(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 5 , Page No: 305-321
September-October 2023

IJMSCR

Advancements in Diagnostics and Emerging Therapies for ADPKD: A Glimpse into the Future

Merita Rroji[1], Nereida Spahia[1], Myftar Barbullushi [1] and Goce Spasovski [2].
[1]Department of Nephrology, University of Medicine Tirana, 1001 Tirana, Albania.
[2]University Clinic for Nephrology, Medical Faculty, University St. Cyril and Methodius, 1000 Skopje, North Macedonia

***Corresponding Author:**
Merita Rroji
Department of Nephrology, University of Medicine Tirana, 1001 Tirana, Albania.

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

This review highlights the innovative landscape of diagnostic tools and treatment strategies for Autosomal Dominant Polycystic Kidney Disease (ADPKD). The introduction of proteomic profiling in urine analysis has opened new avenues for early and accurate detection of ADPKD, enabling more precise diagnosis and risk stratification. This diagnostic approach capitalizes on identifying distinct protein patterns associated with the disease, paving the way for improved patient management and tailored interventions.

Concurrently, novel treatment strategies are emerging to tackle the underlying mechanisms driving ADPKD progression. These innovative approaches halt cyst expansion, preserve renal function, and mitigate complications. By targeting specific pathways involved in cyst growth, these treatments hold the potential to significantly affect the disease trajectory and enhance patients' quality of life. These advancements offer hope for improved clinical outcomes and hold promise for alleviating the burden on healthcare systems.

Keywords: ADPKD, CKD, proteomic profiling, novel treatment strategies

Introduction

Chronic Kidney Disease (CKD) is a prevalent health issue that substantially impacts mortality worldwide. Its significance is expected to increase further, affecting more individuals and significantly contributing to mortality. Moreover, CKD adversely affects the quality of life and has notable socioeconomic consequences [1]. Recent research highlights that despite the rarity of inherited kidney diseases (IKDs), a significant portion, around 20% of children and 10% of adults with CKD, possess identifiable genetic variations that contribute to the development of the disease [1]. Among these IKDs, Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the only hereditary kidney disorder documented in national and international registries.

ADPKD, a hereditary kidney disorder, presents a significant medical challenge due to its variable and unpredictable progression. Despite advancements in genetic understanding, the path to end-stage renal disease (ESRD) remains elusive, emphasizing the importance of accurate diagnosis and prognosis prediction [2]. The development of noninvasive biomarkers holds promise in addressing these complexities, aiding in identifying patients at high risk for rapid disease progression and those who would benefit from specific therapies like tolvaptan [3]. Urinary exosomal proteomics has emerged as a valuable tool for considering the influence of therapeutic interventions and revealing distinct pathways and protein profiles associated with disease progression and treatment response [3]. The intricate interplay of genetic factors and molecular pathways

underscores the need for precision medicine approaches, enabling tailored therapeutic strategies that potentially transform the management of ADPKD and improve patient outcomes.

This review is focused on the new potential diagnostic tools in ADPKD and potential therapies that would change the prognosis of this inherited kidney disease.

2. Diagnostic Innovations for ADPKD

ADPKD affect approximately 1:400 to 1:1,000 live births. It is characterized by the continuous growth of bilateral kidney cysts, leading to progressive renal enlargement and increased total kidney volume (TKV). Common complications include hypertension, polyuria, discomfort, nephrolithiasis, hematuria, infections, and kidney function decline, often culminating in end-stage renal disease (ESRD) around age 55. Variability in disease severity and progression exists even within families. The primary loci are PKD1 on chromosome 16p13.3 (78% of cases) and PKD2 on chromosome 4q21 (15% of cases), with minor loci contributing to a minority of cases. The disease course is challenging to predict due to compensatory mechanisms in polycystic kidneys, where residual nephrons maintain kidney function despite the cystic expansion [4,5]. Late-stage disease sees a notable increase in serum creatinine followed by a rapid decline in glomerular filtration rate (GFR) and progression to ESRD [2,5,6]. The familial aggregation of CKD can be explained by genetics in two main ways: Mendelian gene pathogenic variations are rare but significantly impact disease development; examples include ADPKD [7].

On the other hand, common genetic variations are prevalent and only have a minimal impact on the phenotype. In addition, to the advancement of genomic medicine, informed consent, the potential advantages and implications of genetic results, and the present restrictions on the interpretation of genetic results may identify the disease but not always portray the progress of the disease [8].

In clinical settings utilizing estimated GFR (eGFR) equations, notable limitations persist regarding early CKD detection and accurate prediction of CKD progression. Recent research by Rodrigues et al. highlighted significant and unexpected inaccuracies in eGFR calculations for ADPKD patients, averaging around 50 percent deviation from actual renal function. Consequently, whenever possible, measured GFR is recommended for ADPKD patients.

Alongside eGFR, established clinical biomarkers such as albuminuria, serum creatinine (sCr) levels, and urine albumin-to-creatinine ratio (UACR) can detect CKD. However, their efficacy in predicting individual CKD risk or the likelihood of progressing to end-stage renal disease (ESRD) remains limited. While methods like ultrasonography, MRI, family history, and genetic analysis aid diagnosis, they may not fully address complications or correlate with disease progression.

Recent studies have reinforced the role of height-adjusted total kidney volume (htTKV) as a robust biomarker for assessing diminished renal function. These investigations have elucidated htTKV's capacity to accurately reflect subtle changes in kidney morphology and its close association with declining renal power. htTKV evaluated by MRI emerges as a valuable and dynamic parameter facilitating early detection and precise monitoring of renal impairment [9,10].

Due to the substantial advancement in our understanding of cyst development and expansion biology, the ability to detect, assess, and predict disease severity in patients with ADPKD has significantly improved as an attempt to identify noninvasive markers of disease [11,12].

2.1. Urinary biomarkers in ADPKD

Urinary biomarker assays offer a noninvasive and convenient solution to these needs. As a sample source, Urine stands out for its ease of collection, non-invasiveness, and simple fluid availability. Mass spectrometry (MS)-based proteomics emerges as a potential method, addressing fundamental research and practical medical challenges.

Utilizing urinary proteomics, however, presents challenges due to the diverse origins of the urinary proteome, encompassing proteins and peptides from plasma, secreted proteins, microvesicles, and whole cells from the genitourinary tract. Disease-specific protein profiles and variations, influenced by age, sex, diet, and physiological state, add complexity. While urinary proteome analysis is commonly used for assessing kidney function, the correlation between

Volume 6, Issue 5; September-October 2023; Page No 305-321

urinary protein levels and kidney tissue levels remains unclear.

Hence, more than a thousand proteins have been found in the current analysis of human Urine, and studying urinary extracellular vesicles (EVs) proteome has gained significant research attention for establishing disease-related biomarkers due to their involvement in the pathophysiology of the disease and renal function [13,14].

With the intent of identifying and validating urine biomarkers for various kidney diseases, Kistler and colleagues embarked on a significant initiative. They were the first to pinpoint a distinctive urinary proteomic "footprint" specific to autosomal dominant polycystic kidney disease (ADPKD) [15]. This ground breaking research demonstrated that ADPKD patients possess a unique protein profile in their Urine, setting them apart from healthy individuals and those with other kidney-related conditions. Among the 197 proteins showing significant alterations in urine excretion, 38 were represented by identifiable amino acid sequences, predominantly fragments of Collagen type I or III.

Their work unveiled the crucial role of adaptive extracellular matrix (ECM) modifications in ADPKD cyst growth, substantiating earlier findings of ECM anomalies in polycystic kidney dis-ease investigations [16]. Notably, the matrix metalloproteinase inhibitor batimastat could curb cyst formation in a rodent model, and elevated serum enzyme levels were observed in ADPKD patients [17]. Kirstler's team also identified a shared mechanism between ADPKD and renal aging [18]. Furthermore, they detected uromodulin peptides in urine samples, linking them to tubular damage [19].

In a subsequent clinical proteomic study using samples from the CRIPS study, the researchers shed light on young ADPKD individuals with mutations but no visible cysts. Urine proteome analysis enabled the identification of this subgroup, suggesting the potential for refining diagnostic models [20]. The authors hypothesized that cyst formation induces renal ECM reorganization, retarding collagen breakdown and leading to a decline in collagen-derived peptides in Urine. This decline correlated inversely with each individual's height-adjusted total kidney capacity, hinting at collagen fragments as potential prognostic indicators. They also found an increased presence of fibrinogen alpha chain and keratin peptides, aligning with the role of fibronectin and keratin 19 in renal cystogenesis [21].

Notably, a consistent downregulation of uromodulin's c-terminal segments was linked to ADPKD, possibly attributed to less efficient uromodulin breakdown. Elevated osteopontin levels were observed due to reduced urinary excretion of an osteopontin fragment [22]. The diagnostic biomarker model was rigorously tested in a diverse cohort of 481 individuals with renal and extrarenal disorders, confirming its specificity to ADPKD. Proteome changes associated with markers previously linked to acute kidney injury (AKI) were also observed in ADPKD, strengthening the model's diagnostic potential [23-26].

In subsequent investigations, the same research group further extended their initial findings, revealing a predictive biomarker-based classifier consisting of 20 urine peptides at baseline that demonstrated the capacity to forecast the onset of end-stage renal disease (ESRD) over a 10 to 13-year period for individuals aged 24 to 46 [27]. Notably, this biomarker score's efficacy was comparable to the established measure of height-adjusted total kidney volume (htTKV). Notably, combining these biomarkers led to improved predictive accuracy for identifying low or high-risk progression to ESRD. Moreover, this same biomarker model displayed the capability to forecast an 8-year decline in glomerular filtration rate (GFR) amounting to 30 mL/min/1.73 m2 among young individuals (initially aged 24). An intriguing observation emerged from their investigations, where they identified that approximately 80 percent of the predictive peptides originated from proteolytic cleavage of large proteins. This insight underscores the role of proteases beyond protein expression levels in shaping the urinary peptide landscape. In-depth computational analyses revealed nine proteases, including cathepsins D, E, and L, meprin A, and matrix metallopeptidases 2, 3, 8, and 9, involved in producing these predictive peptides. This suggests their potential involvement in remodeling the extracellular matrix (ECM) during cyst growth [28].

In recent work, Rauniyar et al. identified 69 urinary target proteins exhibiting significant dysregulation in ADPKD. These findings propose a framework for classifying ADPKD patients into subgroups

Volume 6, Issue 5; September-October 2023; Page No 305-321

resembling normal controls. This innovative approach holds promise for establishing urinary protein biomarkers to gauge cyst growth rate. However, the potential of this model awaits further validation through longitudinal studies involving larger patient cohorts [29].

Clinical nephrology is witnessing rapid progress in exploring urinary EVs. Advances in quantitative and qualitative analyses of the urine EV proteome now facilitate comprehensive comparisons of protein expression patterns from diverse sources. By scrutinizing uEVs sourced from ADPKD patients alongside healthy controls, notable alterations in protein expression patterns were observed [30]. A novel avenue emerges with the proposition of a urine test evaluating the urine exosomal polycystin-1 (PC1)/Transmembrane Protein 2 (TMEM2) or polycystin-2 (PC2)/TMEM2 ratio, which holds the potential for diagnosing and monitoring polycystic kidney disease [30]. In ADPKD, individuals inherit a faulty copy of PKD1 or PKD2, encoding polycystin-1 (PC1) or polycystin-2 (PC2). These proteins are released in urinary exosome-like vesicles (EVs), often in fragmented forms. Notably, PKD1 mutation carriers exhibited reduced levels of PC1 and PC2, while the protein TMEM2, possessing fibrocystin homology, displayed elevated expression. The inverse correlation between PC1/TMEM2 ratio and htTKV potentially signifies prognostic relevance. Individuals with unfavorable disease trajectories might exhibit lower PC1/TMEM2 ratios, likely attributed to null PKD1 alleles and hypomorphic polymorphisms on the other allele. In contrast, those with favorable prognoses may carry missense or hypomorphic mutations that facilitate substantial PC1 loading into uELVs from the defective allele. The findings of this comprehensive investigation not only underscore the potential predictive value of these biomarkers but also support the intriguing hypothesis that EVs play a contributory role in renal physio-pathology, offering a unique avenue for monitoring apical membrane protein expression in the urinary tract without resorting to invasive measures [31].

In the focus of diagnosing ADPKD, exploring urinary extracellular vesicles (EVs) has unveiled potential markers indicative of underlying mechanistic processes. Notably, villin-1, a modulator of actin dynamics governing cell shape and motility, was observed in uEVs [54]. Villin-1, predominantly expressed in the proximal tubules' brush border within the kidney, may be upregulated due to polycystin-1 ab-normalities, potentially contributing to disturbed cell polarity and excessive cell proliferation [32,33]. The involvement of desmosomal proteins (plakins) in uEVs further underscores their pertinence. Desmosomal plaques, crucial for epithelial sheet stabilization through basolateral membrane adhesion, may be affected by polycystin-1 dysfunction, potentially disrupting adhesion, protein sorting, and cell polarity in cystic epithelia [34]. This could explain elevated plakin levels in ADPKD uEVs, given the altered localization of desmosomal proteins due to polycystin-1's mis-polarization [35].

Complement proteins within uEVs pose intriguing questions, considering their larger size and limited filtration propensity [13,36]. A plausible explanation could involve local renal epithelial production and elimination of complement to combat bacterial intrusion, potentially amplified in ADPKD due to increased cyst epithelial cell proliferation. However, these factors may prove more pertinent in advanced ADPKD stages or treatment assessment [36]. Proteome profiling via mass spectrometry was leveraged to delineate protein content within microvesicles and exosomes, distinguishing medullary sponge-related cystogenesis from ADPKD [37].

In this context, 34 core proteins emerged as discriminators between microvesicles and exosomes in the medullary sponge kidney and ADPKD [38,39].

These discerning molecular insights collectively elucidate key facets of cyst formation and expansion, tubular cell proliferation, extracellular matrix perturbations, and the intricate mechanisms underpinning transepithelial fluid secretion into the cyst lumen, thus characterizing the complex landscape of ADPKD pathology.

The clinical management of autosomal dominant polycystic kidney disease (ADPKD) faces the challenge of variable disease progression rates, often eluding predictability despite knowledge of causative genes (PKD-1 or PKD-2) and specific mutations. A pivotal advancement would involve the development of a noninvasive biomarker capable of predicting and monitoring disease trajectory during prolonged treatment. In this context, urinary exosomal

Volume 6, Issue 5; September-October 2023; Page No 305-321

proteomics emerged as a potent investigative tool, facilitating the assessment of the impact and efficacy of long-term tolvaptan therapy on ADPKD progression [40].

Distinct dichotomies between rapid and slowly progressive profiles manifested across all stages of functional deterioration among ADPKD patients. These profiles revealed specific pathways and proteins, encompassing Notch, integrins, growth factor signaling, microtubule kinase, vesicle proteins, and epidermal growth factor substrate. Furthermore, a comparative analysis of urinary exosomal proteins before and after a four-year tolvaptan regimen showed diverse pathway modification patterns contingent upon the therapeutic response's efficacy. Patients with favorable tolvaptan responses exhibited characteristic upregulation of Wnt signaling and vesicle proteins. At the same time, those with less responsive outcomes demonstrated augmented angiogenic signaling pathways and additional forms of the vasopressin receptor AVPR2 [40,41].

A summary of Studies on Proteomic Analysis, Urinary Extracellular Vesicles (uEV), and and Urinary Exosomes in ADPKD) is presented to the table 1.

The proteomic profiling of urinary exosomes bears remarkable potential as a universally applicable approach for identifying and monitoring individuals with rapidly progressive ADPKD, susceptible to poor outcomes, who may optimally benefit from tolvaptan therapy. As an essential stride toward the realization of individualized susceptibility assessment and personalized pharmacotherapy, establishing a urinary exosomal protein expression atlas holds the promise of identifying suitable candidates for treatment, thereby advancing the frontiers of precision medicine [42].

3.Navigating Therapeutic Avenues: Treatment Strategies in ADPKD

The progressive nature of the disease and its associated morbidity have prompted intensive research into novel therapeutic strategies that aim to mitigate or delay its natural course. Most focus on interventions target the key molecular pathways, cellular mechanisms, and signaling cascades implicated in cystogenesis. By elucidating the mechanisms underlying these promising therapies, a comprehensive understanding of their potential to alter the trajectory of ADPKD can be gained. Ultimately, this exploration offers valuable insights into the evolving treatment paradigm for ADPKD, potentially revolutionizing the clinical management of this debilitating condition.

3.1. Tolvaptan therapy

In recent years, Tolvaptan, a vasopressin V2 receptor antagonist, has emerged as a promising pharmacological intervention. Mechanistically, Tolvaptan disrupts cyclic adenosine monophosphate (cAMP) signaling, arresting cyst-lining epithelial cell proliferation. Clinical trials have provided a nuanced understanding of Tolvaptan's impact on ADPKD. The landmark TEMPO 3:4 [43], 4;4 [44] and REPRISE trials [45] demonstrated Tolvaptan's efficacy in slowing total kidney volume expansion and preserving renal function. Recent analyses have further dissected the temporal trajectory of Tolvaptan's effects, indicating sustained benefits over extended treatment periods. Notably, Tolvaptan's capacity to delay renal function decline is emerging as a critical hallmark, heralding a potential paradigm shift in disease management. Challenges encompass nuanced patient selection, optimal dosing strategies, and judicious management of potential hepatotoxicity and polyuria. The post-TEMPO era has witnessed a surge in real-world studies probing Tolvaptan's effects across diverse patient cohorts. The REPRISE trial (Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD) was conducted to assess the effects of tolvaptan on total kidney volume and renal function in ADPKD patients. The trial consisted of two phases: a randomized, double-blind, placebo-controlled phase and an open-label phase.

In the randomized phase, ADPKD patients were assigned to receive either tolvaptan or placebo. The primary endpoint was the change in total kidney volume over a 1-year period. The trial demonstrated that tolvaptan significantly slowed the increase in total kidney volume compared to placebo. Additionally, tolvaptan was associated with a slower decline in estimated glomerular filtration rate (eGFR), indicating a potential benefit in preserving kidney function.

Studies have explored Tolvaptan's role in special populations, such as pediatric and elderly patients,

Volume 6, Issue 5; September-October 2023; Page No 305-321

expanding its therapeutic scope. Ongoing investigations, such as the REPRISE Extension study, try to reveal Tolvaptan's long-term impact and the potential for sustained benefits beyond the confines of controlled clinical trials [46]. The synergy between Tolvaptan and emerging therapeutic agents presents a compelling avenue. Combinations with mTOR inhibitors and other disease-modifying agents hold the potential to augment therapeutic outcomes, potentially heralding a new era of combination therapy. Notably, advancements in precision medicine and individualized treatment approaches may leverage Tolvaptan's efficacy within tailored therapeutic regimens [47].

3.2. Somatostatin Analogs: Targeting cAMP-Mediated Pathways

The exploration of somatostatin analogs as cAMP-modulating agents unveils a promising avenue in ADPKD management. Recent therapeutic studies have looked at how somatostatin analogs, especially octreotide, can slow down the cystogenesis of ADPKD. The ALADIN 1 study, a pivotal randomized controlled trial, looked at the effects of octreotide-LAR on the growth of the kidneys and liver. A post hoc analysis of the ALADIN study confirmed that octreotide had a beneficial effect on the slope of measured GFR from the first to the third year of treatment. The subsequent ALADIN 2 study extends these observations by investigating the sustained impact of octreotide -LAR on patients with eGFR ≤ 40 mL/ min/1.73 m2, revealing that in later-stage ADPKD, octreotide-LAR slowed kidney growth and delayed progression to ESRD, in particular in CKD stage 4 (adjusted HR [95% CI]: 0.121 [0.017 to 0.866], p = 0.036) [48].

Lately, the DIPAK study A more extensive, open-label randomized controlled trial (DIPAK 1 study) was performed in the Netherlands, investigating the effects of lanreotide in 305 ADPKD patients with CKD3 after 2.5 years of treatment. Lanreotide significantly reduced the growth of liver and kidney cysts, but no influence was found on eGFR [49,50].

Until now, there is no evidence that somatostatin analogs should be used in patients with polycystic renal disease. However, they should be considered in patients with high-volume polycystic livers to prevent liver transplantation. While the findings from these trials provide valuable insights into potential therapeutic interventions, further research is essential to establishing their long-term efficacy.

3.3. Metformin in ADPKD Management: An Evolving Avenue

TAME-PKD is a Phase II, double-blind, randomized, placebo-controlled trial to see if metformin could delay the advancement of ADPKD. Metformin works by stopping the production of cyclic AMP and turning on an enzyme called AMP-activated protein kinase (AMPK), which may prevent cysts from growing. Non-diabetic adults with ADPKD and an eGFR ≥50 ml/min/1.73m² were recruited, and participants were randomly assigned to receive metformin or placebo [51]. Safety, tolerability, and efficacy were assessed through measures such as rates of hypoglycemia, adverse events, kidney and liver volumes, pain, quality of life, and urinary metabolomic biomarkers [51]. The study's goal is to learn more about metformin's potential as a treatment for ADPKD. Investigating the safety and tolerability of metformin in adults with ADPKD revealed that it was well-tolerated and safe. While a modest reduction was observed in the decline of eGFR, the effect was not statistically significant. As a result, assessing metformin's efficacy necessitates a more extensive trial with increased statistical power to detect meaningful differences in endpoints [52,53].

3.4. mTOR Inhibitors Use in ADPKD

Two crucial studies collectively provide insights into the effects of mTOR inhibitors, specifically sirolimus and everolimus, on disease progression in ADPKD. Sirolimus Study (Serra et al., 2010): This 18-month, open-label, randomized controlled trial aimed to investigate the impact of sirolimus on total kidney volume (TKV) in patients with ADPKD. One hundred patients aged 18 to 40 were randomized to receive either sirolimus (target dose, 2 mg daily) or standard care. The primary outcome, TKV at 18 months, revealed no significant difference between the sirolimus and standard care groups. Secondary outcomes, including glomerular filtration rate (GFR) and urinary albumin excretion rate, also showed no significant differences. These results suggest that sirolimus did not lead to a significant reduction in TKV or improvement in GFR during the study period [54-56].

Volume 6, Issue 5; September-October 2023; Page No 305-321

Everolimus Study (Walz et al., 2010) [57]: This two-year, double-blind study investigated the impact of everolimus on changes in total kidney volume (TKV) among ADPKD patients. 433 patients were randomized to receive either a placebo or everolimus. The co-primary outcomes were changes in TKV at 12 and 24 months. Over the first year, TKV increased significantly less in the everolimus group compared to the placebo group. However, this difference was no longer statistically significant at the two-year mark. Additionally, the study assessed changes in estimated glomerular filtration rate (eGFR) and found no significant difference between the everolimus and placebo groups. Adverse event rates and dropout rates were higher in the Everolimus group. These findings suggest that everolimus may have a limited impact on slowing TKV growth and preserving renal function in ADPKD patients over the two-year study period.

While sirolimus did not demonstrate a significant reduction in TKV or improvement in GFR, the impact of everolimus on TKV growth and renal function appears limited within the two-year study period. Further research is needed to fully understand mTOR inhibitors' potential benefits and limitations in treating ADPKD.

In a recent systematic review, were evaluated the therapeutic efficacy of various treatments for autosomal dominant polycystic kidney disease (ADPKD) by analyzing a range of randomized controlled trials. Tolvaptan is the gold standard for treating ADPKD. Compared to a placebo, it showed a standardized mean difference (SMD) of 0.24 and a mean difference (MD) of -2.70 in keeping kidney function and stopping total kidney volume (TKV) growth. Notably, tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors also favorably impact TKV growth compared to placebo. Somatostatin analogs emerged as particularly effective, showing significant TKV growth inhibition compared to placebo and tolvaptan, with MD values of -5.69 and -2.99, respectively. While metformin tended to preserve renal function, the effect did not reach statistical significance (SMD: 0.28, p = 0.09). This comprehensive analysis underscores the reasonable therapeutic efficacy of tolvaptan and highlights the notable potential of somatostatin analogs in inhibiting TKV growth in ADPKD patients. The findings shed light on the comparative effectiveness of different ADPKD treatments, contributing valuable insights into managing this condition [58].

3.5. Exploring SGLT2 Inhibitors for ADPKD: Potential Benefits and Considerations

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) represent a class of medications that target sodium-glucose cotransporters in the proximal tubule of the kidneys. By doing so, they induce glycosuria, which is the excretion of glucose in the urine, and enhance the delivery of sodium to a specific kidney structure known as the macula densa. This process ultimately leads to the constriction of afferent arterioles, reducing the pressure within the glomeruli, the kidney's filtering units. Consequently, this intricate mechanism helps moderate the workload of tubular transport and decreases the demand for oxygen in the kidney cortex [59].

SGLT2is has demonstrated significant effectiveness in slowing the deterioration of kidney function and delaying the progression to end-stage kidney disease (ESKD). The precise mechanisms behind these benefits are not yet fully elucidated, but evidence suggests that SGLT2is might offer advantages to patients with chronic kidney disease (CKD) irrespective of their diabetic status.

One unique thing about how SGLT2i work is that they cause glycosuria, natriuresis (the release of sodium in the urine), and osmotic diuresis driven by glucose. This prompts the release of vasopressin, a hormone that promotes cyst growth. Patients with ADPKD who are also treated with vasopressin receptor antagonists like tolvaptan should pay special attention to this interaction. In such cases, the combined treatment may disrupt the usual water reabsorption process, raising concerns about potential complications such as hypovolemia (low blood volume), hypernatremia (high sodium levels), and acute kidney injury. Clinical observations have indeed reported cases of acute kidney injury in patients prescribed tolvaptan and SGLT2is, highlighting the need for further research to comprehensively assess the combined effects of these medications on urinary output [60,61].

However, a significant subset of ADPKD patients faces challenges with tolvaptan therapy due to adverse effects and the associated risk of liver injury.

Volume 6, Issue 5; September-October 2023; Page No 305-321

In particular, older ADPKD patients may derive limited benefit from tolvaptan. For this subgroup, the potential advantages offered by SGLT2is hold considerable appeal. It is important to note, though, that the efficacy of SGLT2is in animal models of ADPKD has yielded inconsistent results. The underlying hypothesis revolves around the notion that SGLT2is' reduction of hyperglycemia could attenuate cyst formation. Nevertheless, experimental outcomes from various ADPKD rodent models have yielded contradictory findings. Further complicating matters is the observation that existing rodent models do not perfectly replicate the genetic mutations characteristic of ADPKD, highlighting the challenges of modeling this complex condition [62].

Beyond their role in preserving kidney function, SGLT2is offer additional advantages. SGLT2is has been shown to slow the rate of kidney function loss in CKD more than renin-angiotensin-aldosterone system inhibitors (RAASis) [63] and tolvaptan. However, it is essential to acknowledge that ADPKD patients exhibit unique patterns of renal function changes, limiting direct comparisons. While all three categories of medications have shown promise in delaying progression to ESKD, only SGLT2is has demonstrated a mortality benefit for CKD patients. This has significant implications for ADPKD, where cardiovascular disease is a leading cause of mortality.

In general, SGLT2is holds promise as a therapeutic intervention in CKD management, particularly in the context of ADPKD. Their ability to preserve kidney function and confer unique benefits beyond standard treatments underscores their potential utility. Despite uncertainties regarding their combined use with tolvaptan and their potential impact on cyst growth, SGLT2is presents a compelling option for ADPKD patients who cannot tolerate or do not respond to tolvaptan. Their multifaceted advantages, including mortality reduction and potential anemia management, position them as a promising avenue in the evolving landscape of kidney disease management [64].

3.6. Diet in ADPKD

Dietary salt restriction is emphasized in evaluating sodium intake, primarily through 24-hour urine collection [65]. Despite some ongoing debates, clinicians have a consensus that individuals should avoid high-sodium diets (>5g per day). Current guidelines from KDIGO recommend a daily target intake of <2g of sodium (<5g of table salt) for all CKD patients, particularly those with hypertension or proteinuria. Notably, excessive sodium intake can potentially undermine the efficacy of RAAS blockade therapy, as seen in trials involving diabetic and non-diabetic CKD patients [66].

In the context of ADPKD, where salt-sensitive hypertension is prevalent, optimal RAAS blockade is essential. Evidence from the CRISP trial suggests a link between higher urinary sodium excretion, increased total kidney volume (TKV) growth rate, and a decline in glomerular filtration rate (GFR) [67].

Post-hoc analysis of HALT-PKD trials supports effective sodium reduction for ADPKD patients. These studies indicated that each 18mEq (414mg) increase in daily urinary sodium excretion corresponded to increased TKV and accelerated eGFR decline. Notably, slow eGFR decline in early-stage ADPKD patients and including mild cases in the study may have masked significant associations. Despite an initial daily sodium intake of 178mEq (4.1g of sodium), modest reductions led to 12mEq (276mg) and 26mEq (598mg) reductions in studies A and B, respectively [68-70].

While evidence on dietary protein restriction in ADPKD is limited, KDIGO advises reducing protein intake (<0.8g/kg per day for eGFR <30 ml/min/1.73 m2) and avoiding high protein intake (>1.3 g/kg per day) for CKD patients at risk of progression. Given its role in glomerular hyperfiltration and nitrogenous waste accumulation, research supports protein restriction.

Promoting salt and protein reduction through 24-hour urine collections, multidisciplinary education, and motivational interviewing aligns with KDIGO guidelines. A balanced diet of complex carbohydrates, fruits, and vegetables, with limited sodium (<2.3 mg per day) and protein (<0.8 g/kg per day) content is recommended [66,71].

The role of water intake in ADPKD management is also significant. Higher circulating levels of AVP are associated with disease progression. Fluid intake regulates AVP levels, offering a potential treatment approach. Observational studies demonstrated the safety and tolerability of water prescriptions to

Volume 6, Issue 5; September-October 2023; Page No 305-321

reduce urine osmolality and AVP concentrations. Ongoing randomized trials explore this further.

Patients with eGFR >30ml/min/1.73 m2, not on diuretics, without AVP-altering conditions, and urological abnormalities may benefit from increased water intake targeting urinary osmolality <250mosm/kg H2O, generally involving >3l per day. This approach aims to counteract impaired urinary concentration while considering potential hyponatremic risks [72,73].

4.Conclusion:

In the analysis provided, we aimed to demonstrate the role of urine biomarkers and proteomic profiling in individuals with ADPKD. This innovative approach holds promise for constructing diagnostic and prognostic models specific to these conditions. Such models can significantly enhance diagnostic accuracy, deepen our understanding of the underlying molecular mechanisms driving these diseases, enable effective monitoring of patients with rapidly advancing conditions, and ultimately pave the way for personalized medical interventions tailored to each patient.

Creating a comprehensive urinary exosomal protein expression database for ADPKD could be pivotal in identifying individuals requiring timely intervention and likely to respond positively to extended pharmacological treatment.

Besides, the potential impact of new therapies on the progression of ADPK holds immense promise for transforming the landscape of patient care. As our knowledge of the molecular mechanisms underlying ADPKD deepens, innovative treatments targeting these pathways can significantly alter the disease's trajectory. The advent of precision medicine, driven by advancements in genetics and personalized therapies, has the potential to revolutionize how we approach ADPKD treatment.

Emerging therapies, such as novel pharmacological agents targeting the dysregulated pathways involved in cyst formation and growth, are vital in slowing disease progression and improving patient outcomes. Early clinical trials have shown encouraging results, suggesting that these therapies could attenuate cyst expansion, preserve renal function, and alleviate the burden of complications associated with ADPKD.

References:

1. Kovesdy, C.P. Epidemiology of chronic kidney disease: an update 2022. Kidney International Supplements. 2022, 12(1), 7-11. doi:10.1016/j.kisu.2021.11.003
2. Bergmann, C., Guay-Woodford, L. M., Harris, P. C., Horie, S., Peters, D. J. M., & Torres, V. E. (2018). Polycystic kidney disease. *Nature reviews. Disease primers*, *4*(1), 50. https://doi.org/10.1038/s41572-018-0047-y
3. Uhlén, M., Fagerberg, L., Hallström, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., Sivertsson, Å., Kampf, C., Sjöstedt, E., Asplund, A., Olsson, I., Edlund, K., Lundberg, E., Navani, S., Szigyarto, C. A., Odeberg, J., Djureinovic, D., Takanen, J. O., Hober, S., Alm, T., … Pontén, F. (2015). Proteomics. Tissue-based map of the human proteome. *Science (New York, N.Y.)*, *347*(6220), 1260419. https://doi.org/10.1126/science.1260419
4. Reiterová, J., & Tesař, V. (2022). Autosomal Dominant Polycystic Kidney Disease: From Pathophysiology of Cystogenesis to Advances in the Treatment. International journal of molecular sciences, 23(6), 3317. https://doi.org/10.3390/ijms23063317
5. Nobakht, N., Hanna, R. M., Al-Baghdadi, M., Ameen, K. M., Arman, F., Nobahkt, E., Kamgar, M., & Rastogi, A. (2020). Advances in Autosomal Dominant Polycystic Kidney Disease: A Clinical Review. *Kidney medicine*, *2*(2), 196–208. https://doi.org/10.1016/j.xkme.2019.11.009
6. Vasileva, V.Y.; Sultanova, R.F.; Sudarikova, A. V., Ilatovskaya, D. V. Insights Into the Molecular Mechanisms of Polycystic Kidney Diseases. Frontiers in Physiology. 2021,12(September). doi:10.3389/fphys.2021.693130
7. Groopman, E.E.; Rasouly, H.M.; Gharavi, A.G. Kidney genomics. Nature Reviews Nephrology. 2018,14(2), 83-104. doi:10.1038/nrneph.2017.167.Genomic
8. Köttgen, A.; Cornec-Le Gall, E.; Halbritter, J.; et al. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2022, 101(6), 1126-1141. doi:10.1016/j.kint.2022.03.019

Volume 6, Issue 5; September-October 2023; Page No 305-321

9. Tangri, N.; Hougen, I.; Alam, A.; Perrone, R.; McFarlane, P.; Pei Y. Total kidney volume as a biomarker of disease progression in autosomal dominant polycystic kidney disease. Canadian Journal of Kidney Health and Disease. 2017,4. doi:10.1177/2054358117693355
10. Harris, T.; Sandford, R.; De Coninck, B.; et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD Forum and Multispecialist Roundtable partici-pants. Nephrology Dialysis Transplantation. 2018, 33(4), 563-573. doi:10.1093/ndt/gfx327
11. Pejchinovski, M.; Mischak, H. Clinical Proteomics in Kidney Disease: From Discovery to Clinical Application. PRILOZI. 2017,38(3),39-54. doi:10.2478/prilozi-2018-0005
12. Rinschen, M.M.; Saez-Rodriguez, J. The tissue proteome in the multi-omic landscape of kidney disease. Nature Reviews Nephrology. 2021, 17(3), 205-219. doi:10.1038/s41581-020-00348-5
13. Salih, M.; Zietse, R.; Hoorn, E.J. Urinary extracellular vesicles and the kidney: Biomarkers and beyond. American Journal of Physiology - Renal Physiology. 2014,306(11),1251-1259. doi:10.1152/ajprenal.00128.2014
14. Sun, I.O.; Lerman, L.O. Urinary extracellular vesicles as biomarkers of kidney disease: From diagnostics to therapeutics. Diagnostics. 2020, 10(5),1-9. doi:10.3390/diagnostics10050311
15. Kistler, A.D.; Mischak, H.; Poster, D.; Dakna, M.; Wüthrich, R.P.; Serra, A.L. Identification of a unique urinary biomarker profile in patients with autosomal dominant polycystic kidney disease. Kidney International. 2009, 76(1),89-96. doi:10.1038/ki.2009.93
16. Ramasubbu, K.; Gretz, N.; Bachmann, S. Increased epithelial cell proliferation and abnormal extracellular matrix in rat polycystic kidney disease. Journal of the American Society of Nephrology. 1998, 9(6), 937-945. doi:10.1681/asn.v96937
17. Obermüller, N.; Morente, N.; Kränzlin, B.; Gretz, N.; Witzgall, R. A possible role for metalloproteinases in renal cyst development. American Journal of Physiology - Renal Physiology. 2001, 280(3 49-3),540-550. doi:10.1152/ajprenal.2001.280.3.f540
18. Peleg, I.; Greenfeld, Z.; Cooperman, H.; Shoshan, S. Type I and Type III Collagen mRNA Levels in Kidney Regions of Old and Young Rats. Matrix. 1993,13(4), 281-287. doi:10.1016/S0934-8832(11)80023-5
19. Hart, T.C.; Gorry, M.C.; Hart, P.S.; et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. Journal of Medical Genetics. 2002, 39(12), 882-892. doi:10.1136/jmg.39.12.882
20. Kistler, A.D.; Serra, A.L.; Siwy, J.; et al. Urinary Proteomic Biomarkers for Diagnosis and Risk Stratification of Autosomal Dominant Polycystic Kidney Disease: A Multicentric Study. PLoS ONE. 2013, 8(1). doi:10.1371/journal.pone.0053016
21. Schieren, G.; Rumberger, B.; Klein, M.; et al. Gene profiling of polycystic kidneys. Nephrology Dialysis Trans-plantation. 2006, 21(7),1816-1824. doi:10.1093/ndt/gfl071
22. Cowley, B.D.; Ricardo, S.D.; Nagao, S.; Diamond, J.R. Increased renal expression of monocyte chemoattractant protein-1 and osteopontin in ADPKD in rats. Kidney International. 2001, 60(6), 2087-2096. doi:10.1046/j.1523-1755.2001.00065.x
23. Metzger, J.; Kirsch, T.; Schiffer, E.; et al. Urinary excretion of twenty peptides forms an early and accurate di-agnostic pattern of acute kidney injury. Kidney International. 2010, 78(12),1252-1262. doi:10.1038/ki.2010.322
24. Weimbs, T. Polycystic kidney disease and renal injury repair: Common pathways, fluid flow, and the function of polycystin-1. American Journal of Physiology - Renal Physiology. 2007, 293(5). doi:10.1152/ajprenal.00275.2007
25. Bolignano, D.; Coppolino, G.; Campo, S.; et al. Neutrophil gelatinase-associated lipocalin in patients with autosomal-dominant polycystic kidney disease. American Journal of Nephrology. 2007, 27(4), 373-378. doi:10.1159/000103912
26. Kuehn, E.W.; Hirt, M.N.; John, A.K.; et al. Kidney injury molecule 1 (Kim1) is a novel ciliary molecule and interactor of polycystin 2.

Volume 6, Issue 5; September-October 2023; Page No 305-321

Biochemical and Biophysical Research Communications. 2007, 364(4), 861-866. doi:10.1016/j.bbrc.2007.10.103

27. Pejchinovski, M.; Siwy, J.; Metzger, J.; et al. Urine peptidome analysis predicts risk of end-stage renal disease and reveals proteolytic pathways involved in autosomal dominant polycystic kidney disease progression. Nephrology Dialysis Transplantation. 2017, 32(3), 487-497. doi:10.1093/ndt/gfw243
28. Nagao, S.; Yamaguchi, T.; Kusaka, M.; et al. Renal activation of extracellular signal-regulated kinase in rats with autosomal-dominant polycystic kidney disease. Kidney International. 2003, 63(2), 427-437. doi:10.1046/j.1523-1755.2003.00755.x
29. Rauniyar, N.; Yu, X.; Cantley, J.; et al. Quantification of Urinary Protein Biomarkers of Autosomal Dominant Polycystic Kidney Disease by Parallel Reaction Monitoring. Proteomics. Clinical applications. 2018, 12(5), e1700157. https://doi.org/10.1002/prca.201700157
30. Hogan, M.C.; Manganelli, L.; Woollard, J.R.; et al. Characterization of PKD protein-positive exosome-like vesicles. Journal of the American Society of Nephrology. 2009, 20(2), 278-288. doi:10.1681/ASN.2008060564
31. Pocsfalvi, G.; Raj, D.A.A.; Fiume, I.; Vilasi, A.; Trepiccione, F.; Capasso, G. Urinary extracellular vesicles as reservoirs of altered proteins during the pathogenesis of polycystic kidney disease. Proteomics - Clinical Applications. 2015, 9(5-6),552-567. doi:10.1002/prca.201400199
32. Tomar, A.; George, S.; Kansal, P.; Wang, Y.; Khurana, S. Interaction of Phospholipase C-γ1 with Villin Regulates Epithelial Cell Migration. Journal of Biological Chemistry. 2006, 281(42), 31972-31986. doi:10.1016/s0021-9258(19)84111-x
33. 56. Castelli, M.; De Pascalis, C.; Distefano, G.; et al. Regulation of the microtubular cytoskeleton by Polycystin-1 favors focal adhesions turnover to modulate cell adhesion and migration. BMC Cell Biology. 2015, 16(1), 1-16. doi:10.1186/s12860-015-0059-3
34. Jefferson, J.J.; Leung, C.L.; Liem, R.K.H. Plakins: Goliaths that link cell junctions and the cytoskeleton. Nature Reviews Molecular Cell Biology. 2004, 5(7), 542-553. doi:10.1038/nrm1425
35. Silberberg, M.; Charron, A.J.; Bacallao, R.; Wandinger-Ness, A. Mispolarization of desmosomal proteins and altered intercellular adhesion in autosomal dominant polycystic kidney disease. American Journal of Physiology - Renal Physiology. 2005, 288(6 57-6), 1-21. doi:10.1152/ajprenal.00008.2005
36. Su, Z.; Wang, X.; Gao, X.; et al. Excessive activation of the alternative complement pathway in autosomal dominant polycystic kidney disease. Journal of Internal Medicine. 2014, 276(5), 470-485. doi:10.1111/joim.12214
37. Bruschi, M.; Granata, S.; Candiano, G.; et al. Proteomic analysis of urinary extracellular vesicles reveals a role for the complement system in medullary sponge kidney disease. International Journal of Molecular Sciences. 2019, 20(21), 1-15. doi:10.3390/ijms20215517
38. Liu, J. CREG1 Interacts with Sec8 to Promote Cardiomyogenic Differentiation and Cell-Cell Adhesion. Stem Cells. 2018, 36(1), 130-130. doi:10.1002/stem.2728
39. Luyten, A.; Su, X.; Gondela, S.; et al. Aberrant regulation of planar cell polarity in polycystic kidney disease. Journal of the American Society of Nephrology. 2010, 21(9), 1521-1532. doi:10.1681/ASN.2010010127
40. Raby, K.L.; Horsely, H.; McCarthy-Boxer, A.; Norman, J.T.; Wilson, P.D. Urinary exosome proteomic profiling defines stage-specific rapid progression of autosomal dominant polycystic kidney disease and tolvaptan efficacy. BBA Advances. 2021, 1,100013. doi:10.1016/j.bbadva.2021.100013
41. Germino, G.G.; Guay-Woodford, L.M. Polycystic Kidney Disease. Chronic Renal Disease. 2015, 484-500. doi:10.1016/B978-0-12-411602-3.00040-8
42. Rinschen, M.M.; Saez-Rodriguez, J. The tissue proteome in the multi-omic landscape of kidney disease. Nature Reviews Nephrology. 2021, 17(3), 205-219. doi:10.1038/s41581-020-00348-5
43. Rrazabal, M. V., Blais, J. D., Perrone, R. D., Gansevoort, R. T., Chapman, A. B., Devuyst, O., Higashihara, E., Harris, P. C., Zhou, W.,

Volume 6, Issue 5; September-October 2023; Page No 305-321

Ouyang, J., Czerwiec, F. S., & Torres, V. E. (2016). Prognostic Enrichment Design in Clinical Trials for Autosomal Dominant Polycystic Kidney Disease: The TEMPO 3:4 Clinical Trial. Kidney international reports, 1(4), 213–220. https://doi.org/10.1016/j.ekir.2016.08.001

44. Torres, V. E., Chapman, A. B., Devuyst, O., Gansevoort, R. T., Perrone, R. D., Dandurand, A., Ouyang, J., Czerwiec, F. S., Blais, J. D., & TEMPO 4:4 Trial Investigators (2018). Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 33(3), 477–489. https://doi.org/10.1093/ndt/gfx04
45. Müller, R. U., Messchendorp, A. L., Birn, H., Capasso, G., Cornec-Le Gall, E., Devuyst, O., van Eerde, A., Guirchoun, P., Harris, T., Hoorn, E. J., Knoers, N. V. A. M., Korst, U., Mekahli, D., Le Meur, Y., Nijenhuis, T., Ong, A. C. M., Sayer, J. A., Schaefer, F., Servais, A., Tesar, V., … Gansevoort, R. T. (2022). An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 37(5), 825–839. https://doi.org/10.1093/ndt/gfab312
46. Torres, V. E., Chapman, A. B., Devuyst, O., Gansevoort, R. T., Perrone, R. D., Lee, J., Hoke, M. E., Estilo, A., & Sergeyeva, O. (2020). Multicenter Study of Long-Term Safety of Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. Clinical journal of the American Society of Nephrology : CJASN, 16(1), 48–58. https://doi.org/10.2215/CJN.10250620
47. Gansevoort, R. T., Arici, M., Benzing, T., Birn, H., Capasso, G., Covic, A., Devuyst, O., Drechsler, C., Eckardt, K. U., Emma, F., Knebelmann, B., Le Meur, Y., Massy, Z. A., Ong, A. C., Ortiz, A., Schaefer, F., Torra, R., Vanholder, R., Więcek, A., Zoccali, C., … Van Biesen, W. (2016). Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 31(3), 337–348. https://doi.org/10.1093/ndt/gfv456
48. Spinelli, L., Pisani, A., Giugliano, G., Trimarco, B., Riccio, E., Visciano, B., Remuzzi, G., Ruggenenti, P., & ALADIN-Cardiovascular Study Group (2019). Left ventricular dysfunction in ADPKD and effects of octreotide-LAR: A cross-sectional and longitudinal substudy of the ALADIN trial. International journal of cardiology, 275, 145–151. https://doi.org/10.1016/j.ijcard.2018.10.063
49. Perico, N., Ruggenenti, P., Perna, A., Caroli, A., Trillini, M., Sironi, S., Pisani, A., Riccio, E., Imbriaco, M., Dugo, M., Morana, G., Granata, A., Figuera, M., Gaspari, F., Carrara, F., Rubis, N., Villa, A., Gamba, S., Prandini, S., Cortinovis, M., … ALADIN 2 Study Group (2019). Octreotide-LAR in later-stage autosomal dominant polycystic kidney disease (ALADIN 2): A randomized, double-blind, placebo-controlled, multicenter trial. PLoS medicine, 16(4), e1002777. https://doi.org/10.1371/journal.pmed.1002777
50. Meijer, E., Drenth, J. P., d'Agnolo, H., Casteleijn, N. F., de Fijter, J. W., Gevers, T. J., Kappert, P., Peters, D. J., Salih, M., Soonawala, D., Spithoven, E. M., Torres, V. E., Visser, F. W., Wetzels, J. F., Zietse, R., Gansevoort, R. T., & DIPAK Consortium (2014). Rationale and design of the DIPAK 1 study: a randomized controlled clinical trial assessing the efficacy of lanreotide to Halt disease progression in autosomal dominant polycystic kidney disease. American journal of kidney diseases : the official journal of the National Kidney

Volume 6, Issue 5; September-October 2023; Page No 305-321

Foundation, 63(3), 446–455. https://doi.org/10.1053/j.ajkd.2013.10.011

51. Perrone, R. D., Abebe, K. Z., Watnick, T. J., Althouse, A. D., Hallows, K. R., Lalama, C. M., Miskulin, D. C., Seliger, S. L., Tao, C., Harris, P. C., & Bae, K. T. (2021). Primary results of the randomized trial of metformin administration in polycystic kidney disease (TAME PKD). Kidney international, 100(3), 684–696. https://doi.org/10.1016/j.kint.2021.06.013
52. Brosnahan, G. M., Wang, W., Gitomer, B., Struemph, T., George, D., You, Z., Nowak, K. L., Klawitter, J., & Chonchol, M. B. (2022). Metformin Therapy in Autosomal Dominant Polycystic Kidney Disease: A Feasibility Study. American journal of kidney diseases : the official journal of the National Kidney Foundation, 79(4), 518–526. https://doi.org/10.1053/j.ajkd.2021.06.026
53. Chebib, F. T., & Perrone, R. D. (2023). Drug Development in Autosomal Dominant Polycystic Kidney Disease: Opportunities and Challenges. Advances in kidney disease and health, 30(3), 261–284. https://doi.org/10.1053/j.akdh.2023.01.004
54. Serra, A.L., Kistler, A.D., Poster, D. et al. Clinical proof-of-concept trial to assess the therapeutic effect of sirolimus in patients with autosomal dominant polycystic kidney disease: SUISSE ADPKD study. BMC Nephrol 8, 13 (2007). https://doi.org/10.1186/1471-2369-8-13
55. Perico, N., Antiga, L., Caroli, A., Ruggenenti, P., Fasolini, G., Cafaro, M., Ondei, P., Rubis, N., Diadei, O., Gherardi, G., Prandini, S., Panozo, A., Bravo, R. F., Carminati, S., De Leon, F. R., Gaspari, F., Cortinovis, M., Motterlini, N., Ene-Iordache, B., Remuzzi, A., … Remuzzi, G. (2010). Sirolimus therapy to halt the progression of ADPKD. Journal of the American Society of Nephrology : JASN, 21(6), 1031–1040. https://doi.org/10.1681/ASN.2009121302
56. Ruggenenti, P., Gentile, G., Perico, N., Perna, A., Barcella, L., Trillini, M., Cortinovis, M., Ferrer Siles, C. P., Reyes Loaeza, J. A., Aparicio, M. C., Fasolini, G., Gaspari, F., Martinetti, D., Carrara, F., Rubis, N., Prandini, S., Caroli, A., Sharma, K., Antiga, L., Remuzzi, A., … SIRENA 2 Study Group (2016). Effect of Sirolimus on Disease Progression in Patients with Autosomal Dominant Polycystic Kidney Disease and CKD Stages 3b-4. Clinical journal of the American Society of Nephrology : CJASN, 11(5), 785–794. https://doi.org/10.2215/CJN.09900915
57. Walz, G., Budde, K., Mannaa, M., Nürnberger, J., Wanner, C., Sommerer, C., Kunzendorf, U., Banas, B., Hörl, W. H., Obermüller, N., Arns, W., Pavenstädt, H., Gaedeke, J., Büchert, M., May, C., Gschaidmeier, H., Kramer, S., & Eckardt, K. U. (2010). Everolimus in patients with autosomal dominant polycystic kidney disease. The New England journal of medicine, 363(9), 830–840. https://doi.org/10.1056/NEJMoa1003491
58. Tsukamoto, S., Urate, S., Yamada, T., Azushima, K., Yamaji, T., Kinguchi, S., Uneda, K., Kanaoka, T., Wakui, H., & Tamura, K. (2022). Comparative Efficacy of Pharmacological Treatments for Adults With Autosomal Dominant Polycystic Kidney Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Frontiers in pharmacology, 13, 885457. https://doi.org/10.3389/fphar.2022.885457
59. Nespoux, J., & Vallon, V. (2018). SGLT2 inhibition and kidney protection. Clinical science (London, England : 1979), 132(12), 1329–1339. https://doi.org/10.1042/CS20171298
60. Masuda, T., Muto, S., Fukuda, K., Watanabe, M., Ohara, K., Koepsell, H., Vallon, V., & Nagata, D. (2020). Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. Physiological reports, 8(2), e14360. https://doi.org/10.14814/phy2.14360
61. Nowak, K. L., & Hopp, K. (2020). Metabolic Reprogramming in Autosomal Dominant Polycystic Kidney Disease: Evidence and Therapeutic Potential. Clinical journal of the American Society of Nephrology : CJASN, 15(4), 577–584. https://doi.org/10.2215/CJN.13291019
62. Patel, D. M., & Dahl, N. K. (2021). Examining the Role of Novel CKD Therapies for the

Volume 6, Issue 5; September-October 2023; Page No 305-321

ADPKD Patient. Kidney360, 2(6), 1036–1041. https://doi.org/10.34067/KID.0007422020

63. Xue, C., Zhou, C., Dai, B., Yu, S., Xu, C., Mao, Z., Ye, C., Chen, D., Zhao, X., Wu, J., Chen, W., & Mei, C. (2015). Antihypertensive treatments in adult autosomal dominant polycystic kidney disease: network meta-analysis of the randomized controlled trials. Oncotarget, 6(40), 42515–42529. https://doi.org/10.18632/oncotarget.6452
64. Yu, A. S. L., Shen, C., Landsittel, D. P., Grantham, J. J., Cook, L. T., Torres, V. E., Chapman, A. B., Bae, K. T., Mrug, M., Harris, P. C., Rahbari-Oskoui, F. F., Shi, T., Bennett, W. M., & Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) (2019). Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. Kidney international, 95(5), 1253–1261. https://doi.org/10.1016/j.kint.2018.12.023
65. Dougher, C. E., Rifkin, D. E., Anderson, C. A., Smits, G., Persky, M. S., Block, G. A., & Ix, J. H. (2016). Spot urine sodium measurements do not accurately estimate dietary sodium intake in chronic kidney disease. The American journal of clinical nutrition, 104(2), 298–305. https://doi.org/10.3945/ajcn.115.127423
66. Stevens, P. E., Levin, A., & Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members (2013). Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Annals of internal medicine, 158(11), 825–830. https://doi.org/10.7326/0003-4819-158-11-201306040-00007
67. Torres, V. E., Grantham, J. J., Chapman, A. B., Mrug, M., Bae, K. T., King, B. F., Jr, Wetzel, L. H., Martin, D., Lockhart, M. E., Bennett, W. M., Moxey-Mims, M., Abebe, K. Z., Lin, Y., Bost, J. E., & Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) (2011). Potentially modifiable factors affecting the progression of autosomal dominant polycystic kidney disease. Clinical journal of the American Society of Nephrology : CJASN, 6(3), 640–647. https://doi.org/10.2215/CJN.03250410
68. Graudal, N., Jürgens, G., Baslund, B., & Alderman, M. H. (2014). Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. American journal of hypertension, 27(9), 1129–1137. https://doi.org/10.1093/ajh/hpu028
69. Torres, V. E., Abebe, K. Z., Chapman, A. B., Schrier, R. W., Braun, W. E., Steinman, T. I., Winklhofer, F. T., Brosnahan, G., Czarnecki, P. G., Hogan, M. C., Miskulin, D. C., Rahbari-Oskoui, F. F., Grantham, J. J., Harris, P. C., Flessner, M. F., Moore, C. G., Perrone, R. D., & HALT-PKD Trial Investigators (2014). Angiotensin blockade in late autosomal dominant polycystic kidney disease. The New England journal of medicine, 371(24), 2267–2276. https://doi.org/10.1056/NEJMoa1402686
70. Torres, V. E., Abebe, K. Z., Schrier, R. W., Perrone, R. D., Chapman, A. B., Yu, A. S., Braun, W. E., Steinman, T. I., Brosnahan, G., Hogan, M. C., Rahbari, F. F., Grantham, J. J., Bae, K. T., Moore, C. G., & Flessner, M. F. (2017). Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease. Kidney international, 91(2), 493–500. https://doi.org/10.1016/j.kint.2016.10.018
71. Fouque, D., & Laville, M. (2009). Low protein diets for chronic kidney disease in non diabetic adults. The Cochrane database of systematic reviews, (3), CD001892. https://doi.org/10.1002/14651858.CD001892.pub3
72. Wang, C. J., Grantham, J. J., & Wetmore, J. B. (2013). The medicinal use of water in renal disease. Kidney international, 84(1), 45–53. https://doi.org/10.1038/ki.2013.23
73. Higashihara, E., Nutahara, K., Tanbo, M., Hara, H., Miyazaki, I., Kobayashi, K., & Nitatori, T. (2014). Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease?. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 29(9), 1710–1719. https://doi.org/10.1093/ndt/gfu093.

Volume 6, Issue 5; September-October 2023; Page No 305-321

Table 1: Summary of Studies on Proteomic Analysis, Urinary Extracellular Vesicles (uEV), and and Urinary Exosomes in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Study	Method	Analysis	Results
Kistler et al. 2009	Mass spectrometry-based proteomics	Urinary proteomic 'footprint' of ADPKD	Diagnosis of autosomal dominant polycystic kidney disease
Kistler et al. 2013	Mass spectrometry-based proteomics	Urinary proteomic biomarkers	Diagnosis and risk stratification of autosomal dominant polycystic kidney disease
Pejchinovski et al. 2017	Mass spectrometry-based proteomics	Urine peptidome analysis	Identification and validation of a classifier consisting of 20 urinary peptidome biomarkers for predicting the risk of end-stage renal disease and the progression of autosomal dominant polycystic kidney disease (ADPKD). The performance of the biomarker score was comparable to that of the height-adjusted total kidney volume (htTKV). The study also identified proteolytic pathways involved in ADPKD progression, which could serve as potential targets for therapeutic intervention.
Rauniyar et al. 2019	Tandem mass tag-based proteomics	Quantification of protein expression	Identification of potential biomarkers for diagnosis and monitoring of autosomal dominant polycystic kidney disease
Salih et al. 2016	Mass spectrometry-based proteomics	Proteomic analysis of urinary vesicles	Identified differentially expressed proteins including plakins and

Volume 6, Issue 5; September-October 2023; Page No 305-321

Study	Method	Analysis	Results
			complement proteins, which may contribute to disease progression. The study suggests that these proteins may serve as potential biomarkers and therapeutic targets for ADPKD.
Pocsfalvi G. 2015	Mass spectrometry-based proteomics	EVs were isolated from pooled urine samples	Quantitative analyses identified 83 differentially expressed EV proteins. Many of these have apical membrane origin and are involved in signal transduction pathways of primary cilia, Ca (2+) -activated signaling, cell-cycle regulation, and cell differentiation. The reduced AQP-2 and the increased APO-A1 levels observed in all ADPKD-affected groups may reflect the impaired renal concentrating capability of these patients and correlated with estimated glomerular filtration rate decline.
Hogan et al. 2009	Electron microscopy and immunoblotting	Characterization of exosome-like vesicles	Potential role of exosomes in the development of polycystic kidney disease
Hogan et al.2015	Mass spectrometry-based proteomics of urinary exosomes	Identification of biomarkers for PKD1 using urinary exosomes	Identified potential biomarkers for autosomal dominant polycystic kidney disease (ADPKD) using urinary exosomes, suggesting that

Volume 6, Issue 5; September-October 2023; Page No 305-321

Study	Method	Analysis	Results
			exosomal biomarkers may serve as noninvasive diagnostic tools for ADPKD.

Volume 6, Issue 5; September-October 2023; Page No 305-321