10.5152/turkjnephrol.2020.3554

Review

Turkish Journal of Nephrology

Urinary Findings and Biomarkers in Autosomal Dominant Polycystic Kidney Disease

İsmail Koçyiğit[1], Eray Eroğlu[1], Tevfik Ecder[2]

[1]Division of Nephrology, Erciyes University School of Medicine, Kayseri, Turkey
[2]Division of Nephrology, İstanbul Bilim University School of Medicine, İstanbul, Turkey

Abstract

Autosomal dominant polycystic kidney disease (ADPKD), characterized by the development of multiple cysts in the kidneys and other organs, is the most common hereditary renal disorder and the fourth leading cause of end-stage renal disease. In adults with a positive family history, the diagnosis of ADPKD is made based on the radiologic evidence of bilateral, fluid-filled renal cysts. Furthermore, initial symptoms including pain, increased thirst, polyuria, nocturia, and increased urinary frequency may lead to the diagnosis of ADPKD. An easily accessible, applicable, and cost-effective biomarker is needed to predict the clinical course of ADPKD due to its progressive pattern. Urine is an easily obtainable and widely used test specimen for diagnosis and follow-up in several renal diseases. Thus, the aim of the present study was to review and assess new urinary biomarkers and urinary findings in ADPKD.

Keywords: Polycystic kidney disease, biomarkers, urine

Corresponding Author: İsmail Koçyiğit ✉ iikocyigit@gmail.com

Received: 04.09.2018 **Accepted:** 10.10.2018

Cite this article as: Koçyiğit İ, Eroğlu E, Ecder T. Urinary Findings and Biomarkers in Autosomal Dominant Polycystic Kidney Disease. Turk J Nephrol 2020; 29(1): 66-76

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the common genetic causes of end-stage renal disease (ESRD) (1). It is also a systemic disorder that is characterized by renal and extrarenal involvement (2). ADPKD is caused by mutations in either of the two genes encoding the plasma membrane-spanning polycystin 1 (PKD1) and polycystin 2 (PKD2). Polycystin 1 is a membrane receptor and plays a role in maintaining intracellular responses active in several pathways. Polycystin 2 acts as a calcium-permeable channel. Moreover, polycystins regulate tubular and vascular development in the kidneys and other organs (liver, brain, heart, and pancreas) (3-5).

The two types of ADPKD have similar pathological and physiological features. However, type II ADPKD has a later onset of symptoms and a slower rate of progression to ESRD (6). Although the proposed gene PKD3 has not yet been determined, some patients with typical features of ADPKD have no mutations in PKD1 or PKD2, suggesting that there is a rare third form of the disease (7, 8).

The diagnosis of ADPKD is made based on the radiologic evidence of bilateral, fluid-filled renal cysts in adults with a positive family history. Ultrasonography findings have revealed cysts measuring ≥1 cm in diameter and that ADPKD is highly sensitive to be diagnosed in adults (9). Moreover, the presence of ≥3 (unilateral or bilateral) renal cysts is enough for establishing a diagnosis in individuals aged 15-39 years, ≥2 cysts in each kidney for subjects aged 40-59 years, and ≥4 cysts in each kidney for subjects aged ≥60 years belonging to families with unknown genotype (10).

Several clinical complaints might be related to ADPKD and lead to the diagnosis of the disease. In particular, increased thirst, polyuria, nocturia, urinary frequency, and urinary concentrating defects are the most common initial symptoms and functional abnormalities of

ADPKD (11). It is plausible to find a cheaper, applicable, and easily accessible biomarker to predict the clinical course of ADPKD due to its progressive pattern. Urine is one of the important materials for finding a noninvasive prognostic and therapeutic monitoring test for renal diseases. Here the aim of the present study was to review and discuss the urinary abnormalities in ADPKD as well as to assess new urinary biomarkers and urinary findings in ADPKD.

Urine Osmolality

The antidiuretic hormone arginine vasopressin (AVP) plays an important role in osmoregulation. AVP is secreted by the pituitary gland and activates the V2 receptors of renal collecting duct cells when the plasma osmolality increases (12); in turn, this activation induces the translocation of aquaporin 2 to the luminal surface of these cells, making them permeable to water (13). AVP is needed in the physiological stimulation of water reabsorption, and it also plays an important role in the pathophysiology of ADPKD (14). A large-scale trial showed that blocking the AVP V2 receptor with a V2 receptor antagonist leads to a reduced rate of cyst growth and renal function decline in patients with ADPKD (15, 16). It is widely established that a urine osmolality of <285 mosM/kg H_2O, or lower than plasma osmolality, reflects adequate suppression of AVP (17, 18).

Similar to other causes of chronic kidney disease (CKD), a defect in the kidney's capacity to conserve water has been described in patients with ADPKD (11, 19). Vasopressin-resistant renal concentrating defect has been shown in ADPKD prior to the deterioration of kidney function (20). Urine concentrating defect is one of the common clinical findings in patients with ADPKD (21). Decreased urinary osmolality, which may be caused by the disruption of the renal architecture by the cysts, is thought to interfere with the countercurrent exchange and multiple mechanisms in the kidney regardless of age, glomerular filtration rate, and solute excretion in patients with ADPKD (22, 23).

Gabow et al. (11) suggested that a defect in the extracellular matrix in ADPKD affects renal epithelial transport or vasopressin responsiveness, thus producing a concentrating defect. Moreover, structural abnormalities in the polycystic kidneys might affect the physics of the concentrating mechanism and produce a concentrating defect. The urinary concentration defect that develops as the disease progresses is thought to be due to impaired renal medullar osmolar gradient by cyst formation in patients with ADPKD. This lack of renal concentrating capacity is expected to lead to a lower urine osmolality, a higher plasma osmolality, and a compensatory high level of AVP. Clinically, it has been observed that in the later stages of the disease, urine osmolality can indeed be low, whereas AVP is high (11-14). Interestingly, Ho et al. (24) reported that patients with ADPKD show both a central and peripheral defect in osmoregulation early in the course of the disease. They identified a central defect, which parallels the expression of polycystic kidney disease genes in hypothalamic neurons that synthesize and release AVP as a novel extrarenal manifestation of ADPKD (24). The results of this study provided insights into the role of polycystins in the brain and are relevant when considering treatments targeting AVP in ADPKD.

Hematuria

Hematuria is the most common presenting symptom of ADPKD, usually occurring before the loss of kidney function and is frequently associated with cyst wall calcifications on renal imaging (1, 25). It develops in 35%-50% of patients with ADPKD throughout their life and can be acute. It is commonly associated with infection or severe physical activity and acute cyst expansion. It generally presents with local pain, fever, and dysuria without infection (1, 2, 25). When these symptoms occur, it is important to eliminate pyelonephritis, nephrolithiasis, and lower urinary tract infections (UTIs), particularly in women.

Rupture of a cyst into the collecting system is the most common cause of macroscopic and microscopic hematuria in ADPKD. Hematuria due to cyst rupture tends to improve within approximately 1 week with conservative therapy. Rarely, hematuria can persist for several weeks and can be more severe requiring interventional therapy modalities including transcatheter renal arterial embolization, transfusion, or nephrectomy (26).

Patients with ADPKD and gross hematuria have increased total kidney volume (TKV). Hematuria is also closely associated with rapid disease progression and hypertension. Gross hematuria may have an unfavorable effect on long-term renal function, possibly reflecting accelerated cyst expansion (25, 27). Moreover, frequent episodes of gross hematuria may accelerate renal function decline, by causing acute kidney injury (AKI) and/or chronic iron toxicity. Cyst ruptures with gross hematuria may lead to the release and deposition of free iron and heme, promoting the generation of reactive oxygen species and proinflammatory cytokines (25, 28).

Although most patients report trauma or strict exercise as possible triggers, a precise association has not been identified between such triggering mechanisms and the condition. Although polycystic kidneys are quite resistant to traumatic damage, mild trauma may lead to intrarenal or retroperitoneal bleeding, which may present with intense pain and require administration of aggressive medical therapy, especially narcotics (29-31).

When gross hematuria first occurs after the age of 50 years, malignancy should be screened. However, gross hematuria can be associated with renal or extrarenal hemorrhage or bleeding into the urinary collecting system, which may be detected via computerized tomography (CT) or magnetic resonance imaging. Acute clots in the collecting system may result in severe renal pain. In such a situation, hydration to increase the urinary flow rate to 2-3 L/day, rest, and analgesics are recommended. Patients should be informed regarding self-treatment options for repeated episodes. Hematuria generally decreases to micro-

scopic levels in a few days. The use of antiplatelet or anticoagulants should be avoided in the absence of a strong indication in patients with a history of gross hematuria (2, 32, 33). Gabow et al. (25) found that male athletes with ADPKD who participated in contact sports have more hematuria episodes and develop kidney failure faster than those who did not participate in such sports. Thus, all patients with ADPKD should be warned to avoid sports that may cause abdominal trauma.

Cysts are associated with excessive angiogenesis indicated by fragile vessels stretched across their distended walls. These vessels present an array of malformations, including aneurysms and spiral shapes. Hemorrhage may occur spontaneously in the cyst due to these vessels, and the cysts can enlarge rapidly resulting in severe pain (34, 35). Gabow et al. (25) investigated the clinical profiles of patients with ADPKD and showed that patients with ADPKD and visible hematuria have increased TKV and worse renal function. These results suggest that visible hematuria has an unfavorable effect on long-term renal function, which might reflect accelerated cyst expansion. In addition, it has been hypothesized that recurrent gross hematuria results in tubular obstruction and triggers the fibrotic process by disrupting the renal parenchyma. It appears that the relationship with hematuria and disease progression affects each other vice versa (21, 25). According to the current literature, there is no method (except urine microscopic evaluation of the characteristics of red blood cells) to differentiate the origin of the blood. Direct microscopic evaluation may help to distinguish the origin of red blood cells, that is, whether they are from the superior or inferior urinary system.

Additionally, the coincidence of hematuria, overt proteinuria, and rapid renal dysfunction in patients with ADPKD may be related to proliferative glomerulonephritis and rapidly progressive glomerulonephritis, including an antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis (36, 37).

Proteinuria

Proteinuria usually occurs at mild to moderate levels in approximately 25% of patients with ADPKD. The presence and severity of proteinuria is a negative prognostic risk factor and is associated with greater prevalence of increased TKV, hypertension, and renal deterioration (38, 39). Urinary albumin excretion (UAE) was positively correlated with TKV and negatively correlated with estimated glomerular filtration rate (eGFR) in the HALT Progression of Polycystic Kidney Disease study at baseline (40). Thus, it is proposed that increased levels of UAE are a valuable predictive marker of ADPKD severity before renal function decline. Higher levels of proteinuria were also associated with a faster decline in GFR among patients with ADPKD in the Modification of Diet in Renal Disease study (41).

Chapman et al. (38) reported that approximately 20% of 270 patients with ADPKD have overt proteinuria (>300 mg/day), which is associated with worse renal function, hypertension, and increased TKV. Patients with overt proteinuria reached a serum creatinine level of 1.5 mg/dL at a significantly younger age compared with those with mild proteinuria. Additionally, microalbuminuria was observed in 20 out of 49 patients with ADPKD, hypertension, and left ventricular hypertrophy. Blood pressure and TKV were significantly higher in patients with microalbuminuria. In addition, the degree of albuminuria was correlated with TKV and kidney volume growth rate in a study of 100 young patients with ADPKD and preserved renal function (42). Meijer et al. (43) showed a high prevalence of microalbuminuria in young adult patients with ADPKD.

If proteinuria exceeds 1 g/day, the possibility of another independent glomerular disease should be considered. The association of nephrotic syndrome (NS) with ADPKD is very rare (44, 45) and, if possible, needs to be investigated further to exclude coexisting glomerular disease. The determination of the exact reason of proteinuria in this subgroup of patients often requires kidney biopsy. Indeed, there are some cases of ADPKD associated with NS; focal segmental glomerulosclerosis is the most common presented type of NS in this population (45). In addition, proteinuria may not be specific to ADPKD; it may be the result of CKD.

Pyuria

Although it is quite common in patients with ADPKD, the etiology, incidence, and clinical implications of pyuria are not well identified. Asymptomatic pyuria often persists or relapses without treatment in ADPKD (46). The microorganisms in the urine cultures of these patients with asymptomatic pyuria are similar in UTIs (47). This suggests that asymptomatic pyuria is a type of subclinical bacterial infection in patients with ADPKD. Chronic asymptomatic pyuria may also increase the risk of developing overt UTI and may contribute to the deterioration of kidney function in ADPKD. It has been well established that chronic UTI is an important risk factor for renal function decline (47). In addition, women are more susceptible to UTI than men as with the general population, and they also have a higher incidence of parenchymal and cyst infections in the ADPKD population (48). Radiologic and urologic evaluation is needed in male patients with ADPKD. Acute pyelonephritis and symptomatic cyst infection indicate hospitalization, with positive blood or urine cultures. Coliforms are the most common detected pathogens. Antibiotics are administered intravenously until fever and renal pain cease for these infections in both sexes (2, 49).

The diagnosis of cystic infections may be difficult in the presence of hemorrhage. Positron emission tomography-CT allows us to distinguish hemorrhages from cystic infections (50, 51). Evidence from CT scans suggests that intracystic hemorrhage, shown as hyperdense subcapsular cysts, is present in 90% of patients with ADPKD (1, 52).

UTI is a risk factor for renal progression in patients with ADPKD (53). A recent study showed that asymptomatic pyuria and overt UTI were associated with rapid decline in renal function, but it is unclear whether this result was independent of other factors, such as baseline GFR and TKV (53).

Urinary Calculi

The prevalence of urinary calculi is greater in patients with ADPKD than in the general population (54). Kidney stone formation has been reported in 20%-36% of patients with ADPKD (54, 55). Uric acid is the major constituent of stones in patients with ADPKD, with an incidence of approximately 60% among patients with ADPKD and urinary calculi (54, 56). Calcium oxalate-containing stones occur less frequently, with an incidence that is lower than that in the general population (56). Risk factors for stone formation in ADPKD include metabolic abnormalities and anatomic obstruction with resultant urinary stasis (57, 58). There is also a relationship between nephrolithiasis and an increased number and size of renal cysts in patients with ADPKD, suggesting that compression associated with distortion of the medullary architecture results in urinary stasis (57). Urinary citrate excretion, which is decreased in patients with ADPKD before the loss of kidney function, may be an important contributing factor (57-59). A crucial risk factor for uric acid stone formation in patients with ADPKD is a low urinary pH. Urinary pH has been shown to be <5.5 in >50% of patients with ADPKD and is independently associated with urinary calculi (59). The ionization constant (pKa) for uric acid is 5.5 (60); therefore, when the urine pH is <5.5, urine becomes supersaturated with undissociated uric acid that precipitates, forming uric acid stones (61). The low urine pH in ADPKD may be attributed to a defective ammonium excretion (20, 62). Other important risk factors for increased urinary calculi in patients with ADPKD include low urine flow states or low fluid intake, hypercalciuria, and hyperuricosuria similar to non-ADPKD population (54, 63).

Nishiura et al. (59) reported that hyperuricosuria is less prevalent in ADPKD, with an incidence similar to normal subjects. Moreover, they found that hyperoxaluria is significantly higher in patients with ADPKD, particularly those with urinary calculi. The higher percentage of hyperoxaluria and hypocitraturia in ADPKD is reported by other studies (54, 57). These findings remain to be explained. In addition, most patients with ADPKD and urine calculi had a urinary pH of <5.5, either spontaneously (62% of them) or after NH4Cl load (30% of them), indicating that a low rather than a high urine pH has been commonly observed in these patients, which is consistent with previous reports (20, 54, 56, 64, 65). Indeed, patients with ADPKD and urine calculi exhibited lower ammonium excretion after NH4Cl load than healthy subjects, suggesting that there is a possible defect in ammonium excretion (61, 62), similar to the one observed in uric acid stone formers (61). It has been suggested that ammonium excretion defect predisposes the formation of uric acid stones (56). However, hyperuricosuria was only found in three out of 28 patients with ADPKD and renal calculi (59).

In addition to hypocitraturia and aciduria, some urinary metabolic abnormalities including hypomagnesuria and low urine volume also predispose stone formation in ADPKD (54, 57). Eventually, the targets should be placed on not only treating nephrolithiasis but also predisposing metabolic and structural factors.

Urine Biomarkers

Although there is ongoing research, specific therapies for ADPKD are still lacking, and one of the challenges is the absence of appropriate biomarkers to predict and monitor disease progression before significant impairment occurs (21). Currently, TKV is a widely accepted marker for disease progression; however, it is expensive and unavailable worldwide (66). Therefore, it is plausible to find cheaper, applicable, and easily accessible biomarkers to predict the clinical course of ADPKD due to its progressive pattern.

Urine, as a well-accessible compartment, appears to be an ideal material for finding a noninvasive prognostic and therapy monitoring test for renal diseases. Cystogenesis in ADPKD is a unique process characterized by abnormalities in fluid secretion, tubular cell proliferation, extracellular matrix formation, apoptosis, and cell polarity (67, 68). The process results in an impaired filtration barrier, diminished tubular reabsorption, upregulation of tubular proteins, and release of markers by recruited cells, which can be detected in the urine of patients with ADPKD (69). Therefore, the application of a noninvasive urine biomarker is needed to understand the pathophysiological processes and potential therapeutic options for these patients (70). Moreover, the recent focus of interest has shifted toward urine biomarkers in patients with ADPKD (Table 1).

Urinary angiotensinogen (UAGT), a marker of intrarenal renin angiotensin system (RAS), has been shown to be associated with hypertension in patients with ADPKD (71). This finding suggests that UAGT is a potential novel biomarker of intrarenal RAS status in patients with hypertension with ADPKD. Moreover, UAGT levels may be an applicable and useful index to predict future cardiovascular complications and progressive kidney disease in patients with ADPKD. In addition, Park et al. (72) reported that UAGT is positively correlated with TKV and negatively correlated with eGFR.

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of superfamily of lipocalin proteins, which is expressed in the lung, kidney, and gastrointestinal system. It plays a role in iron transport, epithelial differentiation pathways, inflammation, and cell proliferation in the kidneys (73). NGAL expression increases in kidney epithelial cells in response to injury. In addition, the predictive value of urinary NGAL levels has been shown for AKI occurrence in several studies in many populations rather than ADPKD (74, 75). NGAL levels are thought to increase in urine as ADPKD kidneys show inflammation, cyst proliferation, and kidney enlargement. More recently, it has been reported in two different studies that urinary NGAL excretion is mildly and stably elevated in ADPKD, but does not correlate with changes in TKV or kidney function (70, 76). However, Vareesangthip et al. (77) demonstrated a negative correlation between urinary NGAL and eGFR in patients with ADPKD. Similarly, Bolignano et al. (78) reported markedly higher urinary NGAL levels in patients with ADPKD at the late stage than in healthy volunteers. Meijer et al. (79) found a correlation between urinary NGAL lev-

Table 1. Urine parameters and biomarkers in autosomal dominant polycystic kidney disease

Biomarker	Association/Change
Urine osmolality	Urine osmolality reduced in ADPKD (680±14 mOsm/kg) compared to non-ADPKD subjects (812±13 mosm/kg).
Hematuria	The incidence of gross hematuria is increased in ADPKD patients and it is associated with rapid renal disease progression.
Proteinuria	Microalbuminuria and mild proteinuria is associated with cardiovas- cular disease and renal function decline and increased total kidney volume.
Pyuria	Asymptomatic pyuria is associated with urinary tract infection and precedes kidney function deterioration.
Urine pH	Urinary pH <5.5 occurs in >50% of patients with ADPKD and it is inde- pendently associated with urinary calculi, particularly uric acid stones.
Hypocitraturia, hyperoxaluria, hypercalciuria	Hypocitraturia, hyperoxaluria, and hypercalciuria were observed in ADPKD patients.
Urinary angiotensinogen	Increased urinary angiotensinogen levels in patients with ADPKD, par- ticularly hypertensive ones and correlated with total kidney volume.
Urinary neutrophil gelatinase-associated lipo- calin	Urinary NGAL is mildly elevated ADPKD patients compared to healthy controls and some studies found correlation with total kidney volume and decreased eGFR.
Urinary interleukin-18	Urinary IL-18 is mildly elevated in ADPKD patients.
Urinary complement proteins	Urinary complement changes: Increased levels of factor B (CFB), SERP- ING1 and C9 and decreased levels of complement component1, C1RL, CD55 and CD59 were correlated with the different stages of ADPKD.
Urinary proteomics	These marker proteins, most of which were collagen fragments, such as uromodulin were found at significantly different levels in ADPKD patients than controls.
Secreted Frizzled-related	
protein 4	sFRP4 was detected in the urine of both ADPKD patients and animals with PKD.
Hyperphosphaturia	The tubular maximum of phosphate reabsorption per glomerular filtration rate was found to be lowest in 100 ADPKD patients in compar- ison with 20 non-diabetic CKD patients, 26 diabetic patients and 20 healthy controls.
Urinary copeptin	Urinary copeptin/urinary creatinine is associated with the TKV and eGFR which is harbinger of disease severity in ADPKD
Urinary fetuin alpha	Urinary Fetuin-A levels were significantly higher in 66 ADPKD patients compared to 17 healthy volunteers and 50 control patients with renal diseases of other causes.
Urine micro-RNA	Primary cell cultures were obtained from urine specimens of 20 patients with ADPKD and 20 patients with CKD. The abundance of mir- 223; mir-199a and mir-199b in ADPKD urine cells have been reported.
Urinary heparin-binding EGF-like growth factor	Urinary HB-EGF excretion and plasma concentration were higher in 27 patients with ADPKD than in 27 controls and it is correlated with disease severity in ADPKD.

eGFR: Estimated glomerular filtration rate; mir: microRNA; ADPKD: Autosomal dominant polycystic kidney disease; NGAL: Neutrophil gelatinase-associated lipocalin; IL-18: Interleukin-18; CFB: Complement factor B; SERPING 1: Serpin Family G Member 1 (The human complement factor 1-inhibitor gene); C9: Complement factor 9; C1RL: Complement C1r subcomponent Like; sFRP4: Secreted frizzled-related protein 4; CKD: Chronic kidney disease; PKD: Polycystic kidney disease; TKV: Total kidney volume; HB-EGF: Heparin-binding epidermal growth factor-like growth factor

els with TKV in a cohort of 102 patients with ADPKD. Briefly, urinary NGAL levels may increase only in advanced disease, and data about the predictive role of NGAL in ADPKD are not enough in the current literature.

Interleukin-18 (IL-18), a member of the IL-1 family of cytokines, is synthesized as an inactive 23-kDa precursor by several tissues including monocytes, macrophages, and proximal tubular epithelial cells and is processed into an active 18.3 kDa cytokine by caspase-1 (80). It has been demonstrated that urinary IL-8 could be a biomarker of AKI (81). Several clinical trials have focused on the diagnostic accuracy of IL-18 level in predicting AKI in recent years (82-84). Urinary IL-18 is elevated during apoptosis and necrosis of renal tubular cells, which is associated with

AKI in animal and human studies. Parikh et al. (70) demonstrated that urine IL-18 levels are mildly elevated in patients with ADPKD, but do not correlate with changes in kidney function and TKV. They speculated that urine IL-18 levels are enriched in cyst fluid derived from patients with ADPKD, demonstrating the translation of the findings from murine and rat models to human disease (70).

Recently, the role of complement system activation has been thought to be related in ADPKD. Furthermore, it has been shown that substantial amounts of complement proteins are present in the renal cyst fluid of patients with ADPKD (85). In this regard, over a hundred different glycoproteins and glycopeptides in the urine were identified; however, significant expression changes were only observed in six complement components in the urine from patients with ADPKD by using a robust quantitative proteomics screen. In conclusion, it has been found that the increased levels of urinary complement components complement factor B, SERPING1, and C9, and the decreased levels of complement component 1, r subcomponent-like, CD55, and CD59 were correlated with the different stages of ADPKD (86).

Multidimensional nuclear magnetic resonance (NMR) spectroscopy was used to investigate the urine specimens of patients with ADPKD and compared with those of healthy controls (87). In the present study, the authors showed that the support vector machine-based classification of urinary NMR fingerprints yielded to discriminate patients with early-stage ADPKD from patients with ESRD and healthy subjects (87, 88). In addition to the NMR-based metabolomics approach pursued in the present study, urinary proteomics has been successfully applied to the prediction of ADPKD. There were many proteins with significantly altered urinary excretion, most of which were collagen fragments. Uromodulin peptides, previously implicated in tubular injury, were also found in urine specimens. These marker proteins were found to distinguish patients from controls with a high degree of accuracy (89). The coupling of capillary electrophoresis to mass spectrometry allowed the identification of a unique set of proteins serving as reliable biomarkers for the prediction of ADPKD. The use of NMR-based metabolomics offers the additional advantage of only minimal required sample pretreatment and easy sample handling, enabling fast and fully automatic data collection (88).

Secreted frizzled-related protein 4 (sFRP4) expression promotes cyst formation in ADPKD. sFRP4 is induced by a similar mechanism that antagonizes the Wnt signaling cascade as a differentially regulated gene in cystogenesis. Cyst fluid from ADPKD kidneys activates the production of sFRP4 protein in renal tubular epithelial cell lines (90, 91). Vasopressin 2 receptor antagonism resulted in a decrease of promoter activity and tubular sFRP4 expression. Moreover, sFRP4 was found in the urine of patients and animals with ADPKD, indicating that sFRP4 may be a potential biomarker for monitoring the progression of ADPKD (92).

Fibroblast growth factor 23 (FGF23) associated with increased phosphate levels in urine is substantially higher in patients with ADPKD than in other patients with CKD (93). Moreover, polycystin 1 is highly expressed in osteoblasts and osteocytes, which are the main sources for FGF23 production (94). It could be hypothesized that polycystin 1 is directly involved in the regulation of FGF23 production and that mutant polycystin 1 is responsible for the increased FGF23 secretion in ADPKD. The finding of elevated FGF23 levels in ADPKD with normal renal function, normal parathyroid hormone, and renal leak of phosphate represents an early manifestation of ADPKD (93).

It has been well established that patients with ADPKD already have decreased urinary concentration capacity (43) and that plasma osmolality is maintained within the normal range at higher plasma copeptin and AVP levels (23). Plasma copeptin is elevated in patients with ADPKD and predicts disease progression (95, 96). Nakajima et al. (97) showed that urinary copeptin/u-Cr is closely associated with the two important markers of disease severity in ADPKD (positively with TKV and negatively with eGFR). They suggested that U-copeptin/u-Cr is a preferable and easily measured surrogate marker to help predict disease progression in ADPKD.

Fetuin alpha (FETUA) expression is restricted to the liver in adults; however, it is expressed in many organs including the kidney, brain, liver, bone, lungs, and heart in the fetal period (98). Despite the absence of FETUA mRNA genetically, the FETUA protein has been detected in proximal tubule epithelial cells of rat kidneys in a previous study (99). Thus, it is speculated that FETUA may reach proximal tubule cells by reabsorption from the tubule lumen after passing from plasma through the glomerular filtration barrier (99, 100). Recently, Piazzon et al. (101) observed higher urinary FETUA levels in patients with ADPKD than in healthy controls.

MicroRNAs (miRs) are noncoding, small RNA molecules that modulate gene expressions by regulating many different intracellular pathways at the posttranscriptional level. There are many multiple putative targets for each miR, and they can also change between cell types and over time. It appears that they may play an important role in cell physiology (102). miRs play a role in both embryonic development and kidney disease processes. Their different blood or urine levels have been associated with several specific kidney diseases in animal models and human studies (103-105). miRs may play a crucial role in the regulation of profibrotic calcium signaling depending on some studies that have investigated their effect in ADPKD (106). Serum miR-3907 levels were recently demonstrated to be associated with disease progression of ADPKD (107). Indeed, urine has been widely used as a specimen to detect protein biomarkers in polycystic kidney disease (89). Ben-Dov et al. (108) evaluated the miRs in urine specimens and kidney epithelial cells of patients with ADPKD and without ADPKD. They demonstrated that miRNA previously implicated as kidney tumor suppressors

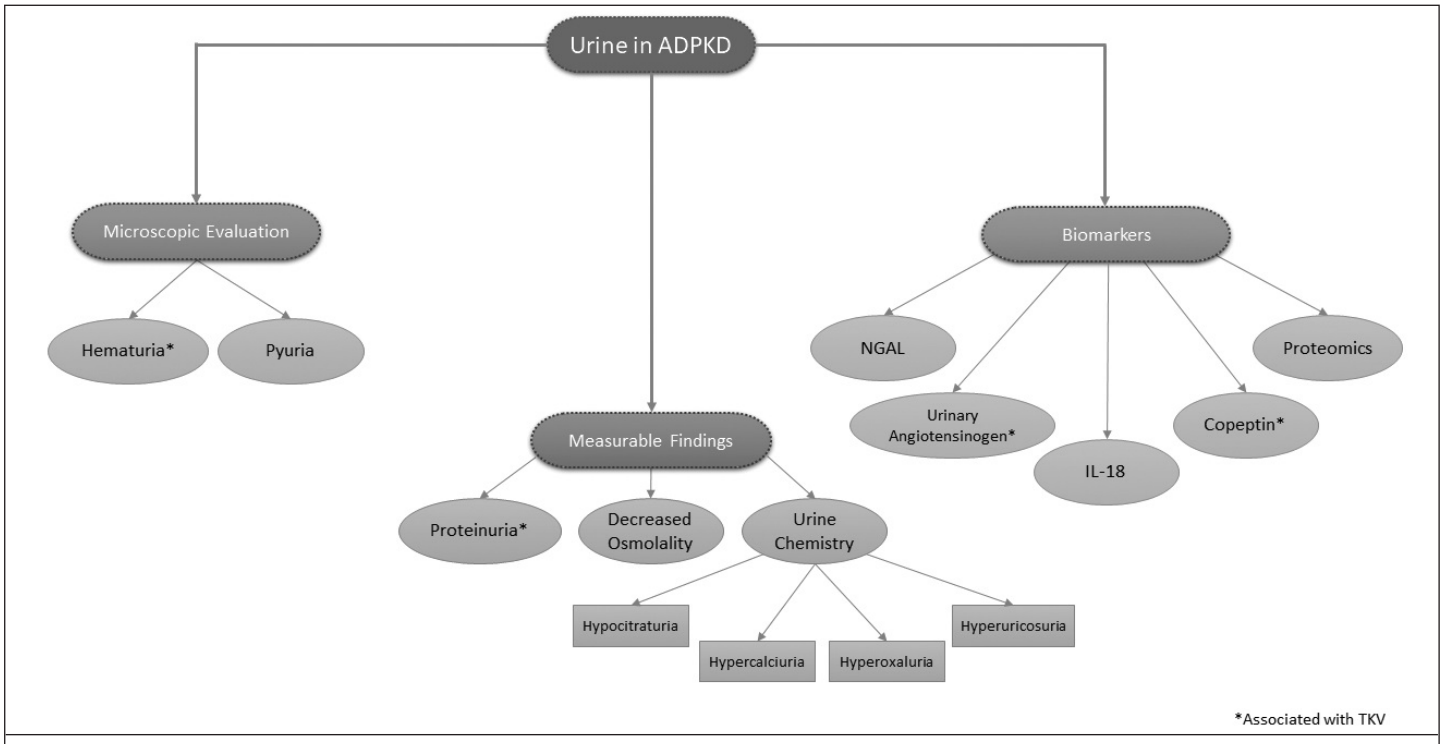

Figure 1. The evaluation of urinary specimen in autosomal dominant polycystic kidney disease.

(miR-1 and miR-133), as well as miRNA of presumed inflammatory and fibroblast cell origin (miR-223/miR-199), is dysregulated in ADPKD urine specimens compared with other patients with CKD (109).

Recently, urine proteome or peptidome markers have become clinically useful as urine biomarkers. Kistler et al. (89) defined the urinary biomarker profile of ADPKD and found a low molecular (<15 kDa) proteome fraction in the urine. Bakun et al. (109) studied the proteins of masses >10 kDa by using two-dimensional tryptic peptides separation. They showed that an ADPKD-characteristic footprint of 155 proteins significantly up- or down-regulated in the urine specimens of patients with ADPKD. There were significant differences in proteins of complement system, apolipoproteins, serpins, some growth factors, collagens, and extracellular matrix components in patients with ADPKD compared with those in healthy controls (109).

Epidermal growth factor (EGF) receptor pathway is shown to be involved with growth, migration, and proliferation of renal tubular cells (110). Dysregulation of this pathway has been suggested to play a role in the pathogenesis of ADPKD (64, 67). Heparin-binding EGF-like growth factor (HB-EGF) is known to be a more potent mitogen for renal tubular epithelia than EGF (111). Harskamp et al. (112) reported that EGF receptor ligands, such as HB-EGF, EGF, and transforming growth factor-α, are measured in blood and urine concentrations in patients with ADPKD at baseline and after treatment with a vasopressin V2 receptor antagonist (V2RA). Higher urinary HB-EGF excretion was found to be correlated with the severity of the disease in patients with ADPKD. Interestingly, HB-EGF excretion increased during V2RA treatment. In addition, further studies are needed to explain this result in patients with ADPKD.

Finally, Kawano et al. (113) analyzed many urine biomarkers in patients with ADPKD and compared them with those in healthy controls. There were significant differences between healthy subjects and patients with ADPKD with respect to several biomarkers including von Willebrand factor, IL-8, macrophage colony-stimulating factor, interferon receptor 2, perpetual flowering 1, trefoil factor family 3, hepatocyte growth factor, multicopper oxidase-1, 8-hydroxydeoxyguanosine, NGAL, liver-type fatty acid-binding protein (L-FABP), angiotensinogen, and ceruloplasmin. The levels of markers for multiple parts of the nephron are increased in patients with ADPKD. In addition to the measurement of UAE, the measurement of urinary β (2)-microglobulin, kidney injury molecule-1, heart-type-FABP, monocyte chemoattractant protein-1, N-acetyl-β-d-glucosaminidase, and endothelin-1 could be of value for determining the disease severity in patients with ADPKD (76, 79, 114-116).

CONCLUSION

Important new findings of the urine evaluation have improved our understanding with several pathogenic mechanisms including inflammation, cystogenesis, and disease progression in patients with ADPKD. Recent insights have highlighted the fact that urine concentration defect, hematuria, proteinuria, pyuria, urine calculi, and several urine biomarkers are not only pathological findings but also help clinicians with respect to disease progression during the follow-up of patients with ADPKD (Fig-

ure 1). In addition, several urine biomarkers in ADPKD were found to be associated with the severity of the disease and may be important in the near future to predict disease progression. Further studies are needed to clarify the mechanisms that lead to urine abnormalities of ADPKD from other kidney diseases.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.K.; Design - E.E., İ.K.; Supervision - İ.K.; Resource - E.E.; Materials - E.E.; Data Collection and/or Processing - E.E.; Analysis and/or Interpretation - E.E., İ.K.; Literature Search - E.E.; Writing - E.E., İ.K.; Critical Reviews - T.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Gabow PA. Autosomal dominant polycystic kidney disease. N Engl J Med 1993; 329: 332-42. [CrossRef]
2. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med 2008; 359: 1477-85. [CrossRef]
3. Igarashi P, Somlo S. Genetics and pathogenesis of polycystic kidney disease. J Am Soc Nephrol 2002; 13: 2384-98. [CrossRef]
4. The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. Cell 1994; 17; 77: 881-94. [CrossRef]
5. Mochizuki T, Wu G, Hayashi T, Xenophontos SL, Veldhuisen B, Saris JJ, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 1996; 272: 1339-42. [CrossRef]
6. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet 1999; 353: 103-7. [CrossRef]
7. Ariza M, Alvarez V, Marín R, Aguado S, López-Larrea C, Alvarez J, et al. A family with a milder form of adult dominant polycystic kidney disease not linked to the PKD1 (16p) or PKD2 (4q) genes. J Med Genet 1997; 34: 587-9. [CrossRef]
8. Pei Y, Paterson AD, Wang KR, He N, Hefferton D, Watnick T, et al. Bilineal disease and trans-heterozygotes in autosomal dominant polycystic kidney disease. Am J Hum Genet 2001; 68: 355-63. [CrossRef]
9. Taylor M, Johnson AM, Tison M, Fain P, Schrier RW. Earlier diagnosis of autosomal dominant polycystic kidney disease: importance of family history and implications for cardiovascular and renal complications. Am J Kidney Dis 2005; 46: 415-23. [CrossRef]
10. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009; 20: 205-12. [CrossRef]
11. Gabow PA, Kaehny WD, Johnson AM, Duley IT, Manco-Johnson M, Lezotte DC, et al. The clinical utility of renal concentrating capacity in polycystic kidney disease. Kidney Int 1989; 35: 675-80. [CrossRef]
12. Dunn FL, Brennan TJ, Nelson AE, Robertson GL. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 1973; 52: 3212-9. [CrossRef]
13. Gattone VH 2nd, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 2003; 9: 1323-6. [CrossRef]
14. Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. Curr Opin Nephrol Hypertens 2013; 22: 459-70. [CrossRef]
15. Gattone VH 2nd, Grantham JJ. Understanding human cystic disease through experimental models. Semin Nephrol 1991; 11: 617-31.
16. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012; 367: 2407-18. [CrossRef]
17. Torres VE, Bankir L, Grantham JJ. A case for water in the treatment of polycystic kidney disease. Clin J Am Soc Nephrol 2009; 4: 1140-50. [CrossRef]
18. Wang CJ, Grantham JJ, Wetmore JB. The medicinal use of water in renal disease. Kidney Int 2013; 84: 45-53. [CrossRef]
19. Martinez-Maldonado M, Yium JJ, Eknoyan G, Suki WN. Adult polycystic kidney disease: studies of the defect in urine concentration. Kidney Int 1972; 2: 107-13. [CrossRef]
20. Preuss H, Geoly K, Johnson M, Chester A, Kliger A, Schreiner G. Tubular function in adult polycystic kidney disease. Nephron 1979; 24: 198-204. [CrossRef]
21. Schrier RW, Brosnahan G, CadnapaphornchaiMA, Chonchol M, Friend K, Gitomer B, et al. Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol 2014; 25: 2399-418. [CrossRef]
22. Casteleijn NF, Zittema D, Bakker SJ, Boertien WE, Gaillard CA, Meijer E, et al. Urine and plasma osmolality in patients with autosomal dominant polycystic kidney disease: reliable indicators of vasopressin activity and disease prognosis? Am J Nephrol 2015; 41: 248-56. [CrossRef]
23. Zittema D, Boertien WE, van Beek AP, Dullaart RP, Franssen CF, de Jong PE, et al. Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. Clin J Am Soc Nephrol 2012; 7: 906-13. [CrossRef]
24. Ho TA, Godefroid N, Gruzon D, Haymann JP, Maréchal C, Wang X, et al. Autosomal dominant polycystic kidney disease is associated with central and nephrogenic defects in osmoregulation. Kidney Int 2012; 82: 1121-9. [CrossRef]
25. Gabow PA, Duley I, Johnson AM. Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1992; 20: 140-3. [CrossRef]
26. Ubara Y, Katori H, Tagami T, Tanaka S, Yokota M, Matsushita Y, et al.Transcatheter renal arterial embolization therapy on a patient with polycystic kidney disease on hemodialysis. Am J Kidney Dis 1999; 34: 926-31. [CrossRef]
27. Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. Kidney Int 1992; 41: 1311-9. [CrossRef]
28. Tracz MJ, Alam J, Nath KA. Physiology and pathophysiology of heme: implications for kidney disease. J Am Soc Nephrol 2007; 18: 414-20. [CrossRef]
29. Leslie CL, Simon BJ, Lee KF, Emhoff TA, Munshi IA. Bilateral rupture of multicystic kidneys after blunt abdominal trauma. J Trauma 2000; 48: 336-7. [CrossRef]
30. Mufarrij AJ, Hitti E. Acute cystic rupture and hemorrhagic shock after a vigorous massage chair session in a patient with polycystic kidney disease. Am J Med Sci 2011; 342: 76-8. [CrossRef]
31. Bajwa ZH, Gupta S, Warfield CA, Steinman TI. Pain management in polycystic kidney disease. Kidney Int 2001; 60: 1631-44. [CrossRef]

32. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. J Am Soc Nephrol 1997; 8: 1560-7. [CrossRef]
33. Schrier RW, Brosnahan G, Cadnapaphornchai MA, Chonchol M, Friend K, Gitomer B, et al. Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol 2014; 25: 2399-418. [CrossRef]
34. Bello-Reuss E, Holubec K, Rajaraman S. Angiogenesis in autosomal-dominant polycystic kidney disease. Kidney Int 2001; 60: 37-45. [CrossRef]
35. Wei W, Popov V, Walocha JA, Wen J, Bello-Reuss E. Evidence of angiogenesis and microvascular regression in autosomal-dominant polycystic kidney disease kidneys: a corrosion cast study. Kidney Int 2006; 70: 1261-8. [CrossRef]
36. Licina MG, Adler S, Bruns FJ. Acute renal failure in a patient with polycystic kidney disease. JAMA 1981; 245: 1664-5. [CrossRef]
37. Sumida K, Ubara Y, Hoshino J, Hayami N, Suwabe T, Hiramatsu R, et al. Myeloperoxidase-antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis in autosomal dominant polycystic kidney disease. BMC Nephrol 2013; 14: 94. [CrossRef]
38. Chapman AB, Johnson AM, Gabow PA, Schrier RW. Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1994; 5: 1349-54.
39. Bakker J, Olree M, Kaatee R, de Lange EE, Moons KG, Beutler JJ, et al. Renal volume measurements: accuracy and repeatability of US compared with that of MR imaging. Radiology 1999; 211: 623-8. [CrossRef]
40. Torres VE, Chapman AB, Perrone RD, Bae KT, Abebe KZ, Bost JE, et al.HALT PKD Study Group. Analysis of baseline parameters in the HALT polycystic kidney disease trials. Kidney Int 2012; 81: 577-85. [CrossRef]
41. Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. J Am Soc Nephrol 1995; 5: 2037-47.
42. Kistler AD, Poster D, KrauerFetal.Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. Kidney Int 2009; 75: 235-41. [CrossRef]
43. Meijer E, Rook M, Tent H, Weishaupt D, Raina S, Senn O, et al. Early renal abnormalities in autosomal dominant polycystic kidney disease. Clin J Am SocNephrol 2010; 5: 1091-8. [CrossRef]
44. Visciano B, Di Pietro RA, Rossano R, Mancini A, Zamboli P, Ciancia-ruso B, et al. Nephrotic syndrome and autosomal dominant polycystic kidney disease. Clin Kidney J 2012; 5: 508-11. [CrossRef]
45. Contreras G, Mercado A, Pardo V, Vaamonde CA. Nephrotic syndrome in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1995; 6: 1354-9.
46. Chow CL, Ong AC. Autosomal dominant polycystic kidney disease. Clin Med 2009; 9: 278-283. [CrossRef]
47. Hwang JH, Park HC, Jeong JC, Ha Baek S, Han MY, Bang K, et al. Chronic asymptomatic pyuria precedes overt urinary tract infection and deterioration of renal function in autosomal dominant polycystic kidney disease. BMC Nephrol 2013: 14; 1. [CrossRef]
48. Sklar AH, Caruana RJ, Lammers JE, Strauser GD. Renal infections in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1987; 10: 81-8. [CrossRef]
49. Gibson P, Watson ML. Cyst infection in polycystic kidney disease: a clinical challenge. Nephrol Dial Transplant 1998; 13: 2455-7. [CrossRef]
50. Piccoli GB, Arena V, Consiglio V, Deagostini MC, Pelosi E, Dourou-kas A, et al.Positron emission tomography in the diagnostic pathway for intracystic infection in ADPKD and "cystic" kidneys. A case series. BMC Nephrol 2011; 12: 48. [CrossRef]
51. Jouret F, Lhommel R, Beguin C, Devuyst O, Pirson Y, Hassoun Z, et al. Positron-emission computed tomography in cyst infection diagnosis in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol 2011; 6: 1644-50. [CrossRef]
52. Levine E, Grantham JJ. High-density renal cysts in autosomal dominant polycystic kidney disease demonstrated by CT. Radiology 1985; 154: 477-82. [CrossRef]
53. Ahmed ER, Tashkandi MA, Nahrir S, Maulana A. Retrospective analysis of factors affecting the progression of chronic renal failure in adult polycystic kidney disease. Saudi J Kidney Dis Transpl 2006; 17: 511-5.
54. Torres VE, Erickson SB, Smith LH, Wilson DM, Hattery RR, Segura JW. The association of nephrolithiasis and autosomal dominant polycystic kidney disease. Am J Kidney Dis 1988; 11: 318-25. [CrossRef]
55. Levine E, Grantham JJ. Calcified renal stones and cyst calcifications in autosomal dominant polycystic kidney disease: clinical and CT study in 84 patients. AJR Am J Roentgenol 1992; 159: 77-81. [CrossRef]
56. Torres VE, Wilson DM, Hattery RR, Segura JW. Renal stone disease in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1993; 22: 513-9. [CrossRef]
57. Grampsas SA, Chandhoke PS, Fan J, Glass MA, Townsend R, Johnson AM, et al. Anatomic and metabolic risk factors for nephrolithiasis in patients with autosomal dominant polycystic kidney disease. Am J Kidney Dis 2000; 36: 53-7. [CrossRef]
58. Gambaro G, Fabris A, Puliatta D, Lupo A. Lithiasis in cystic kidney disease and malformations of the urinary tract. Urol Res 2006; 34: 102-7. [CrossRef]
59. Nishiura JL, Neves RF, Eloi SR, Cintra SM, Ajzen SA, Heilberg IP. Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. Clin J Am Soc Nephrol 2009; 4: 838-44. [CrossRef]
60. Riese RJ, Sakhaee K. Uric acid nephrolithiasis: pathogenesis and treatment. J Urol 1992; 148: 765-71. [CrossRef]
61. Sakhaee K, Adams-Huet B, Moe OW, Pak CY. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int 2002; 62: 971-9. [CrossRef]
62. Torres VE, Keith DS, Offord KP, Kon SP, Wilson DM. Renal ammonia in autosomal dominant polycystic kidney disease. Kidney Int 1994; 45: 1745-53. [CrossRef]
63. Cheidde L, Ajzen SA, Tamer Langen CH, Christophalo D, Heilberg IP. A critical appraisal of the radiological evaluation of nephrocalcinosis. Nephron Clin Pract 2007; 106: c119-24. [CrossRef]
64. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet 2007; 369: 1287-301. [CrossRef]
65. Idrizi A, Barbullushi M, Petrela E, Kodra S, Koroshi A, Thereska N. The influence of renal manifestations to the progression of autosomal dominant polycystic kidney disease. Hippokratia 2009; 13: 161-4. [CrossRef]
66. Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, et al. Volume progression in polycystic kidney disease. N Engl J Med 2006; 354: 2122-30.[CrossRef]
67. Harris PC, Torres VE. Polycystic Kidney Disease. Annu Rev Med 2009; 60: 321-7. [CrossRef]
68. Ong AC, Harris PC. Molecular pathogenesis of ADPKD: the polycystin complex gets complex. Kidney Int 2005; 67: 1234-47. [CrossRef]

69. Briggs JP. The hunt for the perfect biomarker for acute kidney injury: back to gamma-trace? Kidney Int 2008; 74: 987-9. [CrossRef]
70. Parikh CR, Dahl NK, Chapman AB, Bost JE, Edelstein CL, Comer DM, et al. Evaluation of urine biomarkers of kidney injury in polycystic kidney disease. Kidney Int 2012; 81: 784-90. [CrossRef]
71. Kocyigit I, Yilmaz MI, Unal A, Ozturk F, Eroglu E, Yazici C, et al.A link between the intrarenal renin angiotensin system and hypertension in autosomal dominant polycystic kidney disease. Am J Nephrol 2013; 38: 218-25. [CrossRef]
72. Park HC, Kang AY, Jang JY, Kim H, Han M, Oh KH, et al.Increased urinary angiotensinogen/creatinine (AGT/Cr) ratio may be associated with reduced renal function in autosomal dominant polycystic kidney disease patients. BMC Nephrol 2015; 20; 16: 86. [CrossRef]
73. Kjeldsen L, Johnsen AH, Sengeløv H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. J Biol Chem 1993; 268: 10425-32.
74. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14: 2534-43. [CrossRef]
75. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int 2008; 73: 1008-16. [CrossRef]
76. Petzold K, Poster D, Krauer F, Spanaus K, Andreisek G, Nguyen-Kim TD, et al.Urinary biomarkers at early ADPKD disease stage. PLoS One 2015; 10: e0123555. [CrossRef]
77. Vareesangthip K, Vareesangthip K, Limwongse C, Reesukumal K. Role of urinary neutrophil gelatinase-associated lipocalin for predicting the severity of renal functions in patients with autosomal-dominant polycystic kidney disease. Transplant Proc 2017; 49: 950-4. [CrossRef]
78. Bolignano D, Lacquaniti A, Coppolino G, Donato V, Campo S, Fazio MR, et al. Neutrophilgelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clin J Am Soc Nephrol 2009; 4: 337-44. [CrossRef]
79. Meijer E, Boertien WE, Nauta FL, Bakker SJ, van Oeveren W, Rook M, et al. Association of urinary biomarkers with disease severity in patients with autosomal dominant polycystic kidney disease: a cross-sectional analysis. Am J Kidney Dis 2010; 56: 883-95. [CrossRef]
80. Dinarello CA. Interleukin-18 and the pathogenesis of inflammatory diseases. Semin Nephrol 2007; 27: 98-114. [CrossRef]
81. Lin X, Yuan J, Zhao Y, Zha Y. Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. J Nephrol 2015; 28: 7-16. [CrossRef]
82. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis 2004; 43: 405-14. [CrossRef]
83. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 2006; 70: 199-203. [CrossRef]
84. Parikh CR, Jani A, Mishra J, Ma Q, Kelly C, Barasch J, et al.Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. Am J Transplant 2006; 6: 1639-45. [CrossRef]
85. Lai X, Bacallao RL, Blazer-Yost BL, Hong D, Mason SB, Witzmann FA. Characterization of the renal cyst fluid proteome in autosomal dominant polycystic kidney disease (ADPKD) patients. Proteomics Clin Appl 2008; 2: 1140-52. [CrossRef]
86. Su Z, Wang X, Gao X, Liu Y, Pan C, Hu H, et al. Excessive activation of the alternative complement pathway in autosomal dominant polycystic kidney disease. J Intern Med 2014; 276: 470-85. [CrossRef]
87. Gronwald W, Klein MS, Kaspar H, Fagerer SR, Nürnberger N, Dettmer K, et al. Urinary metabolite quantification employing 2D NMR spectroscopy. Anal Chem 2008; 80: 9288-97. [CrossRef]
88. Gronwald W, Klein MS, Zeltner R, Schulze BD, Reinhold SW, Deutschmann M, et al. Detection of autosomal dominant polycystic kidney disease by NMR spectroscopic fingerprinting of urine. Kidney Int 2011; 79: 1244-53. [CrossRef]
89. Kistler AD, Mischak H, Poster D, Dakna M, Wüthrich RP, Serra AL. Identification of a unique urinary biomarker profile in patients with autosomal dominant polycystic kidney disease. Kidney Int 2009; 76: 89-96. [CrossRef]
90. Dennis S, Aikawa M, Szeto W, d'Amore PA, Papkoff J. A secreted frizzled related protein, FrzA, selectively associates with Wnt-1 protein and regulates wnt-1 signaling. J Cell Sci 1999; 112: 3815-20.
91. Benzing T, Simons M, Walz G. Wnt signaling in polycystic kidney disease. J Am Soc Nephrol 2007; 18: 1389-98. [CrossRef]
92. Romaker D, Puetz M, Teschner S, Donauer J, Geyer M, Gerke P, et al. Increased expression of secreted frizzled-related protein 4 in polycystic kidneys. J Am Soc Nephrol 2009; 20: 48-56. [CrossRef]
93. Pavik I, Jaeger P, Kistler AD, Poster D, Krauer F, Cavelti-Weder C, et al. Patients with autosomal dominant polycystic kidney disease have elevated fibroblast growth factor 23 levels and a renal leak of phosphate. Kidney Int 2011; 79: 234-40. [CrossRef]
94. Xiao Z, Zhang S, Mahlios J, Zhou G, Magenheimer BS, Guo D, et al. Cilia-like structures and polycystin-1 in osteoblasts/osteocytes and associated abnormalities in skeletogenesis and Runx2 expression. J Biol Chem 2006; 281: 30884-95. [CrossRef]
95. Boertien WE, Meijer E, Zittema D, van Dijk MA, Rabelink TJ, Breuning MH, et al. Copeptin, a surrogate marker for vasopressin, is associated with kidney function decline in subjects with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2012; 27: 4131-7. [CrossRef]
96. Kocyigit I, Yilmaz MI, Gungor O, Eroglu E, Unal A, Orscelik O, et al. Vasopressin-related copeptin is a novel predictor of early endothelial dysfunction in patients with adult polycystic kidney disease. BMC Nephrol 2016; 17: 196. [CrossRef]
97. Nakajima A, Lu Y, Kawano H, Horie S, Muto S. Association of arginine vasopressin surrogate marker urinary copeptin with severity of autosomal dominant polycystic kidney disease (ADPKD). ClinExpNephrol 2015; 19: 1199-205. [CrossRef]
98. Denecke B, Gräber S, Schäfer C, Heiss A, Wöltje M, Jahnen-Dechent W. Tissue distribution and activity testing suggest a similar but not identical function of fetuin-B and fetuin-A. Biochem J 2003; 376: 135-45. [CrossRef]
99. Matsui I, Hamano T, Mikami S, Inoue K, Shimomura A, Nagasawa Y, et al. Retention of fetuin-A in renal tubular lumen protects the kidney from nephrocalcinosis in rats. Am J Physiol Renal Physiol 2013; 304: F751-60. [CrossRef]
100. Matsui I, Hamano T, Mikami S, Fujii N, Takabatake Y, Nagasawa Y, et al. Fully phosphorylated fetuin-A forms a mineral complex in the serum of rats with adenine-induced renal failure. Kidney Int 2009; 75: 915-28. [CrossRef]
101. Piazzon N, Bernet F, Guihard L, Leonhard WN, Urfer S, Firsov D, et al. UrineFetuin-A is a biomarker of autosomal dominant polycystic kidney disease progression. J Transl Med 2015; 13: 103. [CrossRef]

102. Wing MR, Ramezani A, Gill HS, Devaney JM, Raj DS. Epigenetics of progression of chronic kidney disease: fact or fantasy? Semin Nephrol 2013; 33: 363-74. [CrossRef]
103. Duan ZY, Cai GY, Bu R, Lu Y, Hou K, Chen XM. Selection of urinary sediment miRNAs as specific biomarkers of IgA nephropathy. Sci Rep 2016: 22; 23498 [CrossRef]
104. Liep J, Kilic E, Meyer HA, Busch J, Jung K, Rabien A. Cooperative Effect of miR-141-3p and miR-145-5p in the Regulation of Targets in Clear Cell Renal Cell Carcinoma. PLoS One 2016; 11: e0157801. [CrossRef]
105. Patel V, Williams D, Hajarnis S, Hunter R, Pontoglio M, Somlo S, et al. miR-17~92 miRNA cluster promotes kidney cyst growth in polycystic kidney disease. Proc Natl Acad Sci U S A 2013; 110: 10765-70. [CrossRef]
106. Pandey P, Qin S, Ho J, Zhou J, Kreidberg JA. Systems biology approach to identify transcriptome reprogramming and candidate microRNA targets during the progression of polycystic kidney disease. BMC Syst Biol 2011; 5: 56. [CrossRef]
107. Kocyigit I, Taheri S, Sener EF, Eroglu E, Ozturk F, Unal A, et al. Serum micro-rna profiles in patients with autosomal dominant polycystic kidney disease according to hypertension and renal function. BMC Nephrol 2017; 18: 179. [CrossRef]
108. Ben-Dov IZ, Tan YC, Morozov P, Wilson PD, Rennert H, Blumenfeld JD, et al. Urine microRNA as potential biomarkers of autosomal dominant polycystic kidney disease progression: description of miRNA profiles at baseline. PLoS One 2014; 9: e86856. [CrossRef]
109. Bakun M, Niemczyk M, Domanski D, Jazwiec R, Perzanowska A, Niemczyk S, et al. Urine proteome of autosomal dominant polycystic kidney disease patients. Clin Proteomics 2012; 9: 13. [CrossRef]
110. Melenhorst WB, Mulder GM, Xi Q, Hoenderop JG, Kimura K, Eguchi S, et al. Epidermal growth factor receptor signaling in the kidney: key roles in physiology and disease. Hypertension 2008; 52: 987-93. [CrossRef]
111. Horikoshi S, Kubota S, Martin GR, Yamada Y, Klotman PE. Epidermal growth factor (EGF) expression in the congenital polycystic mouse kidney. Kidney Int 1991; 39: 57-62. [CrossRef]
112. Harskamp LR, Gansevoort RT, Boertien WE, van Oeveren W, Engels GE, van Goor H, et al. Urinary EGF receptor ligand excretion in patients with autosomal dominant polycystic kidney disease and response to tolvaptan. Clin J Am SocNephrol 2015; 10: 1749-56. [CrossRef]
113. Kawano H, Muto S, Ohmoto Y, Iwata F, Fujiki H, Mori T, et al. Exploring urinary biomarkers in autosomal dominant polycystic kidney disease. Clin Exp Nephrol 2015; 19: 968-73. [CrossRef]
114. Birenboim N, Donoso VS, Huseman RA, Grantham JJ. Renal excretion and cyst accumulation of beta 2 microglobulin in polycystic kidney disease. Kidney Int 1987; 31: 85-92. [CrossRef]
115. Park HC, Hwang JH, Kang AY, Ro H, Kim MG, An JN, et al. Urinary N-acetyl-β-D glucosaminidase as a surrogate marker for renal function in autosomal dominant polycystic kidney disease: 1 year prospective cohort study. BMC Nephrol 2012; 13: 93. [CrossRef]
116. Raina R, Lou L, Berger B, Vogt B, Do AS, Cunningham R, et al. Relationship of urinary endothelin-1 with estimated glomerular filtration rate in autosomal dominant polycystic kidney disease: a pilot cross-sectional analysis. BMC Nephrol 2016; 17: 22. [CrossRef]