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REVIEW ARTICLE

New Therapies on the Horizon for Preventing the Progression of Chronic Kidney Disease in Childhood

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ABSTRACT

The purpose of the review is to summarize the current pharmacological management of chronic kidney disease (CKD) in pediatric patients and critically present emerging evidence for the use of mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.
Globally, CKD is the 19th leading cause of years of life lost and the current total number of children and adolescents affected with CKD Stages II-V is predicted to exceed 2 million in a global population of 2 billion children. The severity of kidney disease is strongly correlated with the extent of proteinuria. Agents that target the renin-angiotensin-aldosterone-system reduce proteinuria in mild to moderate CKD, slowing disease progression. Recent clinical trials evaluating mineralocorticoid receptor antagonists, such as finerenone and SGLT2 inhibitors, demonstrate similar results. However, additional pediatric clinical trials are necessary to determine their complete therapeutic potential.

Keywords: Chronic Kidney Disease, RAAS, SGLT2 Inhibitors

INTRODUCTION

Between 1990-2017, the global mortality rate attributed to chronic kidney disease (CKD) for all ages has increased by 41.5%.[1,2] The global prevalence of CKD Stages I-V is estimated to affect around 843.6 million individuals,[3] making it the 19th leading cause of years of life lost.[2] Taking into account pediatric epidemiology studies and hospital-based studies, the current total number of children and adolescents affected with CKD Stages II-V is predicted to exceed 2 million in a global population of 2 billion children.[4] While diabetes and hypertension are the leading causes of CKD in adults, the main etiologic factors in pediatric populations include congenital anomalies of the kidney and urinary tract, as well as various glomerulonephritides and genetic renal disease, particularly cystic kidney disease and ciliopathies.[5]

Renal fibrosis is the final common pathological manifestation of many chronic kidney diseases. It represents the healing of wounded kidney tissue after a chronic and sustained injury and manifests as glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[6] Glomerulosclerosis is caused by endothelial damage, dysfunction and proliferation of smooth muscle and mesangial cells within the glomerular tuft.[6] Brenner's hypothesis proposed that patients with a decreased number of nephrons develop hyperfiltration, causing sodium retention, hypertension, further nephron loss, and eventually CKD due to secondary focal segmental glomerulosclerosis.[5] The decreased complement of nephrons initially can maintain a normal GFR due to the nephron enlargement increasing the total surface area for renal work. However, increased sodium retention, hypertension, and glomerular hyperfiltration disrupt renal autoregulatory mechanisms.[7,8] The disruption in the autoregulatory mechanism leads to intraglomerular hypertension and proteinuria, causing nephrons to become sclerotic and senescent, eventually leading to a further decline in nephron numbers and greater hyperfiltration in the remaining nephrons.[5] The progression of established CKD is influenced by various factors, and the first one that will be discussed is proteinuria. Following the pathophysiology of proteinuria, this review will cover the treatment of CKD

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with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), as well as newer agents on the horizon such as mineralocorticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Physiology and Pathophysiology of Proteinuria

The loss of serum proteins into the urine following filtration by the kidneys is a key diagnostic indicator of renal dysfunction. The extent of proteinuria is strongly correlated with the severity of kidney disease in both diabetic and non-diabetic populations.[9] Regardless of the underlying etiology of chronic kidney disease, be it congenital or acquired, the progression of CKD is typically associated with a loss of integrity of the glomerular filtration barrier (GFB) and progressive proteinuria with subsequent scarring of the kidney.

The GFB is made up of 3 layers: the endothelium, basement membrane, and podocytes.[10] The podocytes support the basement membrane and have foot processes that wrap around the glomerular capillaries. Between these interdigitating foot processes is a space spanned by the slit diaphragm that prevents entry of proteins greater than 60 A^0 into the filtrate. Enhanced glomerular capillary pressure causes widening of the glomerular capillaries and thus widening of the slit diaphragm, leading to increased glomerular permeability to macromolecules such as proteins. In a healthy individual, proteinuria typically does not exceed 150 mg per day, as pathways exist involving endocytic receptors (megalin and cubilin) on the apical membrane of the proximal tubular epithelial cells (PTECs) that resorb the majority (70%) of filtered protein.[11]

However, proteinuria can result when tubular resorption of protein is overwhelmed or stressed. In response to excess protein in the glomerular filtrate, PTECs secrete cytokines which attract inflammatory cells, and podocytes release transforming growth factor beta which induces profibrotic changes. The direct cellular toxicity of serum proteins such as albumin also occurs, resulting in apoptosis of PTECs. Overall, the upregulation of cytokines, growth factors, and apoptosis culminates in abnormal cell proliferation and extracellular matrix deposition, further attracting proinflammatory cells such as neutrophils and myofibroblasts. The persistent activation of this cycle of inflammation and cellular response is responsible for progressive tubular injury and interstitial fibrosis, as seen in CKD.[11] Regardless of the underlying cause, proteinuria is not only considered a marker of renal injury, but also the final common pathway of end stage renal disease.[12] Given the strong association between proteinuria and the progression of CKD, treatment of proteinuria is one of the mainstays of CKD progression (i.e., nephroprotection).

RAAS

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the regulation of blood pressure, electrolytes, and vascular resistance. In addition to homeostasis, RAAS overactivation is implicated in the pathophysiology of CKD.[13] Activation of RAAS occurs via stimuli such as a drop in blood pressure sensed by baroreceptors, a decrease in NaCl delivery to the macula densa, and an increase in sympathetic tone through activation of renal beta 1 adrenergic receptors. These stimuli result in the cleavage of prorenin to renin by juxtaglomerular cells within the renal afferent arteriole. Once secreted into the blood, renin converts circulating angiotensinogen into angiotensin I. The angiotensin-converting enzyme (ACE) produced by pulmonary endothelium then converts angiotensin I into angiotensin II.[14]

Angiotensin II has various physiological effects throughout the body that increase both intravascular blood volume and blood pressure. Angiotensin II stimulates the posterior pituitary to release antidiuretic hormone (ADH), which acts on principal cells within the collecting duct to increase water reabsorption via apical membrane aquaporin 2 pores. Angiotensin II binds to and activates angiotensin II type 1 receptors, increasing the endothelin-1 paracrine release from vascular endothelial cells and leading to the vasoconstriction of the arterioles.[15]

Within the kidney, angiotensin II stimulates basolateral Na+/H+ ATPase activity in the proximal convoluted tubule, thereby increasing sodium reabsorption. Angiotensin II also promotes the release of aldosterone from the zona glomerulosa in the outer zone of the adrenal cortex. Aldosterone acts on principal cells in the collecting duct and distal collecting tubule to increase Na+ reabsorption and K+ secretion via activation of basolateral Na+/K+ ATPase and increased apical translocation of epithelial Na+ channels (ENaC). These mechanisms serve to increase sodium reabsorption.[14] Aldosterone also works directly on the alpha-intercalated cells of the collecting duct to increase H+ ATPase activity, enhancing H+ secretion.[14] Overall, the effect of increased sodium and water reabsorption by the kidneys increases total blood volume, which in turn increases blood pressure.

ACE inhibitors/ARBs

Aside from hypertension control, blocking RAAS with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), are recommended first line agents in the prevention and management of CKD and its associated cardiovascular outcomes.[16,17] RAAS inhibitors prevent the production and action of angiotensin II, and therefore ACEIs and ARBs are effective antiproteinuric agents with potential protective effects on the renal system.

The primary antiproteinuric action of ACEIs and ARBs occurs via vasodilation of the afferent glomerular arteriole, which decreases GFR and consequently reduces pressure across the glomerular filtration barrier.[18]

Studies on COL4α3 knockout mice, one of the mouse models for Alport syndrome and a surrogate for CKD progression, have demonstrated the nephroprotective effects of ramipril and candesartan. This nephroprotection is mediated in part through the down-regulation of TGF-beta1, ultimately reducing proteinuria and fibrosis, delaying CKD progression, and increasing animal lifespan.[19,20]

Treatment with ACEIs and ARBs has been demonstrated to slow the progression of CKD.[21] In 2009, the Effect of Strict Blood Pressure Control and ACE Inhibition of the Progression of Chronic Renal Failure (CRF) in Pediatric Patients (ESCAPE) trial emphasized the importance of blood pressure control (targeting a BP < 50th percentile) on the advancement of CKD.[22] A greater degree of proteinuria was associated with a 50% decline in the GFR or progression-to-end stage renal disease (hazard ratio 1.46 [95% CI [1.35, 1.59]; $p < 0.001$]).[22]

However, although clinical trials with ACEIs and ARBs showed an initial decline in the plasma level of aldosterone, long-term administration in 10%-53% of patients results in "aldosterone breakthrough," whereby aldosterone concentration may climb to or exceed pretreatment levels.[21] In patients with diabetic nephropathy, aldosterone breakthrough results in a poorer antiproteinuric effect and accelerated eGFR decline.[21,23] Aldosterone breakthrough can limit the efficacy of ACEIs and ARBs, especially in patients with advanced kidney disease who already have a lowered eGFR. Therefore, aldosterone breakthrough constitutes a rationale for the use of combined or alternative therapeutic agents in CKD.

Controversies Surrounding ACEI and ARB Therapy in Patients with Advanced CKD

Treatment with ACEIs and ARBs has many benefits, including reduction in blood pressure, proteinuria, and eGFR decline in mild-to-moderate CKD.[24–26] Despite this, limited evidence exists, as well as many contradictory results surrounding the efficacy of ACEIs and ARBs in advanced CKD.

For example, the STOP-ACEi multi-center randomized trial has investigated the impact of ACEI or ARB discontinuation in patients (median age of 63 years) with advanced and chronic kidney disease (eGFR, <30 ml per min per 1.73 m^2 of body-surface area). The group that was assigned to discontinue ACEIs and ARBs were permitted any guideline-recommended anti-hypertensive agent other than RAAS inhibitors for blood pressure control. In the third year, patients in the discontinuation group had no significantly different increase in eGFR. This lack of clinically relevant eGFR rise was further seen upon subgroup analysis by age, severity of chronic kidney disease, and proteinuria. Furthermore, blood pressure control, initiation of renal replacement therapy, and incidence of cardiovascular events and death showed similarities between groups. Notably, subjective measures of quality of life and exercise capacity were also analogous between cohorts. This trial has limitations, including generalizability to patients from non-Caucasian backgrounds and to patients with increased proteinuria.[27]

The results from other trials are inconsistent with these findings. For instance, a 2020 observational study analyzed the Swedish Renal Registry between 2007-2017 and included patients who had developed advanced CKD and been referred to nephrologist care (eGFR, <30 ml per min per 1.73 m^2 of body-surface area) while on RAAS inhibitor therapy. The results from this analysis indicated RAAS inhibitor discontinuation is associated with a higher risk of death and major adverse cardiovascular events (MACE). The analysis also described an association between discontinuation of RAAS inhibitors and a lower risk of kidney transplantation or initiating maintenance dialysis.[28]

Another study conducted in the same year found that, while discontinuation of ACEI and ARB is associated with increased risk of death and MACE, no significant difference was found for the risk of end-stage renal disease as ascertained by kidney transplant and dialysis status.[29]

Overall, given the variable nature of the present data surrounding ACEI and ARB efficacy in advanced CKD, more research is needed to evaluate the therapeutic benefit of RAAS inhibition in patients with advanced CKD and specifically in the pediatric population.

Mineralocorticoid Receptor Physiology

Aside from ACEI and ARB therapy, mineralocorticoid receptors (MR) are target options for blockade of RAAS. Mineralocorticoid receptors are members of the nuclear receptor superfamily of ligand-dependent transcription factors. The effects of MRs are mediated through genomic and non-genomic pathways.[30] The genomic effects of MRs occur when they bind mineralocorticoids such as aldosterone, cortisol, and deoxycorticosterone. Although MRs bind cortisol and aldosterone with equal affinity, specificity to aldosterone is conferred via the presence of 11β-hydroxysteroid dehydrogenase type 2. Thus, due to the presence of 11β-hydroxysteroid dehydrogenase type 2 in the epithelial cells of the renal collecting duct, aldosterone is the main mineralocorticoid hormone in the RAAS that activates MRs.[31]

MRs are inactive in the cytosol and are bound to chaperones Hsp70 and 90, along with various immunophilins. Upon the binding of aldosterone, these chaperones dissociate, and the ligand-receptor complex translocates from the cytosol to the nucleus. In the nucleus, it undergoes homodimerization and binds to hormone response elements within the promoter region of the target genes to influence transcription.[32]

MRs are present in a variety of cells, including cardiomyocytes, endothelial cells, inflammatory cells, vascular smooth muscle cells, and fibroblasts. For example, in renal epithelial cells, the activation of MRs results in the upregulation of ENaC transcription, promoting sodium and water reabsorption and ultimately regulating homeostasis of electrolytes and blood volume.[32]

Another important gene product downstream from the aldosterone activation of MRs is serum glucocorticoid-regulated kinase 1 (SGK-1). SGK-1 is a serine-threonine kinase that further increases the expression of ENaC on the plasma membrane via inhibition of the ubiquitin ligase Nedd4-2 that normally removes ENaC from the cell surface.[33] Moderate-to-heavy albuminuria in CKD patients has been linked to a 2-3.4 fold increase in the expression of SGK-1 mRNA.[34] SGK-1 has also been shown to enhance profibrotic gene expression and

hypertrophy in cardiomyocytes through connective tissue growth factor (CTGF) and p300/GATA4, respectively.[35]

Aldosterone/MR-Induced Podocyte Injury

Patients with CKD have notably elevated aldosterone levels. Moreover, elevated serum aldosterone is considered an independent predictor of increased risk of renal disease advancement, regardless of diabetes status.[36] MR overactivation has been linked to podocyte injury, a critical event in the progression of renal disease. In streptozotocin-induced diabetic rats, enhanced aldosterone levels and MR activation in glomeruli impairs podocyte adhesion capacity.[37] *In vivo* and *in vitro* studies on mice models demonstrate aldosterone-mediated MR activation to induce endoplasmic reticulum (ER) stress and reactive oxygen species (ROS).[38] As a consequence, cellular dysfunction, macrophage infiltration, inflammation, and eventual podocyte effacement and fibrosis results. These findings are consistent with human models.[39]

In 2007, Sprague–Dawley rats were used to elucidate the antiproteinuric effect of MR antagonists. After undergoing a uninephrectomy, rats were infused with aldosterone and fed a high-salt diet. At week 2, blood pressure elevation and proteinuria were observed. This elevation was further increased when measured at weeks 4 and 6. At each point in time, the kidneys were harvested, and histological examination revealed morphological changes such as glomerulosclerosis and tubulointerstitial damage. Degenerative changes in podocytes and the foot process were also reported. However, upon administration of eplerenone (an MR antagonist), blood pressure was significantly reduced and proteinuria and podocyte damage were eliminated.[40]

Human and whole animal studies have implicated pathologic aldosteronism and the associated pathophysiological overactivation of MR in the inflammation and fibrosis associated with CKD.[41,42] In 2022, a prospective observational cohort study of patients with CKD found higher aldosterone levels to be associated with the progression of CKD and increased 24-hour urine protein excretion.[36] These findings are consistent with previous studies and support the use of MR antagonists in CKD.[43-46]

Mineralocorticoid Receptor Antagonists

Currently, mineralocorticoid receptor antagonists (MRAs) such as first-generation spironolactone developed in the 1950s are recommended for patients with CKD and have been used for decades. Notably, because spironolactone can also bind to androgen and progesterone receptors, an increased risk of gynecomastia occurs in men and menstrual disturbances in women.[47] These effects can be mitigated by using eplerenone, a second generation MR that is designed to bind more specifically to the mineralocorticoid receptor.[47] However, like spironolactone, eplerenone administration is associated with an increased risk of hyperkalemia that can result in arrhythmias.[48]

More recently, third-generation MRAs have been developed, which the FDA has approved in North America for adult patients with CKD and type 2 diabetes mellitus (T2DM) to minimize eGFR decline, CKD progression, and cardiovascular death.[49]

Finerenone Pharmacology

Finerenone (BAY 94-8862) is a third-generation, nonsteroidal, selective MRA with greater selectivity than spironolactone and greater affinity than both spironolactone and eplerenone.[50] In rat cardiac and renal tissues, finerenone equally distributes in comparison to spironolactone and eplerenone which predominantly accumulate in renal tissue.[51] Finerenone is also characterized by a bioavailability of 43.5% due to metabolism at the level of the gut wall and liver.[52] Finerenone is a CYP3A4 and CYP2C8 substrate with no active metabolites and has half-life of 2-3 hrs.[52,53]

In contrast to most MRAs, finerenone is an allosteric modulator of the MR. The resultant conformational change leads to prominence of helix 12 of the MR, altering the recruitment of co-activators and co-repressors, nuclear translocation, and downstream signaling.[54] The therapeutic potential finerenone has regarding CKD has been investigated in animal models, with promising results having emerged from adult clinical trials regarding its pharmacokinetics and safety.

Finerenone Animal Models

In a T2DM mouse model where the mice were fed a high-salt diet to accelerate kidney damage, finerenone treatment produced a slight decline in blood pressure and a significant decline in albuminuria.[55]

At non-blood pressure-reducing levels in acetate-/salt-challenged rats, finerenone has been shown to decrease cardiac hypertrophy, natriuretic peptide plasma concentration, and proteinuria more efficiently than eplerenone.[51]

In a mouse model whereby kidney fibrosis was induced via unilateral ureteral obstruction or ischemia, oral finerenone (3 or 10 mg/kg) reduced myofibroblast and collagen deposition as well as albuminuria. In comparison, treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin at 10 or 30 mg/kg/day failed to reduce myofibroblast and collagen deposition yet reduced albuminuria; as such, an additional advantage may be had with finerenone over the SGLT2 inhibitors, which this review will discuss later on.[56]

Finerenone Clinical Trials

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trials were independent, randomized, double-blinded, and placebo-controlled trials for evaluating the efficacy and safety of finerenone. Chiefly, FIDELIO-DKD investigated finerenone's efficacy and safety in delaying CKD progression in T2DM patients with CKD, while FIGARO-DKD assessed finerenone's efficacy and safety in reducing cardiorenal morbidity and mortality in T2DM patients with CKD.[57,58]

In the FIDELIO-DKD trial with a median follow up of 2.6 years, finerenone decreased the incidence of the primary outcome

(i.e., kidney failure), sustained a GFR decrease of ≥ 40%, and a 17.8% decrease in death from renal causes when compared to the placebo group (hazard ratio = 0.82; 95% CI [0.73, 0.93]; p = 0.001). Patients in the finerenone group also had a 13% significantly lower risk of key secondary outcomes (i.e., death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization; hazard ratio = 0.86; 95% CI, [0.75, 0.99]; p = 0.03).[59]

In the FIGARO-DKD trial with a mean follow up of 3.4 years, the primary and secondary outcomes were reciprocal to those in the FIDELIO-DKD trial. In this way, the primary outcome in the FIGARO-DKD trial involved the incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Likewise, the first key secondary outcome was kidney failure, a sustained GFR decrease of ≥ 40%, and decreased risk of death from renal causes. The results from FIGARO-DKD showed a primary outcome reduction of 12.4% (hazard ratio = 0.87; 95% CI [0.76, 0.98]; p = 0.03) and a first key secondary outcome reduction of 9.5% (hazard ratio = 0.87; 95% CI [0.76, 1.01]) when comparing the finerenone group to the placebo group.[60]

Regarding safety in the FIDELIO-DKD and FIGARO-DKD trials, the incidence of adverse effects was similar across the two groups. However, hyperkalemia-related adverse effects were twice as frequent in the finerenone group compared to the placebo control in both trials.[59,60] Importantly, although the incidence of finerenone-associated hyperkalemia is higher when compared to the placebo, the incidence of finerenone-associated hyperkalemia is lower when compared to spironolactone.[61]

While the FIDELIO-DKD and FIGARO-DKD trials provide high-level evidence for MR antagonism, serum aldosterone levels were not measured. Hence, the full extent of finerenone's action mediated through aldosterone is not yet fully understood.[36]

Overall, the FIDELIO-DKD and FIGARO-DKD trials have focused on the use of finerenone in patients with T2DM and associated CKD. Their landmark findings prompted the regulatory approval of finerenone for preventing CKD advancement in patients with diabetes.

Mineralocorticoid receptor overactivation is also implicated in non-diabetic CKD. To this end, two clinical trials are ongoing with the aim of exploring the use of finerenone in patients with non-diabetic CKD.

The Finerenone in Non-Diabetic Chronic Kidney Disease (FIND-CKD) trial, which is expected to be completed in February 2026, has enrolled adult patients with CKD but not diabetes. FIND-CKD will determine whether finerenone, when administered in addition to the participants' current CKD medications, will slow the progression of non-diabetic CKD compared to a placebo. The health of participants will be measured through blood and urine samples. Patients will also be questioned about their general feeling of health and whether they experienced any adverse effects.[62]

In contrast, the Finerenone for the Treatment of Children with Chronic Kidney Disease and Proteinuria (FIONA) trial focuses on children with CKD and is expected to be completed in March 2027. Participants aged 6 months to 17 years, are involved in an 18-month study on the safety of long-term finerenone use when combined with ACEI or ARB treatment. The main outcome of interest is whether the addition of finerenone to either ACE or ARB therapy will reduce proteinuria more than a placebo. Adverse effects will also be monitored.[63]

As of November 8, 2022, patients that had completed the FIONA trial were recruited and began the open label extension trial with finerenone (FIONA-OLE). Participants are aged 1-18 years, and the main outcome is to determine how safe long-term finerenone treatment is in pediatric patients with CKD when taken in combination with an ACEI or ARB. The study team will also measure how well long-term finerenone treatment can reduce proteinuria and maintain kidney function. The study is estimated to be completed in September 2028.[64]

Physiology of Sodium-Glucose Cotransporters

Sodium-glucose cotransporter-2 (SGLT2) channels are found along the luminal membrane of the proximal tubule. Under normal conditions, they work by mediating the reabsorption of about 90% of the filtered glucose.[1] The average adult body should contain approximately 180 grams of glucose.[65]

SGLT2 uses one sodium ion per glucose molecule, whereas SGLT1 uses two sodium ions per glucose molecule, making SGLT2 more energy efficient.[66] SGLT2 inhibitors bind onto the cotransporters at the luminal membrane with greater affinity than glucose, preventing the reabsorption of large amounts of filtered glucose.[67] This increases glucosuria and will lead to a decrease in glucose in the plasma. Less glucose is filtered, and sufficient active transporters can reabsorb a lesser amount of glucose, preventing blood glucose from declining below a euglycemic level.[68] Based on the tubular hypothesis, these inhibitors reduce proximal tubule hyper reabsorption in the diabetic kidney, reducing diabetic glomerular hyperfiltration.[69] SGLT2 inhibitors help induce a sustained urinary glucose loss of 40-80g/day, which decreases glycated hemoglobin by 0.5-0.7% in patients with type 2 diabetes mellitus (T2DM).[69] These inhibitors work by promoting osmotic diuresis and natriuresis, which reduces intravascular volume, preload and, ultimately, cardiac workload. Tubuloglomerular feedback is also assumed to be critical.[69] SGLT2 inhibitors cause an increase in sodium to pass through the nephron. The sodium is sensed by macula cells via adenosine.[70] This promotes constriction of afferent glomerular arterioles, which protects the glomeruli by reducing intraglomerular pressure; this is achieved by glomerular filtration and tubular secretion.[69] These inhibitors can induce an increase in renal expression in genes involved with gluconeogenesis, bicarbonate regeneration, and ammonium formation.[69]

Hyperfiltration can cause even more kidney damage due to the increased risk of developing proteinuria.[65] The protein overload and development of fibrosis are due to a cellular

pathway causing further proliferation and differentiation in the renal epithelial cells.[65] Giving an SGLT2 inhibitor will lower glomerular capillary hypertension and hyperfiltration, reducing the physical stress on the filtration barrier, albuminuria, and the oxygen demand for tubular reabsorption.[69] SGLT2 inhibitors can exert nephroprotection by improving glycemic control and inhibitory effects on the inflammatory and fibrotic responses on the proximal tubular cells to hyperglycemia.[71] Elevated uric acid concentrations that typically accompany insulin resistance are associated with increased cardiovascular risk and are also thought to be associated with renal tubular-interstitial fibrosis and chronic kidney disease progression.[72] The lowering of uric acid observed with each of the SGLT2 inhibitors indicates a class effect with no substantive differences between agents or doses used routinely in treating type 2 diabetes.[72] SGLT2 inhibitors lower urate concentrations by increasing renal urate elimination, which is most likely done by suppressing GLUT9b activity.[72]

Clinical trials on preserving kidney function with SGLT2 inhibitors

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial involved adult patients with and without T2DM with an eGFR of 25-75 ml/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of 200-5000 mg/g.[73,74] The study randomly selected patients to receive dapagliflozin at 10 mg/d or a placebo. The patients were required to be treated with a stable dose of RAAS inhibitor for more than 4 weeks, unless they were medically contraindicated. A prespecified analysis was conducted on the effects of dapagliflozin in patients with Stage IV CKD (eGFR= 30ml/min/1.73 m^2).[73] From baseline to 2 weeks, an evident decline occurred in eGFR with patients on dapagliflozin compared to the placebo group.[73] These inhibitors preserve kidney function by preventing the eGFR from declining too quickly. The outcomes of this trial concluded a 32% lower death rate from any cause, with benefits to those observed among patients with mild to moderate Stage II and III CKD and no safety concern signals.[68,73] For chronic heart failure patients with a reduced ejection fraction, taking dapagliflozin had a decreased risk of CVS death, heart failure hospitalization, and kidney failure.[73,75] Namely, these patients sustained a 40% or greater decline in eGFR.[73,75] The investigation did not include those with Stage V CKD. However, neither dapagliflozin nor the placebo were noted to have been discontinued when the eGFR declined to <15 ml/min/1.73 m^2.

This antiproteinuric effect of SGLT2 inhibitors was replicated in a 2022 pilot study with pediatric proteinuric CKD patients. The pilot study enrolled nine pediatric patients with diagnoses primarily of Alport syndrome and Dent disease (mean age = 10.4 years, mean weight = 34.9kg, mean BMI = 17.8 kg/ m^2, and eGFR = 104.9ml/min/1.73 m^2).[76] The patients were prescribed dapagliflozin at 5 mg or 10 mg per day based on a body weight less than or greater than 30kg, respectively.[76] Overall, the pilot study concluded that dapagliflozin reduced baseline proteinuria by 33.3% at week 4 and 22.6% at week 12 in pediatric patients with proteinuric CKD.[76] Furthermore, a slight dip occurred in eGFR, consistent with SGLT2 inhibitor studies in adult patients. Though studies replicating the efficacy and safety of dapagliflozin in children with inherited proteinuric CKD are limited, the outcomes of this pilot study support the use of dapagliflozin in treatment.

The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KINDEY) was a trial designed to assess the efficacy of empagliflozin on patients with CKD who had an eGFR of 10-45 ml/min/1.73 m^2 or who had an eGFR of 45-90 ml/min/1.73 m^2 and urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200.[77] Patients were required to take an appropriate dose of the single agent RAAS inhibitor; those who were unable to take the RAAS inhibitor due to concomitant medication or comorbidities were still eligible to participate in the trial, but the reasoning for not using the inhibitor was documented.[77] The trial went on for two years and concluded that the progression of kidney disease or death from CVS occurred in 432/3,304 (13.1%) in the empagliflozin group and 558/3,305 (16.9%) in the placebo group. Consistent results were obtained among the different subgroups.[77] The hospitalization rate for any cause was lower compared to the placebo group (hazard ratio = 0.86; 95% CI [0.78, 0.95]; p = 0.003).[77] Evidence is found for an acute decrease in eGFR of 3-5 ml/min/1.73 m^2 once the trial regimen began. In terms of the respective empagliflozin and placebo groups, the initial eGFR dip categories are 28.3% and 13.4% for the eGFR dipper, 41.1% and 39.5% for eGFR intermediate, and 30.5% and 47.1% for the eGFR non-dipper participants.[78] Between the empagliflozin eGFR dippers and non-dippers, the eGFR dippers were older, had a prolonged history of diabetes, and had higher rates of impaired kidney function and albuminuria.[78] Hemoglobin, hematocrit, and albumin levels were also noted to be slightly lower in the eGFR dippers.[78] The rate of annual decline slowed down after the initial decrease. The difference in eGFR between the placebo and the empagliflozin group was 0.75mL/min, favoring the empagliflozin group.[78] The rate of eGFR decline was also noted to be more prominent in the subgroup of patients with faster annual decline rates; this includes patients with a higher eGFR or a higher baseline urinary albumin-to-creatinine ratio.[78] Hospitalization from any cause was lower in the empagliflozin group compared to the placebo group.

The Canagliflozin Cardio Vascular Assessment Study-Renal (CANVAS-R) trial consisted of patients with a mean age of 64 years and T2DM who had inadequate glycemic control ([HbA1. c] ≥7.0% and ≤10.5%), as well as a history or were deemed at an increased risk of cardiovascular disease.[79] Canagliflozin was initiated at a dose of 100 mg daily, but at week 13 or after, the dose could be increased from 100 mg to 300 mg.[79] Patients who had more than half of their glucose measurements from fasting finger-prick readings measure above 6 mmol/ L (110 mg/dL) during the preceding 2 weeks would be encouraged to titrate up.[79] The trial concluded that microalbuminuria was present in 22.3% of patients, 8.7% had macroalbuminuria, and the mean eGFR was 76 ml/ min/ 1.73 m^2. Patients with T2DM, chronic kidney disease, and albuminuria were randomized in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[68] They were

either given canagliflozin at a dose of 100 mg daily or a placebo and had a mean age of 63.[68] The patients chosen for this trial had an estimated GFR of 30-90 ml/ min/ 1.73 m^2, albuminuria, and had already been treated with renin-angiotensin system blockade.[68] The mean glycated hemoglobin value was 8.3%, the mean eGFR was 56.2 ml/ min/1.73 m^2, and the median urinary albumin-to-creatinine ratio was 927 mg/g.[79] The trial concluded that the event rate of the primary composite outcome of end-stage kidney disease, a doubling in serum creatinine levels or renal or cardiovascular death, had been lowered by 30%.[79] During the first 3 weeks, a significant reduction in the eGFR seen was noted to have occurred in patients who were taking canagliflozin compared to the placebo group (-3.72±0.25 vs. -0.55±0.25 ml/ min/ 1.73 m^2), the difference being -3.17 ml/ min/ 1.73 m^2 between the two groups.[68,79]

This led to a slower decline in eGFR in the canagliflozin group compared to the placebo group (2.74 ml /min/ 1.73 m^2).[80] Although the decrease in eGFR was evident in these trials, the canagliflozin group experienced a greater risk of amputation, mainly in the lower extremities, compared to the placebo group.[77,80] All these trials show SGLT2 inhibitors to significantly preserve kidney function by slowing the decline in GFR.

CONCLUSION

The main goal for managing CKD in pediatric patients is to decrease hyperfiltration, control nephron injury, minimize nephron stress, and prevent disease progression.[81] The degree of proteinuria in CKD is strongly associated with disease severity, and treatment with ACEIs and ARBs reduces proteinuria and slows disease progression in mild-to-moderate CKD. Recent clinical trials with finerenone and SGLT2 inhibitors in adults with CKD demonstrate a similar potential for minimizing proteinuria and preserving kidney function. However, data from pediatric clinical trials is needed to investigate their therapeutic potential and long-term effects. The outcomes of this research will help attenuate the progression of CKD in pediatric patients, ultimately improving survival rates.

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