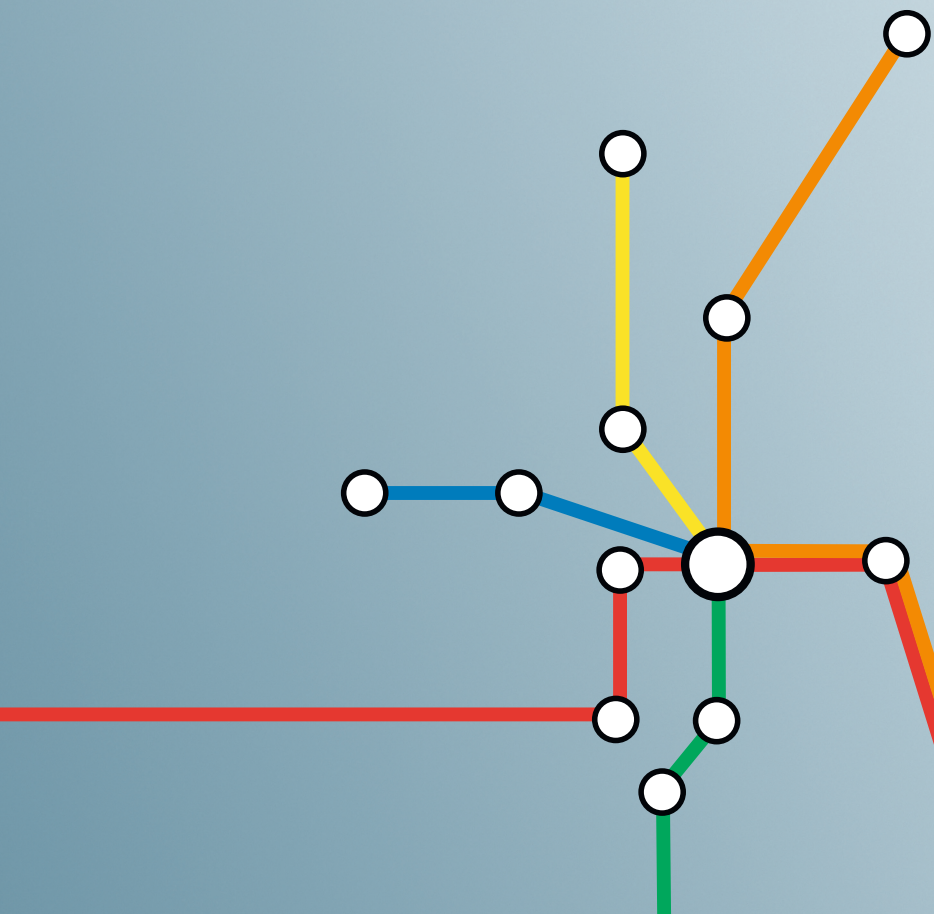
Metabolomics to predict progression in chronic kidney disease

Dekker, S.E.I.



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Urinary biomarkers as predictors for disease progression in CKD patients with ADPKD: a narrative review

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease with a prevalence of 3 to 4 per 10.000.[1] It is characterized by progressive cyst formation in both kidneys and variable renal function decline.[2] ADPKD frequently leads to end stage renal disease (ESRD) between the fourth and seventh decade of life.[3] The disease is caused by mutations in the *PKD1* (78% of cases) or *PKD2* gene (15% of cases).[4] There are many different pathogenic mutations in these genes. Patients with a mutation in the *PKD1* gene, especially a truncating mutation, generally reach ESRD at a younger age than those with a *PKD2* mutation.[2] However, even in patients with the same genotype, the phenotype may vary significantly.[5,6] Research into the pathogenesis of ADPKD has led to preclinical and clinical studies of drugs to treat ADPKD.[7-10] The vasopressin V2 receptor (V2R) antagonist tolvaptan is currently the only approved drug for ADPKD.[11] Two randomized clinical trials have shown that tolvaptan slows the decline of the estimated glomerular filtration rate (eGFR).[7,8] Patients with rapid disease progression benefit most from treatment. The advent of treatment options requires identification of those who are likely to have fast progressing disease, especially in the early-stage disease prior to progressive renal function decline. Predicting disease progression is important for clinicians to inform patients about their prognosis and to support evidence-based decisions for treatment strategies. In clinical ADPKD studies, various renal endpoints have been used to assess disease progression.

Renal endpoints in clinical studies

ESRD, defined as treatment with either maintenance dialysis or kidney transplantation, or doubling of serum creatinine are established clinical endpoints for chronic kidney disease (CKD).[12] However, these occur relatively late in the disease process, which limit their feasibility in clinical studies due to requirements of long duration of follow-up and large sample sizes. A series of studies show that lower thresholds including 30% and 40% decline (time-to-event outcome) in eGFR (by CKD-EPI equation)[13] might be applicable as surrogate clinical endpoints in some settings.[14] However, if baseline eGFR is high or disease progression slow, the limitations regarding the duration of follow-up and sample size persist. The slope of the decline in eGFR has also been evaluated as a surrogate endpoint for CKD progression. The 2-year eGFR slope (annual change in eGFR using ordinary least squares linear regression) is significantly associated with subsequent development of ESRD, also in patients with eGFR > 60 ml/min/1.73m². The association gets stronger when the follow-up is longer (up to 3 years).[15] Another study used statistical simulations of GFR trajectories to define settings in which the eGFR slope (mean rate of change in eGFR) is a strong surrogate endpoint for clinical trials in patients with CKD. In particular when there is no acute therapy effect, the

baseline eGFR is high, and CKD progresses rapidly, the use of slope-based endpoints reduces the required sample sizes and duration of follow-up compared with time-to-event (30% or 40% GFR decline) and clinical (ESRD) endpoints.[16] In large ADPKD trials the eGFR slope has been used as a primary or secondary endpoint.[7,9,17] For ADPKD, another candidate surrogate endpoint has been established: total kidney volume (TKV). Longitudinal studies show that GFR trajectories are nonlinear or relatively stable for prolonged periods in a substantial fraction of ADPKD patients.[18,19] This limits the use of the eGFR slope as an endpoint. TKV has proven to be a good primary or secondary study endpoint in addition to the other endpoints. All these endpoint are not only useful as renal outcomes in clinical trials, but are also the most relevant outcomes for risk prediction models[20] and form the basis for risk stratification by clinicians.[21] In the design of a clinical study of patients with ADPKD or CKD, the optimal endpoint should be chosen based on the population that is to be studied, the intended duration of follow-up and the burden and cost of obtaining the necessary data.

Conventional markers in ADPKD management

In ADPKD various factors have been considered as predictors of the renal outcome, including age in relation to eGFR or to TKV and the affected gene and the type of mutation.[21-23] eGFR indexed for age provides important information on disease progression. It forms the first step in a decision-making algorithm, which includes various indicators of rapid disease progression in a descending order of reliability, for selecting patients who are eligible for treatment with tolvaptan.[24] However, using eGFR for evaluating progression in early-stage ADPKD is limited, because it remains relatively stable for a long period of time and irreversible kidney damage due to progressive cyst formation precedes GFR decline.[19,25] *TKV* is an alternative indicator of disease progression, and is not only widely accepted as a surrogate clinical endpoint, but also as a prognostic biomarker to select patients for clinical studies and for treatment.[26,27] TKV increases at a young age.[28] MRI-derived baseline TKV adjusted for height (htTKV) accurately predicts development of CKD stage 3 within 8 years (area under the curve [AUC] = 0.84).[28] Its predictive value has been validated in several follow-up studies[29-31] and different cohorts,[30,32,33] qualifying TKV as a risk stratification tool in ADPKD (30% decline in eGFR or reaching ESRD at year 3, AUC = 0.71 and 0.94, respectively[30]; reaching CKD stage 3, AUC = 0.79[32]; annual eGFR decline ≥ –3.0 ml/min/1.73m², AUC = 0.71).[33] The Mayo ADPKD classification has been developed to improve the prognostic capability of TKV.[34] A single htTKV value (by CT or MRI) and age at baseline are used to classify patients as 1A–1E. The frequency of ESRD at 10 years increased from subclass 1A (2.4%) to 1E (66.9%) in the Mayo cohort and from 1C (2.2%) to 1E (22.3%) in another cohort with younger patients. Its predictive performance has been validated in various external cohorts[19,29,32,35-37] (annual eGFR decline > –3.5 ml/min/1.73m², AUC = 0.61[36]; reaching CKD stage 3, AUC = 0.72[37] and 0.75),[32]

and in secondary analyses of clinical trials.[38,39] However, the prognostic accuracy for individual patients remains poor,[19] and the classification is not available to a broad range of patients. It is only valid for typical ADPKD patients,[34] and TKV measured by CT or MRI is not generally part of routine clinical care because of the cost and reimbursement policies of healthcare system.[24,40,41] The rate of disease progression is also partly explained by the type of genetic mutation. The *PROPKD prognostic score* incorporates this information. This algorithm includes clinical (gender, hypertension and/or first urological events ≤35 years) and genetic mutation data. It predicts renal survival at 65 years of age with an AUC of 0.84,[42] and its prognostic performance has been confirmed[32,36,37,43,44] (annual eGFR decline > –3.5 ml/min/1.73m², AUC = 0.65[36]; reaching CKD stage 3, AUC = 0.62[37] and 0.71[32]). Because this scoring system requires genetic testing, which is costly and not routinely obtained in many centers, its use in clinical practice is limited.

Urinary markers for ADPKD management

Since conventional risk prediction models have their limitations, alternative biomarkers (a single marker or a panel) would be useful. A surrogate biomarker ideally fulfills the following features to be of clinical relevance: 1) be sensitive and quantitatively reflect disease severity, 2) robustly predict disease progression, in particular prior to eGFR decline, 3) be easy to obtain, and relatively inexpensive to measure, 4) allow repeated measurements during a follow-up period, and 5) rapidly respond to an intervention for assessing efficacy.

Sources of biomarkers

Several sources, including urine and blood have been used for biomarker discovery. Urine is of particular interest because biomarkers can accumulate in urine. Differences in levels of biomarkers in blood are more strictly regulated by homeostatic mechanisms.[45] Furthermore, damage to tubular cells or other cells in the nephron is more likely to be detectable in urine than in blood. Also, the wide availability and non-invasive nature of collecting urine makes this an ideal source. However, urine as a source of biomarkers also poses challenges. First, there is variability between different collection methods, including 24-hour and spot collections.[46] A standardized protocol for collection and sample processing is required. Spot urine sampling is a routine procedure in nephrological practices, and therefore from practical perspectives most accessible. The time of day however matters. Second, urine is subject to proteases that degrade biomarkers. Last, urine concentrations depend on water handling by the nephrons. In CKD the ability to concentrate urine diminishes as CKD progresses.[47] Therefore normalization should be considered based on the context of the biomarker that is to be assayed.[48]

ADPKD cohorts

There are several large ADPKD cohorts. The ones that have been used for urinary biomarker discovery will be briefly discussed.

CRISP cohort

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort was initiated to study new imaging techniques to reliably and accurately measure cyst and renal volume in patients with early-stage ADPKD in order to determine disease progression, and to assess prognostic indicators, and effects of potential interventions.[49] This prospective, observational study included 241 ADPKD patients (age 15 – 46 years, eGFR > 70ml/min/1.73m²) with high-risk of rapid disease progression. TKV and GFR were measured annually over a 3-year follow-up period between January 2001 and August 2005.[25] In the two follow-up studies CRISP II[28] and CRISP III (median follow-up 13.0 years),[29] TKV and GFR were measured every two years. CRISP has identified TKV as a reliable prognostic marker for rate of disease progression in early-stage ADPKD where progressive cyst formation precedes renal function loss.[25,34] The CRISP cohort has recently been used for a peptidomic approach to urinary biomarker discovery by Pejchinovski et al.[31]

TEMPO cohort

The Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial was a multicenter, double-blind randomized-controlled trial. ADPKD patients (n = 1445, age 18 – 50 years, eGFR > 60 mL/min/1.73m², TKV > 750 mL, follow-up 3 years) were included between 2007 and 2009 and were randomized to tolvaptan or placebo. A slower annual TKV growth (from 5.5% to 2.8%) and annual decline in eGFR (−2.72 ml/min/1.73m²/year vs. −3.70 ml/min/1.73m²/year) was found in the tolvaptan group [7]. The TEMPO cohort was used for biomarker research by Grantham et al.[50]

DIPAK cohorts

The Developing Intervention strategies to halt Progression of Autosomal dominant polycystic Kidney disease (DIPAK) Consortium was conducted as an interuniversity collaboration in the Netherlands to study different aspects of ADPKD and to develop treatment strategies. The consortium included two large clinical studies. The DIPAK 1 study, a multicenter, randomized, controlled clinical trial assessing the efficacy of Lanreotide to halt disease progression, included 309 patients with ADPKD (age 18 – 60 years, eGFR 30 – 60 ml/min/1.73m²) between 2012 and 2015. Patients were randomized to lanreotide treatment on top of standard or standard care alone.[51] This study showed that lanreotide did not affect the rate of decline in eGFR over 2.5 years

of follow-up,[9] whereas it significantly slowed the rate of liver volume growth.[52] The DIPAK observational study was initiated to investigate renal disease progression and association of disease biomarkers with renal disease progression and ADPKD-related outcomes. This 6-year follow-up study included 660 patients with ADPKD (age ≥ 18 years, eGFR ≥ 15 ml/ min/1.73m²) between 2013 and 2018. Data on genetic analysis, blood and urine samples (annually), and abdominal MRI (every 3 years) were obtained. These cohorts were used by Messchendorp et al.[36,53]

Clinical urinary markers in literature

Urinary biomarkers have been extensively investigated in ADPKD in the past two decades, with variable results on their clinical performance. **Figure 1** provides an overview of previously investigated urinary biomarkers in ADPKD according to their presumed anatomical site of production or site of tubular handling. Various markers including neutrophil gelatinase-associated lipocalin (NGAL),[54-56] beta-2 microglobulin (β2M),[56-59] monocyte chemoattractant protein-1 (MCP-1)[56,60] and N-Acetyl-β-O-glucosaminidase (NAG)[56-59] associate with baseline GFR and TKV, whereas kidney injury molecule-1 (KIM-1) showed an association with TKV,[56,59] but not with GFR.[55-57,59] Other studies report contradictory data on the relation between NGAL[57,59,61] and GFR and TKV, and of β2M[56] or KIM-1[57] and TKV. The capability to robustly predict disease progression is one of the key features for a surrogate marker to serve as a prognostic tool in clinical practice. Varying results were shown regarding the association of NGAL with disease progression (no predictive capacity reported).[61-63] This also applies to β2M[63], MCP-1[28,64] (reaching CKD stage 3, AUC = 0.75) and NAG[57] (eGFR < 60 ml/min/1.73m², AUC = 0.79; no predictive value for GFR progression). Loss of urine-concentrating capacity, as reflected by lower urinary osmolality, has also been found to be an independent risk factor for faster renal function decline.[65,66] Because almost all markers show at best a potential to serve as a predictive tool based on their association with disease progression in follow-up studies, there is still an unmet clinical need for surrogate markers for risk stratification.

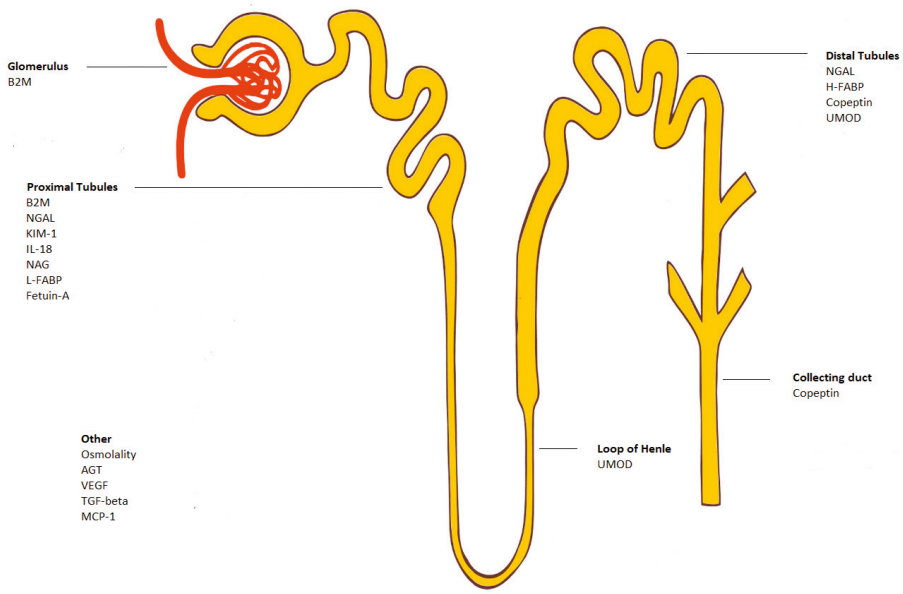

Figure 1. Nephron segment-specific urinary biomarkers related to ADPKD according to their presumed anatomic localization, based on the site of production or site of tubular handling. Modified from the cited literature.[67,68]

Literature search

The aim of this review is to provide an update of the literature up to 2019 on urinary biomarkers for predicting future disease progression in patients with ADPKD. The methodological approach adopted in this paper consisted of a narrative review, which was based on features of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) style.[69] A literature search was conducted in the Pubmed, Embase, Web of Science and Cochrane Library databases to identify publications related to urinary biomarkers in ADPKD and review their role in predicting disease progression. Relevant studies were identified using the following keywords and/or their equivalents: autosomal dominant polycystic kidney disease, urine, biomarker, prediction, disease progression. References in identified studies were scrutinized for additional relevant articles. We reviewed articles published between 2014 and 2019. The search was restricted to human adult research and to articles in English. Studies with a follow-up of < 6 months (concerning evaluation of progression markers) were excluded.

Results

A total of 185 articles were identified with our literature search (**Figure 2**). Duplicate articles (n = 137) in one or more databases were excluded. Unique articles (n = 48) were screened by relevance of title and abstract, followed by a full-text review of the remaining articles (n = 34). A total of 7 articles corresponded with our review purpose (**Table 1**). Novel markers and the most promising markers for use in clinical practice are included in this narrative review.

Inflammation markers

Monocyte chemoattractant protein-1

MCP-1 or chemokine C-C motif ligand 2 is produced by various cell types including renal cells, and acts as a potent chemotactic and activating factor for monocytes/macrophages. MCP-1 controls the recruitment of leukocytes to the side of inflammation and injury and is involved in tissue repair and regenerative processes. It is filtered by glomeruli (13 kDa) and secreted into the urine.[50,70] Recently, four studies evaluated the value of urinary MCP-1 as a marker for progression of ADPKD over time.[7,36,53,71] In two studies, Messchendorp et al investigated various urinary biomarkers including MCP-1, NGAL, β2M, KIM-1 and heart-type fatty acid binding protein (H-FABP) in 104 ADPKD patients (age 40±11 years, baseline eGFR 77±30 ml/min/1.73m^2, follow-up 3.82±1.23 years) in 24-hour urine collections.[36,53] Baseline urinary MCP-1 was associated with the annual change in eGFR over three years of follow-up and remained significant after adjustment for potential confounders (standardized β = –0.29, P = 0.009). In particular when combined with urinary β2M, it showed added value beyond that of conventional risk markers.[53] The authors validated these results in an external cohort (n = 302; age 48±7 years, eGFR 52±12 ml/min/1.73m^2). Longitudinal analyses (n = 152; follow-up 2.43±0.41 years) showed that adding the urinary biomarker score (based on tertiles of MCP-1 and β2M excretion) to a model with age, sex, and eGFR improved the ability to predict a rapid course of disease progression. The AUC increased from 0.66 to 0.77. On its own, the urinary biomarker score had a similar ability to predict the course of disease (AUC = 0.72) as the Mayo htTKV classification (AUC = 0.75). For a model with the combined variables sex, age, eGFR, urine biomarker score and Mayo htTKV classification the AUC was 0.84 (95% CI 0.75-0.93).[36] Another study evaluated various urinary markers including MCP-1, NGAL, β2M, KIM-1, liver-type FABP (L-FABP) and vascular endothelial growth factor (VEGF) in 130 ADPKD patients (age 49±21 years, baseline eGFR 77±30 ml/min/1.73m2, eGFR slope –2.85±1.72 ml/min/1.73m2 per year, follow-up 10 years). Baseline urinary MCP-1 was correlated with eGFR and htTKV at baseline. Linear regression analysis showed that MCP-1 was also significantly associated with the

eGFR slope (standardized β = –0.47, P = 0.007, R^2 = 0.22). A multivariate model, including htTKV, MCP-1, β2M and VEGF, explained 43% of the eGFR slope variability (P < 0.001).[71] In a sub-analysis of the TEMPO 3:4 trial (n = 869 tolvaptan group, eGFR 81.6±21.2 ml/min; n = 438 placebo group, eGFR 82.3±23.2 ml/min; follow-up 36 months),[7] urinary MCP-1 referenced to creatinine was evaluated as a marker of disease progression in relation to tolvaptan efficacy. MCP-1 was higher in most patients with ADPKD than the values seen in healthy controls in other studies. MCP-1 was higher in those with a lower eGFR. During follow-up, urinary MCP-1 decreased relative to baseline in those on tolvaptan, and remained lower during the treatment period, compared with those in the placebo group (P < 0.001).[50] The effect of tolvaptan on urinary MCP-1 levels was in line with the results reported in the TEMPO 3:4 trial showing inhibitory effects of tolvaptan on the rate of eGFR decline and TKV growth.[7]

Neutrophil gelatinase-associated lipocalin

NGAL (25 kDa) or lipocalin-2 (Lcn2) is an ubiquitous glycoprotein and member of the lipocalin superfamily. It is a well-described inflammation marker that was originally identified in activated neutrophils, but is also produced in low concentrations by other human cell types and tissues.[72] NGAL plays a role in multiple biological processes including renal cell differentiation, proliferation, inflammation and fibrosis.[73] In response to renal injury, it is highly upregulated in tubular epithelial cells followed by rapid urinary excretion.[74,75] Two studies by Messchendorp et al[36,53] investigate urinary NGAL as a marker for ADPKD progression. Urinary NGAL did not associate with annual change in eGFR (standardized β = –0.08, P = 0.44) or with change in TKV (standardized β = –0.04, P = 0.73) during follow-up (3.82±1.23 years).[53] These results were in line with a lack of reliable prognostic value found in an external validation study from the same authors[36] and an independent 10-year follow-up study.[71]

Tubular injury markers

Beta-2 microglobulin

β2M, produced by all nucleated cells, interacts with the classical and non-classical major histocompatibility complex I molecules. Under physiological conditions, it is only minimally found in the urine. β2M is freely filtered by the glomerulus (11.8 kDa) and almost entirely reabsorbed and metabolized by proximal tubular cells, so reflecting glomerular and tubular function. Increased urinary β2M excretion indicates tubular injury. Our search found three studies on urinary β2M as a marker for disease progression over time in ADPKD patients.[36,53,71] In a 3-year follow-up study (previously described in the context of above described markers), urinary β2M at baseline was associated with annual change in eGFR (after adjustment for age, sex, baseline eGFR, htTKV, and gene type mutation;

standardized β = –0.35, P = 0.001). In a 10-year follow-up study baseline urinary β2M was associated with htTKV and with renal function decline. The strongest model to explain the eGFR slope included htTKV, urinary β2M, MCP-1 and VEGF (R^2 = 0.43, P < 0.001).[71] As mentioned before, urinary β2M showed added value beyond that of conventional markers in predicting GFR decline, particularly when combined with MCP-1.[36,53]

Kidney injury molecule-1

KIM-1 (38.7 kDa) is a type 1 transmembrane glycoprotein. It is scarcely expressed in normal kidney tissue, but abundantly upregulated in the proximal tubules following renal damage.[76,77] KIM-1 plays a role in renal proliferation and regeneration processes after epithelial injury.[78] In a 3-year follow-up study by Messchendorp et al,[53] baseline urinary KIM-1 was associated with annual change in GFR (after adjustment potential confounders, standardized β = –0.24, P = 0.02), although less so than urinary β2M and MCP-1. This association was confirmed in a validation study (standardized β = –0.24, P = 0.006), and the fit of a conventional model (age, sex, and baseline eGFR) for predicting rapidly progressive disease improved significantly when KIM-1 was added. However, in a model with age, sex and baseline eGFR as fixed variables, only β2M and MCP-1, but not KIM-1, remained significantly associated with the eGFR slope.[36] In another study baseline urinary KIM-1 was also associated with the future eGFR slope (standardized β = –0.26, P = 0.02) in an univariate analysis, but not in a multivariate model.[71]

Other markers of kidney damage

Fetuin-A

Fetuin-A (or α2-Heremans-Schmid glycoprotein) is a 58-kDa multifunctional reverse acute phase protein, which is normally predominantly synthesized in the liver and secreted into the circulation.[79] This glycoprotein is involved in various physiological processes including regulation of bone metabolism, vascular calcification and insulin signaling.[80] Preclinical studies have shown that fetuin-A protein is present in proximal tubular epithelial cells in normal kidneys, without mRNA expression.[81,82] In a ADPKD mouse model fetuin-A in urine is increased. This is probably due to impaired tubular reabsorption rather than increased filtration or secretion.[82] In 66 ADPKD patients (age 43.1±17.2 years, eGFR 71.8±38.8 mL/min/1.73 m^2), urinary fetuin-A, normalized to creatinine, was significantly correlated with the stage of CKD (across stages 1-5, P = 0.023). Patients with more advanced ADPKD had higher levels than those with early-stage disease. For 19 patients (eGFR > 60 mL/min/1.73 m^2), consecutive urine and eGFR data (5 timepoints in 2 years) were available. During follow-up, fetuin-A increased progressively (difference between baseline and year 2: +50%, P = 0.003), while the

eGFR remained stable (Δ –2%, P = n.s.). In these patients with preserved eGFR, urinary fetuin-A levels distinguished ADPKD patients from healthy controls (AUC = 0.74).[82]

Osmolality

The antidiuretic hormone arginine vasopressin (AVP) is a key regulator for osmoregulation. It is secreted by the pituitary gland in response to increased plasma osmolality resulting in activation of V2 receptors in the collecting duct to induce water reabsorption.[83] AVP plays an important role in the pathophysiology of ADPKD.[84] It activates the cAMP pathway which contributes to cyst growth by stimulating both fluid secretion and cell proliferation. V2 receptor antagonists inhibit the rate of eGFR decline and TKV growth in ADPKD patients.[7] AVP-cAMP signaling pathway proteins are reliable surrogate markers for maximal urine-concentrating capacity and suggested to be potential markers for ADPKD, since urinary concentrating capacity decreases in the early-stages of disease. Several studies have evaluated the role of urinary copeptin,[85] cAMP[85] and/or osmolality[55,59,63] with varying results regarding associations between markers and GFR and/or TKV. In 94 ADPKD patients (age 40±10 years, eGFR 72±27 ml/min/1.73 m^2) urinary osmolality was associated with GFR (r = 0.49, P < 0.001), but not with TKV (r = –0.12, P = 0.26). During follow-up (n = 55; 2.8±0.8 years), levels also did not associate with the annual change in eGFR (standardized β = 0.11, P = 0.43).[86] The potential predictive value of other AVP-cAMP signaling pathway proteins has not been reported in literature.

Proteomics (peptides, exosomes)

Proteomics is the assessment of proteomes (proteins and peptides within a particular compartment), which are cell and tissue specific, and change over time in response to different stimuli. Urinary proteomics has been widely used to identify novel biomarkers for renal diseases. It could also provide new insights into pathways of disease progression for potential future therapeutic targets.[87] Research can focus on a direct measurement of proteins in urine, the peptidome, or on proteins isolated from a fraction, like from extracellular vesicles (EVs; 50 to 1000nm) including exosomes. EVs originate from cells and are formed by fusion of internal multivesicular bodies with the plasma membrane of epithelial cells. They contain proteins and nucleic acids, and represent the physiological state of the cell. They are therefore considered to be a rich source of potential biomarkers.[88] Various studies have evaluated urinary proteomes for ADPKD.[89-96] One study reported data on the association of the peptidome with rate of disease progression.[31] In a study including 221 ADPKD patients (age 32.4±8.7 years, eGFR 89±28 ml/min/1.73m², follow-up 9.9±2.9 years), a prognostic urinary peptidomic profile was identified. This profile accurately predicted progression towards ESRD during follow-up (n = 142, age > 24 years, follow-up > 10 years) with an AUC of 0.86, which was comparable to baseline htTKV (AUC = 0.89). The model improved slightly

when the urinary peptidomic profile was combined with htTKV (AUC = 0.92). Even in young patients (n = 30, age < 24 years) with relatively preserved renal function, the urinary profile predicted the renal outcome (GFR decline > 30ml/min/1.73m² over 8 years, AUC = 0.92).[31] Strengths of this study including long follow-up duration (9.9±2.9 years), hard renal outcomes (ESRD/GFR decline > 30ml/min/1.73m² over 8 years), and cohort type (wide distribution in disease progression) contributed to the high achieved prognostic performance of the model.

Discussion

The aim of this review was to provide an overview of urinary biomarkers for predicting disease progression in CKD patients with ADPKD, restricted to studies published between 2014 and 2019. Although various urinary markers have been investigated, few studies have evaluated their predictive value. A promising model for predicting the future eGFR slope consists of a combination of conventional risk markers and the combined urinary biomarkers β2M and MCP-1.[53,71] The biomarker score based on β2M and MCP-1 predicts rapid progressive disease with an AUC of 0.72 (fast vs. slow progressors based on the dichotomized eGFR slope). Combined with the variables sex, age, eGFR, and Mayo htTKV classification the AUC was 0.84.[36] Furthermore, urinary MCP-1 responds to treatment with tolvaptan,[50] which is also an important feature for use in clinical practice. Another tool which holds promise to support patient risk assessment is urinary proteomics. A urinary peptidomic profile had a high predictive power for ESRD (AUC = 0.86) which increased further when combined with htTKV (AUC = 0.92).[31]

To date, none of the surrogate urinary markers are used in clinical practice. An important factor that contributes to their limited use is the lack of validation in external cohorts. Also, none have been studied in a way that looks at the benefit of using these markers to improve patient management. This would require randomized controlled trials that look at patient outcomes with and without the use of such markers. Some markers initially associate with disease severity, but subsequently failed to be of predictive value for disease progression also contributed to their eventual limited use. More recently discovered urinary markers including angiotensinogen,[58,97,98] uromodulin[59] and transforming growth factor β[99-101] were only cross-sectionally evaluated, so their prognostic value remains unclear. Limitations of most urinary markers included the potential of freely glomerular filtration (reflecting rate of filtration rather than disease state) and non-specificity for renal injury. Whether urinary markers are primarily determined by the rate of renal dysfunction or whether they are related to the origin of the kidney disease is unclear. Altered urinary β2M, MCP-l, KIM-1, NGAL, fetuin-A, and osmolality[102-106] are not specific for ADPKD and reflect kidney injury or reduced kidney

function and have therefore also been studied in CKD patients in general. This narrative review is limited to urine markers in ADPKD. To some extent, generalization of results from studies on urine markers in CKD is possible. However, the distinct pathophysiology of ADPKD may limit generalizability.

In the future, several possibilities should be considered to overcome the current lack of implementation of novel prognostic tools into routine clinical practice. First, studies evaluating sequential biomarker measurement are required in order to allow more meaningful interpretation of the data. Second, a risk prediction tool including single or multiple urinary biomarkers combined with clinical, imaging and genetic data, might prove the most accurate approach for predicting disease progression. Third, the benefit of using these markers to improve patient management needs to be studied. Last, other urinary biomarker platforms should be evaluated.

A promising new area is that of metabolomics. Besides the potential to discover novel biomarkers, it could also provide new insights into the pathophysiology of ADPKD. Advantages of nuclear magnetic resonance (NMR)-based metabolomics are that only a minimal sample volume is required, that pretreatment of samples is simple and that analytical reproducibility is unsurpassed. It has been widely applied to the study of various renal diseases,[107-109] but data on ADPKD are limited. Urinary metabolites were found to distinguish ADPKD from other renal diseases, and healthy controls, but data on association with disease progression have not been reported.[110]

In conclusion, extensive investigation has been conducted to discover novel urinary biomarkers for patient risk assessment. Their clinical utility for ADPKD remains unclear, and is therefore still an important area of research. The selection of type of renal outcome plays an important role in assessing the prognostic performance of candidate biomarkers for ADPKD progression. Risk stratification could be improved using a panel of markers as opposed to a single biomarker strategy. Urinary metabolomics is a promising novel area of biomarker discovery and may have potential to support risk stratification.

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