2200 (pg/mg creatinine)
Schanstra et al[48]., 2015	The panel CKD273, was associated with risk of progression.	CKD273 classifier	Spot urine*	CKD	CS	1990 (63.3)	Not reported.
Scherzer et al [49]., 2016	NAG, KIM-1 and α1m were the most distinguishing markers to separate patients in clusters and predict CKD and mortality.	NAG, KIM-1, α1m, IL-18, NGAL, ACR, L-FABP, AAG.	Spot urine	HIV, incident CKD	CS	902 (0)	NAG: 0.9 (mU/mL) KIM-1: 199 (pg/mL) α1m: 0.6 (ng/mL) IL-18: 59 (pg/mL) NGAL: 20 (ng/mL) ACR: 10 (mg/g) L-FABP: 1.9 (ng/mL) AAG (μg/mL)
Sezai et al [50]., 2019	Urinary albumin did not show a significant difference between the febuxostat vs. topiroxostat.	Alb	Spot urine	eGFR ≤ 60 ml/min/1.73 m^2	IS	55 (n. a.)	Not reported.
Sinkala et al [51]., 2017	KIM-1 has a worse ROC than serum creatinine and urea for diagnosing CKD and AKI.	KIM-1	Spot urine*	CKD, AKI	OC	80 (60)	Not reported.
Siwy et al [52]., 2019	Lower renal loss after treatment with linagliptin in patients with high-risk determined with CDK273.	CKD273	Midstream morning urine	T2DM	IS	300 (63.6)	Not reported.
Tay et al [53]., 2015	Both the groups experienced an overall reduction in eGFR and AER. This reduction in eGFR is expected as an age-related change.	AER	24-hour urine samples	T2DM	IS	115 (57)	6 (mg/24 h)
Tiryaki et al [54]., 2016	When T2DM patients were treated with calcitrol, uAGT/uCre levels decreased. Calcitrol had a positive effect on eGFR. Moreover, the T2DM patients exhibited higher uAGT levels than healthy controls.	AGT, Cre	Morning spot urine	T2DM, albuminuria	IS	98 (55)	uAGT/Cre: 12.18 (μg/g)
Titan et al [55]., 2011	MCP-1 levels changed with intervention, in contrast to TGF-β and uVEGF. Indicating that MCP-1 may be a better biomarker.	MCP-1, TGF-β, VEGF	24-hour and early morning spot urine	DN	IS	56 (n. a.)	MCP-1: 34.1 (ng/g creatinine) TGF- β: 1.6 (ng/g creatinine) VEGF: 7.1 (ng/g creatinine)

(*continued on next page*)

Table 1 (*continued*)

First author, year	Biomarker-related findings	Urinary biomarker (s)	Urine sample type	Sample population	Study design	N (male %)	Mean range of biomarker in study population at baseline, not control (unit)
Titan et al [56]., 2012	uRBP and uMCP-1 were associated with risk of CKD progression. TGF-β and uVEGF are not associated with renal outcomes in DN and DM.	RBP, MCP-1, TGF-β, VEGF	24-hour and early morning spot urine	DN, DM	RCT	59 (n. a.)	Log MCP-1: 1.6 (ng/g creatinine) Log TGF- β: 0.02 (ng/g creatinine) Log VEGF: 0.9 (ng/g creatinine) RBP: 0.7 (mg/g creatinine)
Troost et al [57]., 2018	Proteinuria was found to be associated with progression to kidney failure in FSGS.	Proteinuria	24-hour or spot urine	FSGS	RCT	312 (n. a.)	Protein-creatinine ratio: 4.2
Vaidya et al [58]., 2008	Median concentrations of cystatin C, HGF, IL-18, IP-10, KIM-1, NAG, NGAL, VEGF and total protein were significantly higher in patients with acute kidney injury.	Urinary protein, NAG, CysC, KIM-1, NGAL, IL-18, HGF, IP-10, VEGF	Spot urine or catheters	AKI	OS	204 (50)	Not reported.
Waanders et al[59]., 2009	Urinary KIM-1 and NAG levels were found to be increased in patients with proteinuria, without diabetes.	KIM-1, NAG	24-hour urine	Non-diabetic CKD	IS	34 (73.5)	Not reported.
Wei et al [60]., 2018	Urinary mtDNA was associated with serum creatinine and proteinuria.	Mitochondrial DNA	Morning urine	Non-diabetic CKD	OS	102 (46)	Not reported.
Weiner et al [61]., 2019	Higher ACR levels were associated with risk of graft failure, CVD and death.	ACR	Spot urine	CKD with risk of CVD	IS	4110 (62.8)	41.1 (mg/g creatinine)
Wu, et al [62]., 2019	Higher uUMCR levels were related to a decreased risk of CKD in patients with gout. uUMCR levels were positively correlated with eGFR in CKD patients with gout.	UMOD	Spot urine	CKD with gout	CS	114 (78)	5.6 (mg/g creatinine)
Xu, et al [63]., 2015	uAGT was higher in patients with eGFR $>$ 90 ml/min/1.73 m^2 compared to patients with $<$ 90 ml/min/1.73 m^2	AGT	First morning urine	CKD	CS	128 (42.2)	2.02 (ng/mg creatinine)
Zewinger et al[64]., 2018	Urinary DKK3 could be used to distinguish CKD patients with eGFR loss compared to those with stable kidney function.	DKK3	Spot urine	eGFR decline	PCS	1228 (n.a.)	33 (pg/mg creatinine)
Zhang et al [65]., 2018	Urinary ACR, KIM-1 and MCP-1 were associated with development of incident CKD and kidney function decline.	ACR, IL-18, KIM-1, NGAL, MCP-1, YKL-40, β2M, α1M, UMOD	Spot urine	CKD, CVD	CC	9361 (50)	ACR: 18.2 (mg/g creatinine) IL-18: 36.9 (pg/mL) KIM-1: 595.9 (pg/mL) NGAL: 25.9 (ng/mL) MCP-1: 160.2 (pg/mL) YKL-40: 660.8 (pg/mL) β2M: 78.3 (ng/mL) α1M: 4.98 (mg/L) UMOD: 9.95 (μg/mL)
Zittema et al [66]., 2017	AVP secretion was increased in later stage ADPKD after thirsting.	AVP	24-hour urine	ADPKD	CS	30 (66.7)	4.4 (mmol/L)

In some cases, specific urine type was not specified, which are denoted with a *.

Abbreviations: α1m, alpha-1-microglobulin; β2m, beta-2-microglobulin; UMOD, uromodulin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin, NGAL; MCP-1, monocyte chemoattractant protein-1; YKL-40, chitinase-3 like 1; miRNAs, microRNAs; protein-to-creatinine ratio, PCR; albumin-to-creatinine ratio, ACR; retinol-binding protein, RBP; creatinine clearance, CCR; N-Acetyl-Beta-D-Glucosaminidase, NAG; tissue inhibitor of metalloproteinases 2, TIMP-2; urinary decoy receptor 2, uDcR2; beta-trace protein, BTP; Cystatin C, CysC; albumin, Alb; Urinary non-albumin creatinine ratio, Unon-alb/cr; Type III procollagen, PIIINP; Type I procollagen, PINP; urinary uromodulin, uUMOD; liver-type fatty acid-binding protein, L-FABP; urinary red blood cells, uRBC; osteopontin, OPN; 8-hydroxy-2′-deoxyguanosine, 8-OHdG; podocalyxin-like protein 1, PODXL1; Dickkopf-3, DKK3; alpha-1-acid-glycoprotein, AAG; angiotensin, AGT; Cre, creatinine; transforming growth factor- β, TGF- β; vascular endothelial growth factor, VEGF; proteinuria, PU; chemokine interferon-inducible protein 10, IP-10; hepatocyte growth factor, HGF; arginine vasopressin, AVP; observational cohort study, OC; intervention study, IS; case cohort study, CC; longitudinal analysis, LA; post-hoc analysis, PA; randomized controlled trial, RCT; prospective cohort study, PCS; cross-sectional, CS; autosomal dominant kidney disease, ADPKD; diabetic nephropathy, DN; focal segmental glomerulosclerosis, FSGS; systemic lupus erythematosus, SLE; membranous nephropathy, MGN; type 2 diabetes mellitus, T2DM; resistant hypertension, RH; diabetes mellitus, DM; acute kidney injury, AKI.

Table 2
Biomarker types and criteria that are used to determine effectivity and usability for CKD.

Biomarker	Criteria
Diagnostic	• Accurately distinguishes healthy from diseased patients. • Early detection of disease in patients.
Progression	• Distinguishes patients between stable and progressive disease. • Marker increases prior to progression of the disease.
Mortality risk	• Predicts patients at risk of hospitalization within a month. • Predicts the cardiovascular risk in patients with CKD.
Nephrotoxicity risk	• Biomarker increase is related to adverse events following medicine use. • Adverse events can be predicted before they occur in the patient.

predict the further loss of kidney function. By using such a biomarker, treatment can be started or adjusted in time to stop or slow the disease progression[67]. A biomarker that is suitable for progression must be able to distinguish between patients with stable and progressive disease, but also change with progression of the disease. The main urinary biomarkers that were found to be associated with the progression of CKD are DKK3, L-FABP, UMOD and CKD273. Below, each of these biomarkers is elaborated upon, followed by a summary.

4.1. DKK3

DKK3 is a glycoprotein, which is expressed in the PT, and that is increased in patients with declining eGFR compared to patients with stable disease[47,64]. In CKD populations, its concentration ranges between 33 pg/mg creatinine and 22,000 pg/mg creatinine. In addition, this biomarker decreases in the period of time patients have stable disease[47,64]. DKK3 levels are correlated with serum creatinine and eGFR in patients with CKD[71], which makes it a promising marker to monitor progression of disease.

4.2. L-FABP

L-FABP is a biomarker that is expressed in the PT and is increased in kidney diseases. High levels of L-FABP are exhibited when the renal function is deteriorating[30,31,39]. Concentration ranges for L-FABP in urine are between 84 and 122.5 μg/g creatinine. However, L-FABP can also be elevated in liver disease patients. Since kidney disease is a common occurrence in liver disease patients, L-FABP in liver disease patients could already be elevated and not be a functional read-out for their kidney disease[31].

4.3. UMOD

UMOD is produced in the thick ascending limb of Henle (TAL) and has renoprotective effects[16,27]. Decreased UMOD levels can indicate declined or impaired kidney function, as it is considered anti-inflammatory, and anti-infective and has electrolyte handling effects [62]. Ranges for UMOD could not be defined, as some studies did normalize for creatinine and others did not. UMOD can be normal even though people suffer from declining kidney function. However, if normalization of UMOD levels would mean that progression is halting and kidney function is recovering, it has wide possibilities as a biomarker.

4.4. CKD273

CKD273 is a new player on the field and has shown very promising

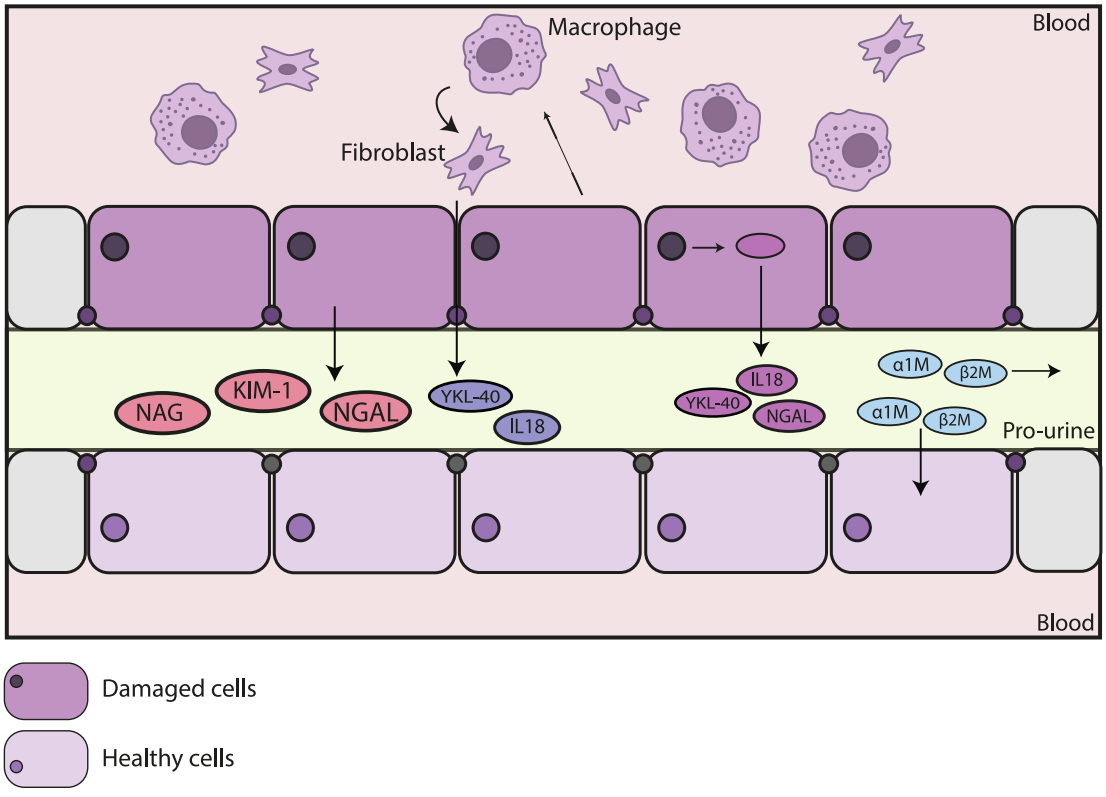

Fig. 2. Different releasing mechanisms of tubular markers. Some biomarkers are shed or release by damaged cells (KIM-1, NGAL, NAG). Others are released by immune cells in the kidney (YKL-40, IL-18). Release by the nucleus and release into the pro-urine also occurs (IL-18, YKL-40, NGAL). In the proximal tubule, damaged cells do not take up some proteins, which causes them to be present in the urine (α1m, β2m). Abbreviations: *α1m, alpha-1-microglobulin; β2m, beta-2-microglobulin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin, NGAL; MCP-1, monocyte chemoattractant protein-1; YKL-40, chitinase-3 like 1; N-Acetyl-Beta-D-Glucosaminidase, NAG.*

results in diabetic nephropathy. It is a proteomics-based classifier consisting of 273 urinary peptides, that can detect diabetic nephropathy years before development of microalbuminuria[72]. Furthermore, another study found that a low CKD273 score was associated with a slow progression of CKD[48]. CKD273 uses cut-off thresholds to predict early and advanced CKD. The sensitivity and specificity in predicting disease progression with the classifier depend upon the used threshold: when using cut-off scores 0.154 and 0.343, sensitivities of respectively 46 % and 42 % are reported[43]. These sensitivities might not be sufficient for a reliable progression marker. Specificities were found to be higher, with 88 % and 94 %, respectively[43].

4.5. Summary

The main urinary biomarkers that were found to be associated with the progression of CKD are DKK3, L-FABP, UMOD and CKD273. DKK3 is the most specific to kidney health, and therefore the most reliable biomarker to use for disease progression. Nevertheless, UMOD is the only protective biomarker, which means that elevated levels are associated with better kidney health. Combining DKK3 with a protective biomarker such as UMOD could lead to an increased sensitivity. Thus, DKK3 and UMOD are both promising markers in determining progression in CKD patients.

5. Mortality risk

Patients with CKD frequently have co-morbidities, including hypertension and high cholesterol[73]. These co-morbidities increase the mortality risk in patients with CKD, defined in this research as, the risk for patients to get hospitalized and the risk to develop cardiovascular diseases (CVD). The strongest predictor and driver of the CVD risk in CKD patients is vascular calcification (VC), a process in which mineral deposition consisting of calcium and phosphate is present in the vasculature. This VC is a silent disease and often undetected, making earlier diagnosis and risk assessment necessary[74]. Traditionally, the mortality risk is often determined using the Framingham prediction model, which is a predictive method that accounts for traditional risk factors including age, smoking, and diabetes. Despite its use in some populations, studies have found that the prediction model lacks accuracy in CKD cohorts[75]. In addition, there is currently no method that can predict the risk of getting hospitalized. Therefore, finding a biomarker that could fill the gap would be essential. A suitable mortality risk biomarker should either predict patients at risk of hospitalization or predict the CVD risk in patients with CKD.

There are two biomarkers described as markers for mortality risk: YKL-40 and IL-18. IL-18 and YKL-40 are both increased in late-stage CKD patients, most likely due to the inflammatory state of the body. The releasing mechanisms of these biomarkers are illustrated in Fig. 2. Each biomarker is explained in the following sections, followed by a summary.

5.1. YKL-40

YKL-40 is involved in tubular injury and repair, and it is found in the renal immune cells[37,65]. In urine, the YKL-40 concentration ranges between 90 pg/mL and 660 pg/mL in different CKD populations. However, YKL-40 is only associated with the risk to get hospitalized and not with the risk to develop CVD events[29].

5.2. IL-18

IL-18 is released by immune cells in the PT of the kidney as a response to injury[32,34]. Its concentration ranges between 36.9 pg/mL and 59 pg/mL. Similar to YKL-40, IL-18 has been associated with hospitalization risk, but not with CVD events[29]. However, even though IL-18 is not described as a suitable biomarker for the risk of developing CVD, it is a key player in VC. It has been shown to induce VC in vascular smooth muscle cells *in vitro*[76]. Furthermore, as IL-18 levels are correlated with AKI, it can be used to differentiate between patients with and without AKI[58]. AKI patients exhibit higher IL-18 levels, and IL-18 could be used to differentiate between patients with and without AKI [58].

5.3. Summary

The definition of mortality risk in this manuscript is the risk for patients to get hospitalized and the risk to develop CVD. Both YKL-40 and IL-18 are promising biomarkers to predict the risk to get hospitalized. However, no biomarkers were found that can directly predict the risk of developing CVD. Therefore, more research is needed to identify a proper biomarker for CVD risk in CKD patients. One of the major risk factors for developing CVD is VC. As such, measuring VC with IL-18, this biomarker could potentially be used as an indirect marker to predict the risk of developing CVD.

6. Nephrotoxicity risk

Patients with CKD are more predisposed to developing nephrotoxicity. For instance, low-level lead exposure can lead to more rapid CKD progression[77]. In addition to nephrotoxicity by lead, compounds and drugs that treat diseases can act as a nephrotoxins. Moreover, in patients without CKD, compounds and drugs can induce AKI which could potentially lead to CKD[78]. Furthermore, since it is important to not affect kidney functioning further in patients with CKD[79]; it is vital to determine the effect of therapeutics on kidney health in healthy and CKD patients. The suitable nephrotoxicity risk biomarker should be able to determine kidney function decline following medicine use and be capable to predict adverse events before they occur in the patient.

IL-18, α1M and MCP-1 have been described that can provide an insight into the nephrotoxicity in patients. Each biomarker is explained in the following sections, followed by a summary.

6.1. IL-18

IL-18, also elaborated on in the mortality risk section, can determine the likelihood of adverse events following anti-hypertensive treatment [16]. Anti-hypertensive treatment is essential for slowing progression of CKD and reducing the cardiovascular risk. Safe blood pressure lowering is essential in CKD, as high blood pressure is a major risk factor for heart disease, stroke and kidney failure. Moreover, in the SPRINT trial, intensive blood pressure lowering to less than 130/80 mmHg, resulted in increasing adverse events[16].

6.2. α1M

α1M as mentioned in the diagnosis section above, is a biomarker for the PT. Jotwani *et al.* showed that α1M can determine tubular toxicity in patients after treatment with tenofovir disoproxil fumurate[28]. The most common cause of mortality and morbidity in HIV-patients includes renal disease[80]. Tenofovir disoproxil fumurate is a first-line treatment for HIV-infected patients, though exposure causes increased risk of proteinuria and rapid decline in kidney function[81]. Thus, monitoring in this patient-group is of extra importance, as tenofovir can cause irreversible kidney toxicity.

6.3. MCP-1

In diabetic nephropathy, MCP-1 is linked with treatment modulation, with worse evolution in patients developing hyperkalemia or acute kidney function deterioration during angiotensin inhibitor use[55]. In CKD populations, its concentrations in urine ranges between 133.5 pg/mL to 205 pg/mL. Angiotensin inhibitors are prescribed often to CKD

patients with hypertension. Since MCP-1 is a measure of treatment modulation in patients with diabetic nephropathy, it is likely that it can also determine the effect of treatment in CKD patients using angiotensin inhibitors.

6.4. Summary

IL-18 and α1M are both biomarkers that are used to determine the effect of specific therapies on the kidney. As IL-18 can provide information on the tubules during anti-hypertensive treatment and α1M can provide information on the toxicity in HIV-patients using tenofovir. MCP-1 is a promising therapeutic biomarker for patients with diabetic nephropathy.

Further research should focus on finding biomarkers for the other commonly used medications by CKD patients, including statins and diuretics. Additionally, urinary biomarkers could also be used for medications that can cause kidney damage. This way, the medicines can be stopped or changed, prior to excessive kidney damage. In addition to assessing toxicity, a biomarker could also identify individuals who are considered "poor responders" to medications. This would offer potential to prevent unnecessary drug usage and aid in finding suitable medication choices.

7. Future perspectives

Urinary biomarkers could be the future of health monitoring in combination with the development of smart toilets. For this purpose, it may be best to create a panel of different biomarkers, since this can provide more information than one biomarker alone. Using a panel of biomarkers can give a wider overview of an individual's health, it can say something about the mortality risk and disease progression for instance. Though, one of the downsides of the biomarkers found in this review is that most are markers of renal damage, as most are only released due to damage to the cells. This could be remedied by using a marker for renal functioning such as creatinine. Another downside to urinary biomarker use, is that it is time consuming for the patient and the health care provider as the urine needs to be collected, sent, measured and saved, making repeated measurements more difficult.

The future of urinalysis may include sampling with a smart toilet, which might enable the use of biomarkers in determining kidney disease. Since sampling would occur every day, more measurements will be taken which will make tracking of patients easier. Moreover, hospital visits for patients could be shortened or lessened, since urine can be sampled at home and results can be sent to a specialist.

However, prior to implementation more research is required. Since the toilet will be using spot measurements, it is necessary to have reference measurements in the toilet in some way. Moreover, to make proper implementation of the urinary biomarkers possible, it is necessary to determine the limit of detection, concentration and what technologies are best for measuring urinary biomarkers.

8. Conclusion

New developments in the field of urinalysis using smart toilets may open up a number of possibilities for urinary biomarkers. This review explored which biomarkers could be used for CKD disease management. KIM-1 is a promising marker for the diagnosis of CKD, whereas DKK3 and UMOD are promising biomarkers for the progression of CKD. Further research should focus on proper implementation of these urinary biomarkers into the smart toilet, by determining concentrations, a proper limit of detection and developing technologies that are able to measure the biomarkers.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Funding

E.K. acknowledges financial support by Provincie Gelderland.

CRediT authorship contribution statement

Esra Canki: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Esther Kho:** Writing – review & editing, Supervision, Conceptualization. **Joost G.J. Hoenderop:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

[1] N.R. Hill, et al., Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis, PLoS One 11 (7) (2016) e0158765.
[2] N.C.F.H. Statistics, *National Center for Health Statistics*, Health, Editor, Hyattsville, MD, 2019.
[3] J. Sundström, et al., Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2· 4 million patients from 11 countries: The CaReMe CKD study, Lancet Regional Health-Europe 20 (2022) 100438.
[4] O.M. Akchurin, Chronic Kidney Disease and Dietary Measures to Improve Outcomes, Pediatr Clin North Am 66 (1) (2019) 247–267, https://doi.org/10.1016/j.pcl.2018.09.007.
[5] H. Shahbaz, M. Gupta, Creatinine Clearance, StatPearls Publishing, Treasure Island (FL), 2022.
[6] M. Mizdrak, et al., Emerging Biomarkers for Early Detection of Chronic Kidney Disease, J. Personalized Med. 12 (4) (2022) 548.
[7] J.H. Ix, et al., Urine Fibrosis Markers and Risk of Allograft Failure in Kidney Transplant Recipients: A Case-Cohort Ancillary Study of the FAVORIT Trial, Am J Kidney Dis 69 (3) (2017) 410–419, https://doi.org/10.1053/j.ajkd.2016.10.019.
[8] M.A. Øvrehus, et al., Urinary proteomics in chronic kidney disease: diagnosis and risk of progression beyond albuminuria, Clin. Proteomics 12 (1) (2015) 21, https://doi.org/10.1186/s12014-015-9092-7.
[9] S. Majumder, M.J. Deen, Smartphone sensors for health monitoring and diagnosis, Sensors 19 (9) (2019) 2164.
[10] S.-M. Park, et al., A mountable toilet system for personalized health monitoring via the analysis of excreta, Nat. Biomed. Eng. 4 (6) (2020) 624–635, https://doi.org/10.1038/s41551-020-0534-9.
[11] M.E. Wasung, L.S. Chawla, M. Madero, Biomarkers of renal function, which and when? Clin. Chim. Acta 438 (2015) 350–357, https://doi.org/10.1016/j.cca.2014.08.039.
[12] K.V. Lemley, An introduction to biomarkers: Applications to chronic kidney disease, Pediatr. Nephrol. 22 (11) (2007) 1849–1859, https://doi.org/10.1007/s00467-007-0455-9.
[13] X. Fuentes-Arderiu, What is a biomarker? It's time for a renewed definition, Clin. Chem. Lab. Med. 51 (9) (2013) 1689–1690, https://doi.org/10.1515/cclm-2013-0240.
[14] R.M. Califf, Biomarker definitions and their applications, Exp Biol Med (maywood) 243 (3) (2018) 213–221, https://doi.org/10.1177/1535370217750088.
[15] W.R. Zhang, C.R. Parikh, Biomarkers of Acute and Chronic Kidney Disease, Annu Rev Physiol 81 (2019) 309–333, https://doi.org/10.1146/annurev-physiol-020518-114605.
[16] S.B. Ascher, et al., Kidney tubule health, mineral metabolism and adverse events in persons with CKD in SPRINT, Nephrol Dial Transplant 37 (9) (2022) 1637–1646, https://doi.org/10.1093/ndt/gfab255.

[17] I.Z. Ben-Dov, et al., Urine microRNA as potential biomarkers of autosomal dominant polycystic kidney disease progression: description of miRNA profiles at baseline, PLoS One 9 (1) (2014) e86856.
[18] L.J. Campbell, et al., Total protein, albumin and low-molecular-weight protein excretion in HIV-positive patients, BMC Nephrol 13 (2012) 85, https://doi.org/10.1186/1471-2369-13-85.
[19] J.L. Carter, et al., Biological Variation of Plasma and Urinary Markers of Acute Kidney Injury in Patients with Chronic Kidney Disease, Clin Chem 62 (6) (2016) 876–883, https://doi.org/10.1373/clinchem.2015.250993.
[20] J. Chen, et al., High-dose HOOK effect in urinary DcR2 assay in patients with chronic kidney disease, Clin Biochem 58 (2018) 32–36, https://doi.org/10.1016/j.clinbiochem.2018.06.001.
[21] C. Donadio, Serum and urinary markers of early impairment of GFR in chronic kidney disease patients: diagnostic accuracy of urinary beta-trace protein, American J. Physiol.-Renal Physiol. 299 (6) (2010) F1407–F1423, https://doi.org/10.1152/ajprenal.00507.2009.
[22] D.Y. Fuhrman, et al., Albuminuria, proteinuria, and renal disease progression in children with CKD, Clin. J. Am. Soc. Nephrol. 12 (6) (2017) 912–920, https://doi.org/10.2215/CJN.11971116.
[23] R. Gupta, et al., Urinary sCD25 as a biomarker of lupus nephritis disease activity, Lupus 24 (3) (2015) 273–279, https://doi.org/10.1177/0961203314555174.
[24] A. Haase-Fielitz, et al., Urine hepcidin has additive value in ruling out cardiopulmonary bypass-associated acute kidney injury: an observational cohort study, Crit Care 15 (4) (2011) R186, https://doi.org/10.1186/cc10339.
[25] W.K. Han, et al., Urinary biomarkers in the early diagnosis of acute kidney injury, Kidney Int 73 (7) (2008) 863–869, https://doi.org/10.1038/sj.ki.5002715.
[26] J. Jantos-Siwy, et al., Quantitative Urinary Proteome Analysis for Biomarker Evaluation in Chronic Kidney Disease, J. Proteome Res. 8 (1) (2009) 268–281, https://doi.org/10.1021/pr800401m.
[27] V. Jotwani, et al., Tubular Biomarkers and Chronic Kidney Disease Progression in SPRINT Participants, Am J Nephrol 51 (10) (2020) 797–805, https://doi.org/10.1159/000509978.
[28] V. Jotwani, et al., Pre-exposure Prophylaxis With Tenofovir Disoproxil Fumarate/Emtricitabine and Kidney Tubular Dysfunction in HIV-Uninfected Individuals, J Acquir Immune Defic Syndr 78 (2) (2018) 169–174, https://doi.org/10.1097/qai.0000000000001654.
[29] V.K. Jotwani, et al., Urinary Biomarkers of Tubular Damage Are Associated with Mortality but Not Cardiovascular Risk among Systolic Blood Pressure Intervention Trial Participants with Chronic Kidney Disease, Am J Nephrol 49 (5) (2019) 346–355, https://doi.org/10.1159/000499531.
[30] A. Kamijo, et al., Clinical evaluation of urinary excretion of liver-type fatty acid-binding protein as a marker for the monitoring of chronic kidney disease: a multicenter trial, J Lab Clin Med 145 (3) (2005) 125–133, https://doi.org/10.1016/j.lab.2004.12.003.
[31] A. Kamijo, et al., Urinary liver-type fatty acid binding protein as a useful biomarker in chronic kidney disease, Mol. Cell. Biochem. 284 (1–2) (2006) 175–182, https://doi.org/10.1007/s11010-005-9047-9.
[32] R.L. Laws, et al., Biomarkers of Kidney Injury among Nicaraguan Sugarcane Workers, Am. J. Kidney Dis. 67 (2) (2016) 209–217, https://doi.org/10.1053/j.ajkd.2015.08.022.
[33] M. Mackay, et al., Establishing Surrogate Kidney End Points for Lupus Nephritis Clinical Trials: Development and Validation of a Novel Approach to Predict Future Kidney Outcomes, Arthritis Rheumatol. 71 (3) (2019) 411–419, https://doi.org/10.1002/art.40724.
[34] R. Malhotra, et al., Effects of Intensive Blood Pressure Lowering on Kidney Tubule Injury in CKD: A Longitudinal Subgroup Analysis in SPRINT, Am J Kidney Dis 73 (1) (2019) 21–30, https://doi.org/10.1053/j.ajkd.2018.07.015.
[35] K. Markoska, et al., Urinary peptide biomarker panel associated with an improvement in estimated glomerular filtration rate in chronic kidney disease patients, Nephrol. Dial. Transplant. 33 (5) (2018) 751–759, https://doi.org/10.1093/ndt/gfx263.
[36] E.R. Miller 3rd, et al., The effects of n-3 long-chain polyunsaturated fatty acid supplementation on biomarkers of kidney injury in adults with diabetes: results of the GO-FISH trial, Diabetes Care 36 (6) (2013) 1462–1469, https://doi.org/10.2337/dc12-1940.
[37] G.N. Nadkarni, et al., Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury: Findings From the ACCORD Trial Study Participants, Am J Kidney Dis 73 (1) (2019) 31–38, https://doi.org/10.1053/j.ajkd.2018.07.016.
[38] T. Nakamura, et al., Beneficial effects of olmesartan and temocapril on urinary liver-type fatty acid-binding protein levels in normotensive patients with immunoglobin A nephropathy, Am J Hypertens 20 (11) (2007) 1195–1201, https://doi.org/10.1016/j.amjhyper.2007.06.003.
[39] T. Nakamura, et al., Effect of pitavastatin on urinary liver-type fatty-acid-binding protein in patients with nondiabetic mild chronic kidney disease, Am J Nephrol 26 (1) (2006) 82–86, https://doi.org/10.1159/000091956.
[40] S.R. Nandula, et al., Role of Canagliflozin on function of CD34+ve endothelial progenitor cells (EPC) in patients with type 2 diabetes, Cardiovasc Diabetol 20 (1) (2021) 44, https://doi.org/10.1186/s12933-021-01235-4.
[41] A. Panagiotou, et al., A Randomized Trial of Recombinant Human C1-Esterase-Inhibitor in the Prevention of Contrast-Induced Kidney Injury, JACC Cardiovasc Interv 13 (7) (2020) 833–842, https://doi.org/10.1016/j.jcin.2019.11.021.
[42] C.R. Parikh, et al., Kidney Biomarkers of Injury and Repair as Predictors of Contrast-Associated AKI: A Substudy of the PRESERVE Trial, Am J Kidney Dis 75 (2) (2020) 187–194, https://doi.org/10.1053/j.ajkd.2019.06.011.
[43] C. Pontillo, et al., Prediction of Chronic Kidney Disease Stage 3 by CKD273, a Urinary Proteomic Biomarker, Kidney International Reports 2 (6) (2017) 1066–1075, https://doi.org/10.1016/j.ekir.2017.06.004.
[44] I. Prkacin, et al., Importance of urinary NGAL, serum creatinine standardization and estimated glomerular filtration rate in resistant hypertension, Coll Antropol 37 (3) (2013) 821–825.
[45] K.L. Raphael, S. Gilligan, J.H. Ix, Urine anion gap to predict urine ammonium and related outcomes in kidney disease, Clin. J. Am. Soc. Nephrol. 13 (2) (2018) 205–212, https://doi.org/10.2215/CJN.03770417.
[46] W. Ribitsch, et al., Neutrophil gelatinase-associated lipocalin (NGAL) fails as an early predictor of contrast induced nephropathy in chronic kidney disease (ANTI-CI-AKI study), Sci Rep 7 (2017) 41300, https://doi.org/10.1038/srep41300.
[47] B. Sanchez-Alamo, et al., Urinary Dickkopf-3: a new biomarker for CKD progression and mortality, Nephrol. Dial. Transplant. 36 (12) (2021) 2199–2207, https://doi.org/10.1093/ndt/gfab198.
[48] J.P. Schanstra, et al., Diagnosis and Prediction of CKD Progression by Assessment of Urinary Peptides, J Am Soc Nephrol 26 (8) (2015) 1999–2010, https://doi.org/10.1681/asn.2014050423.
[49] R. Scherzer, et al., Use of urine biomarker-derived clusters to predict the risk of chronic kidney disease and all-cause mortality in HIV-infected women, Nephrol. Dial. Transplant. 31 (9) (2016) 1478–1485, https://doi.org/10.1093/ndt/gfv426.
[50] A. Sezai, et al., Changeover trial of febuxostat and topiroxostat for hyperuricemia with cardiovascular disease: Sub-analysis for chronic kidney disease (trofeo ckd trial), Ann. Thorac. Cardiovasc. Surg. 26 (4) (2020) 202–208, https://doi.org/10.5761/atcs.oa.19-00162.
[51] M. Sinkala, et al., Performance Characteristics of Kidney Injury Molecule-1 In Relation to Creatinine, Urea, and Microalbuminuria in the Diagnosis of Kidney Disease, Int J Appl Basic Med Res 7 (2) (2017) 94–99, https://doi.org/10.4103/2229-516x.205811.
[52] J. Siwy, et al., Urinary Proteomics as a Tool to Identify Kidney Responders to Dipeptidyl Peptidase-4 Inhibition: A Hypothesis-Generating Analysis from the MARLINA-T2D Trial, Proteomics Clin Appl 13 (2) (2019) e1800144.
[53] J. Tay, et al., Long-Term Effects of a Very Low Carbohydrate Compared With a High Carbohydrate Diet on Renal Function in Individuals With Type 2 Diabetes: A Randomized Trial, Medicine (Baltimore) 94 (47) (2015) e2181.
[54] Ö. Tiryaki, C. Usalan, Z.A. Sayiner, Vitamin D receptor activation with calcitriol for reducing urinary angiotensinogen in patients with type 2 diabetic chronic kidney disease, Ren Fail 38 (2) (2016) 222–227, https://doi.org/10.3109/0886022x.2015.1128250.
[55] S.M. Titan, et al., ACEI and ARB combination therapy in patients with macroalbuminuric diabetic nephropathy and low socioeconomic level: a double-blind randomized clinical trial, Clin Nephrol 76 (4) (2011) 273–283, https://doi.org/10.5414/cn107013.
[56] S.M. Titan, et al., Urinary MCP-1 and RBP: independent predictors of renal outcome in macroalbuminuric diabetic nephropathy, J Diabetes Complications 26 (6) (2012) 546–553, https://doi.org/10.1016/j.jdiacomp.2012.06.006.
[57] J.P. Troost, et al., An outcomes-based definition of proteinuria remission in focal segmental glomerulosclerosis, Clin. J. Am. Soc. Nephrol. 13 (3) (2018) 414–421, https://doi.org/10.2215/CJN.04780517.
[58] V.S. Vaidya, et al., Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans, Clin Transl Sci 1 (3) (2008) 200–208, https://doi.org/10.1111/j.1752-8062.2008.00053.x.
[59] F. Waanders, et al., Effect of renin-angiotensin-aldosterone system inhibition, dietary sodium restriction, and/or diuretics on urinary kidney injury molecule 1 excretion in nondiabetic proteinuric kidney disease: a post hoc analysis of a randomized controlled trial, Am J Kidney Dis 53 (1) (2009) 16–25, https://doi.org/10.1053/j.ajkd.2008.07.021.
[60] Z.P. Wei, et al., Urinary mitochondrial DNA level as a biomarker of tissue injury in non-diabetic chronic kidney diseases, BMC Nephrol. (2018) 19, https://doi.org/10.1186/s12882-018-1178-9.
[61] D.E. Weiner, et al., Albuminuria and Allograft Failure, Cardiovascular Disease Events, and All-Cause Death in Stable Kidney Transplant Recipients: A Cohort Analysis of the FAVORIT Trial, Am J Kidney Dis 73 (1) (2019) 51–61, https://doi.org/10.1053/j.ajkd.2018.05.015.
[62] C.H. Wu, et al., Urinary Uromodulin/Creatinine Ratio as a Potential Clinical Biomarker for Chronic Kidney Disease Patients with Gout: A Pilot Study, Med. Princ. Pract. 28 (3) (2019) 273–279, https://doi.org/10.1159/000496844.
[63] Z. Xu, B. Xu, C. Xu, Urinary angiotensinogen as a potential biomarker of intrarenal renin-angiotensin system activity in Chinese chronic kidney disease patients, Ir. J. Med. Sci. 184 (2) (2015) 297–304, https://doi.org/10.1007/s11845-014-1103-6.
[64] S. Zewinger, et al., Dickkopf-3 (DKK3) in Urine Identifies Patients with Short-Term Risk of eGFR Loss, J Am Soc Nephrol 29 (11) (2018) 2722–2733, https://doi.org/10.1681/asn.2018040405.
[65] W.R. Zhang, et al., Kidney Damage Biomarkers and Incident Chronic Kidney Disease During Blood Pressure Reduction: A Case-Control Study, Ann Intern Med 169 (9) (2018) 610–618, https://doi.org/10.7326/m18-1037.
[66] D. Zittema, et al., Urine Concentrating Capacity, Vasopressin and Copeptin in ADPKD and IgA Nephropathy Patients with Renal Impairment, PLoS One 12 (1) (2017) e0169263.
[67] M.T. James, B.R. Hemmelgarn, M. Tonelli, Early recognition and prevention of chronic kidney disease, Lancet 375 (9722) (2010) 1296–1309, https://doi.org/10.1016/S0140-6736(09)62004-3.
[68] J.V. Bonventre, Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more, Nephrol. Dial. Transplant. 24 (11) (2009) 3265–3268, https://doi.org/10.1093/ndt/gfp010.

[69] V.S. Sabbisetti, et al., Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes, J Am Soc Nephrol 25 (10) (2014) 2177–2186, https://doi.org/10.1681/asn.2013070758.
[70] D. Bolignano, et al., Neutrophil Gelatinase-Associated Lipocalin Reflects the Severity of Renal Impairment in Subjects Affected by Chronic Kidney Disease, Kidney Blood Press. Res. 31 (4) (2008) 255–258, https://doi.org/10.1159/000143726.
[71] P. Dziamałek-Macioszczyk, et al., Patterns of Dickkopf-3 Serum and Urine Levels at Different Stages of Chronic Kidney Disease, J. Clin. Med. 12 (14) (2023) 4705.
[72] P. Zürbig, et al., Urinary Proteomics for Early Diagnosis in Diabetic Nephropathy, Diabetes 61 (12) (2012) 3304–3313, https://doi.org/10.2337/db12-0348.
[73] W.C. Lee, et al., The Number of Comorbidities Predicts Renal Outcomes in Patients with Stage 3–5 Chronic Kidney Disease, J Clin Med 7 (12) (2018), https://doi.org/10.3390/jcm7120493.
[74] C. Marreiros, C. Viegas, D. Simes, Targeting a Silent Disease: Vascular Calcification in Chronic Kidney Disease, Int. J. Mol. Sci. 23 (24) (2022) 16114.
[75] E. Weiner Daniel, et al., The Framingham Predictive Instrument in Chronic Kidney Disease, J. Am. Coll. Cardiol. 50 (3) (2007) 217–224, https://doi.org/10.1016/j.jacc.2007.03.037.
[76] K. Zhang, et al., Interleukin-18 Enhances Vascular Calcification and Osteogenic Differentiation of Vascular Smooth Muscle Cells Through TRPM7 Activation, Arterioscler. Thromb. Vasc. Biol. 37 (10) (2017) 1933–1943, https://doi.org/10.1161/ATVBAHA.117.309161.
[77] M.A. Perazella, Renal Vulnerability to Drug Toxicity, Clin. J. Am. Soc. Nephrol. 4 (7) (2009) 1275–1283, https://doi.org/10.2215/cjn.02050309.
[78] M.A. Perazella, Drug use and nephrotoxicity in the intensive care unit, Kidney Int. 81 (12) (2012) 1172–1178, https://doi.org/10.1038/ki.2010.475.
[79] A. Bosi, et al., Use of nephrotoxic medications in adults with chronic kidney disease in Swedish and US routine care, Clin. Kidney J. 15 (3) (2021) 442–451, https://doi.org/10.1093/ckj/sfab210.
[80] J. Phair, F. Palella, Renal disease in HIV-infected individuals, Curr Opin HIV AIDS 6 (4) (2011) 285–289, https://doi.org/10.1097/COH.0b013e3283476bc3.
[81] R. Scherzer, et al., Association of tenofovir exposure with kidney disease risk in HIV infection, AIDS 26 (7) (2012) 867–875, https://doi.org/10.1097/QAD.0b013e328351f68f.