doi.org/10.36721/PJPS.2026.39.10.288.1

Review

Pharmacological strategies for slowing the rise of creatinine and urea nitrogen in diabetic kidney disease: A scoping review

Daoman Xia[1] and Jiana Zang[2]*

[1]Department of Internal Medicine, Qufu Normal University Hospital, Jining City, Shandong Province, Jining 273100, Shandong, China

[2]Department of Pharmacy, Qufu Normal University (Rizhao Campus) Health Center, Rizhao City, Shandong Province, Rizhao 276800, Shandong, China

Abstract: **Background**: Adolescent diabetic kidney disease (DKD) represents an early-onset microvascular complication characterized by prolonged metabolic exposure and accelerated renal decline. Elevated serum creatinine and blood urea nitrogen (BUN) are key biochemical indicators of impaired renal function. **Objectives**: This scoping review aims to systematically map and evaluate pharmacological strategies for slowing the rise of creatinine and BUN in adolescents (aged 10–19 years) with DKD, with emphasis on renoprotective mechanisms, therapeutic sequencing and the potential applicability of these therapies to adolescent populations. **Methods**: A scoping review was conducted in accordance with PRISMA-ScR guidelines. A comprehensive literature search was performed using PubMed, Scopus and Google Scholar for studies published between 2020 and 2025. Eligible studies included clinical trials, observational studies, clinical guidelines and relevant reviews focusing on pharmacological interventions in adolescents (10–19 years) with diabetic kidney disease. Study selection was based on predefined inclusion and exclusion criteria. **Results**: A total of 35 studies and guideline-based references were included in the final synthesis. Intensive glycemic control (insulin for type 1 diabetes; metformin ± insulin for type 2 diabetes) was associated with improved metabolic control and favorable renal outcomes. Renin–angiotensin system blockers consistently reduced albuminuria and induced an acute hemodynamic reduction but stabilized the long-term decline in estimated glomerular filtration rate (eGFR). Sodium-glucose cotransporter-2 (SGLT2) inhibitors demonstrated additional renoprotective effects in type 2 diabetes; risks (euglycemic DKA) limit use in type 1. In adult studies, finerenone attenuated inflammatory and fibrotic pathways; no adolescent data exist. Glucagon-like peptide-1 receptor agonists improved metabolic control and reduced obesity-associated renal stress. However, pediatric-specific evidence remains limited, and much of the available evidence is derived from adult studies. **Conclusion**: Adult data suggest potential benefits of early multi-target pharmacotherapy, but adolescent-specific evidence is needed to confirm a critical role in delaying renal deterioration. Whether integration of conventional and novel agents improves long-term renal outcomes in adolescents requires direct investigation. Further pediatric-focused research is required to establish safety, efficacy and optimal therapeutic strategies.

Keywords: Adolescents; Blood urea nitrogen; Creatinine; Diabetic kidney disease; Pharmacotherapy; Renoprotection; SGLT2 inhibitors

Submitted on 04-04-2026 – Revised on 27-04-2026 – Accepted on 11-05-2026

INTRODUCTION

Because metabolic damage often starts during active growth and continues into early adulthood, diabetic kidney disease (DKD) is becoming more widely acknowledged as one of the most significant chronic microvascular problems affecting adolescents with diabetes mellitus. Early glomerular changes may appear within a few years of the initiation of diabetes, especially in teenagers with poor glycemic control, obesity, high blood pressure, or hereditary predisposition to renal injury, even though severe renal failure is rare throughout childhood (Lopez *et al*., 2021). Adolescents with type 2 diabetes often have albuminuria or other signs of kidney disease at or soon after diagnosis, whereas adolescents with type 1 diabetes typically develop diabetic kidney disease after 5–10 years of disease duration. Both groups are at significant risk, but the underlying mechanisms differ, including insulin resistance and chronic inflammation in type 2 diabetes, according to pediatric research (Muntean *et al*., 2022). Diabetic renal damage typically shows no symptoms at first. Serum creatinine and blood urea nitrogen are still the most often utilized biochemical markers in ordinary clinical practice because they are affordable, repeatable and accessible in all care settings, even though albuminuria frequently precedes a discernible reduction in filtration capacity (Uwaezuoke, 2020). While a rise in blood urea nitrogen may indicate poor nitrogen clearance, altered protein metabolism, dehydration or tubular dysfunction, a sustained rise in serum creatinine most often suggests a reduction in

**Corresponding author:* e-mail: 13156336713@163.com

glomerular filtration rate (GFR). (Chiarelli and Marcovecchio, 2022).

Today's treatment modalities are not limited to improving glycemic control. They aim to preserve glomerular hemodynamics, to inhibit inflammatory pathways and reduce oxidative stress and to delay fibrosis until the point of no return before irreversible loss of nephrons (KDIGO Diabetes Work Group, 2022). Even with apparently normal conventional renal biochemical values, Current international guidelines (e.g., KDIGO, ADA) recommend initiating renin–angiotensin system blockade in adolescents with persistent albuminuria, particularly when hypertension is also present (Levin *et al*., 2024). The long exposure to hyperglycemia during a phase of ongoing renal development has an impact on the progression of diabetic kidney disease especially in younger patients, perhaps making them more susceptible than adults to structural and functional damage over time (kidney disease: Improving Global Outcomes Diabetes Work Group, 2022). Before a clinically significant reduction in glomerular filtration becomes evident, subclinical alterations such as mesangial expansion, thickening of the basement membrane and early tubular stress may occur. In standard therapy of adolescents with diabetes, biochemical monitoring is therefore important as these pathological changes are often not detected in the early stages. The progression of the disease is further complicated by the hormonal fluctuations of puberty, which can worsen glomerular hyperfiltration and endothelial dysfunction by increasing insulin resistance and intermittent metabolic control (Bjornstad *et al*., 2021). However, renal stress can also build up owing to dietary irregularities, delayed clinical follow-up and poor adherence to insulin therapy, which are commonly observed in adolescents and contribute to progressive renal dysfunction (American Diabetes Association, 2024; Bjornstad *et al*., 2021). This provides some explanation of how renal deterioration is possible despite the apparent sporadic biochemical consistency. This scoping review aims to systematically map current pharmacological strategies used to slow the rise of creatinine and blood urea nitrogen in adolescent diabetic kidney disease, with particular emphasis on renoprotective mechanisms, therapeutic sequencing and the applicability of emerging pharmacological interventions in pediatric populations.

As a consequence, preemptive pharmacological treatment designed to prevent progression from early renal stress to overt kidney disease characterized by a sustained rise in creatinine has garnered more interest in recent years. Besides conventional methods of blood sugar control, new renoprotective drugs are becoming increasingly focused on fibrogenesis inhibition, anti-inflammatory effects, mineralocorticoid blockage and salt control (Tuttle *et al*, 2021). Since early nephron function preservation may significantly change long-term renal prognosis and future cardiovascular risk, this more comprehensive therapeutic approach is especially pertinent to teenagers (American Diabetes Association Professional Practice Committee, 2024). Therefore, this scoping review aims to systematically map and evaluate current pharmacological strategies for managing elevated serum creatinine and blood urea nitrogen in adolescent diabetic kidney disease, with particular emphasis on renoprotective mechanisms, therapeutic sequencing and the applicability of emerging pharmacological interventions in pediatric populations.

MATERIALS AND METHODS

The present study was done as a scoping review in line with the PRISMA-ScR guidelines. In the literature search, articles published between January 2020 and January 2025 were searched in the PubMed, Scopus and Google Scholar databases. Relevant clinical guidelines were identified through database searches and manual screening of references, including internationally recognized guideline documents such as those published by KDIGO and the American Diabetes Association. Keywords used include “adolescent diabetic kidney disease,” “creatinine,” “blood urea nitrogen,” “renoprotection,” “SGLT2 inhibitors,” “finerenone,” and “GLP-1 receptor agonists.”

Research articles about teenagers (10–19 years old) with diabetic kidney disease met the inclusion criteria. Relevant adult research and therapeutic guidelines were also taken into consideration to give contextual information regarding pharmaceutical therapy and renoprotective mechanisms in regions where there was little evidence unique to adolescents. High-quality reviews were used only for background context. Review articles were only considered in synthesizing background data whereas the focus was on original and clinical guideline articles. Review articles were used strictly for contextual understanding and were not considered as primary evidence sources, thereby minimizing bias and ensuring that conclusions were primarily derived from original studies and clinical guidelines.

Articles excluded from this study included those whose focus was adult end stage renal diseases with no consideration for adolescents, non-English articles and those with no relevance to diabetic kidney disease. Database searches turned up 520 documents in all, including PubMed (n = 210), Scopus (n = 220) and Google Scholar (n = 90). After removal of 160 duplicate records, 360 records underwent title and abstract screening. Of these, 240 records were excluded because they were unrelated to diabetic kidney disease, did not involve adolescent populations, did not address pharmacological interventions, or were non-original articles that did not meet the eligibility criteria.

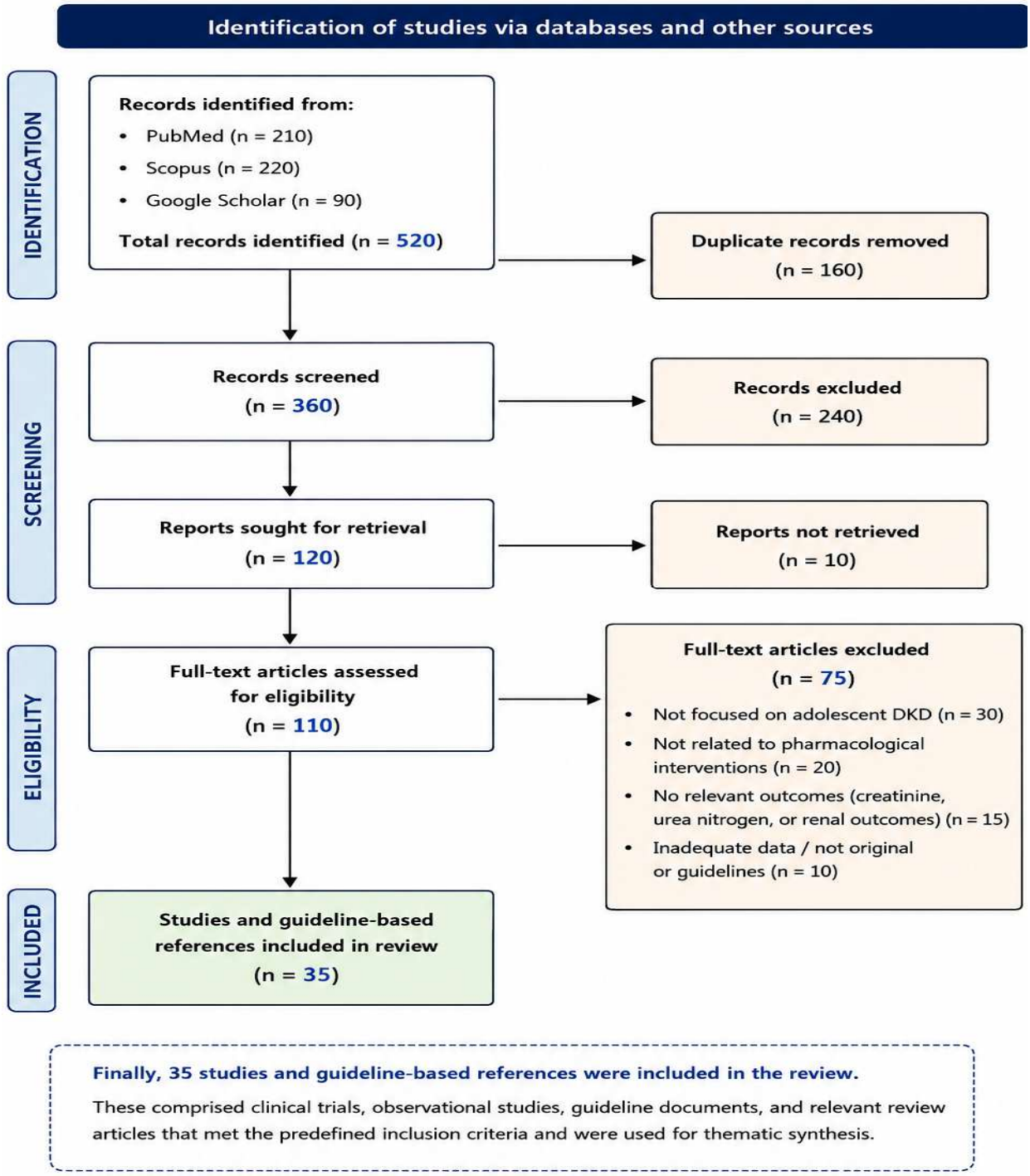

Fig. 1: PRISMA 2020 flow diagram illustrating the study selection process for this scoping review.

Ten of the 120 reports subsequently sought for retrieval could not be obtained. Ten of the 120 reports that were subsequently requested for retrieval were not found. After 110 full-text papers were evaluated for eligibility, 75 of them were eliminated because they did not specifically address adolescent diabetic kidney disease, were irrelevant to pharmacological therapies, lacked pertinent renal outcome measures, or had poor data quality.

RESULTS

Study selection and characteristics

The final synthesis had 35 eligible sources in total, including research with an adolescent focus, pertinent adult studies where there was little data unique to adolescents, clinical guideline documents, and supportive review literature. The study selection procedure is shown in figure 1. Clinical trials, observational studies, clinical

guideline documents found through database and reference-list searches, and a small number of excellent review articles used for contextual interpretation made up the listed sources. While guidelines included suggestions for clinical care and monitoring techniques, the majority of included research assessed pharmacological therapies and renoprotective techniques in diabetic kidney disease. Figure 1 shows the selection process for the study Clinical trials, observational studies, clinical guideline documents found through database and reference-list searches, and a small number of excellent review articles used for contextual interpretation made up the included content.

Evidence mapping

Clinical trials, observational studies, clinical guidelines, and a few excellent review articles published between 2020 and 2025 were all included in the evidence. Most of the research concentrated on pharmaceutical approaches to maintain renal function and slow the course of diabetic kidney disease. Renin-angiotensin system inhibition, sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists, glucagon-like peptide-1 receptor agonists, and intensive glycemic management with insulin and metformin were among the frequently assessed therapies. Recommendations for diabetic kidney disease screening, monitoring, and treatment therapy were given in clinical guideline publications. Some adult research were included to offer contextual information regarding renoprotective mechanisms and new therapy methods because there were few studies specifically focused on adolescents.

DISCUSSION

Pathophysiological basis of elevated creatinine and blood urea nitrogen in adolescent diabetic kidney disease

Glomerular hyperfiltration is the first functional renal impairment in teenagers with diabetes.

Increased sodium-glucose cotransport decreases sodium delivery to the macula densa, while elevated plasma glucose enhances filtered glucose delivery to proximal tubules. This mechanism leads to disruption of tubuloglomerular feedback and contributes to increased intraglomerular pressure, which is a key early event in diabetic kidney disease progression (Kidney Disease: Improving Global Outcomes Diabetes Work Group, 2022; Heerspink *et al*., 2020). Increased intraglomerular pressure results from this disruption of tubule glomerular feedback and afferent arteriolar vasodilation (Kidney Disease: Improving Global Outcomes Diabetes Work Group, 2022).

Persistent intraglomerular stress gradually deteriorates the filtration barrier, even while hyperfiltration initially preserves filtration capacity. Podocyte separation compromises glomerular integrity, basement membrane thickening modifies permeability and mesangial matrix expansion constricts the capillary lumen (Bjornstad *et al*., 2021). Recent molecular research also shows that endothelial glycocalyx damage and podocyte mitochondrial dysfunction cause early nephron instability before the development of overt creatinine increase (Tuttle *et al*, 2021).

Serum creatinine rises through simpler mechanisms than blood urea nitrogen. While dehydration during hyperglycemia, increased protein catabolism and altered tubular reabsorption may further raise circulating levels, reduced filtration directly hinders urea excretion (American Diabetes Association Professional Practice Committee, 2024). Because physical activity, nutrition and hydration vary greatly in teenagers, brief changes are common; consequently, serial measures have more therapeutic relevance than isolated laboratory interpretation.

Clinical interpretation of renal biochemical progression in adolescents

Adolescents' renal biochemical development must be assessed often rather than using a single laboratory interpretation. Because serum creatinine is highly influenced by age, sex, lean body mass and pubertal stage, estimated glomerular filtration rate is a more useful indicator than isolated creatinine concentration (American Diabetes Association, 2024).

Serum creatinine and blood urea nitrogen should always be evaluated in tandem because a single rise may indicate temporary metabolic stress or dehydration rather than progressive nephropathy. Persistent microalbuminuria in adolescents is a strong indicator of biochemical progress later on, when blood pressure also begins to increase (Marcovecchio *et al*., 2021).

In adolescents with diabetes, routine renal monitoring should consist of:

- Serum creatinine
- Urea nitrogen in the blood
- The ratio of urine albumin to creatinine
- The estimated rate of glomerular filtration
- Evaluation of blood pressure

Additionally, in teenagers with comparatively maintained muscle mass, serum cystatin C has proven to be more sensitive than creatinine in detecting early renal impairment (Liao *et al*., 2022).

Pharmacological management strategies

Glycemic pharmacotherapy and renal biochemical stabilization

Stricter glycemic control is still the best modifiable predictor of kidney preservation. Intensive insulin treatment decreases glomerular hyperfiltration and delays nephron injury in adolescents with type 1 diabetes (DCCT/EDIC Research Group, 2021). Basal-bolus insulin therapies are more effective in controlling metabolic

variability by decreasing glycemic oscillation when they are used in combination with continuous glucose monitoring. Time in range is increasingly important due to the fact that glucose fluctuation independently causes endothelial damage. Continuous glucose monitoring plays a crucial role in identifying glycemic variability, which has been linked to microvascular complications including renal injury (Tuttle *et al*., 2021).

Metformin is still the main pharmacological treatment for type 2 diabetes when renal function is preserved. Intensive glycemic control with insulin and metformin was associated with improved glycemic control, reduced albuminuria and preservation of renal function in several included studies, especially in patients with early diabetic kidney disease and preserved renal reserve. Its continued use is supported by clinical guidelines due to its ability to improve insulin sensitivity, reduce systemic inflammation and provide indirect vascular protection (American Diabetes Association, 2024; Graham *et al*., 2022). Insulin sensitization decreases systemic inflammation and vascular stress leading to preservation of renal microcirculation (Graham *et al*., 2022). Diabetic kidney disease often progresses more rapidly in youth than in adults because of metabolic overload starting from childhood and frequent association with obesity. Beyond limiting basement membrane thickening and the progression to chronic albuminuria, early achievement of stable glycemic goals may also attenuate mesangial expansion. Further, continuous glucose monitoring enables early identification of the nocturnal hyperglycemia and postprandial variability that have been associated with progressive renal microvascular injury. Early detection of these glycemic fluctuations allows timely therapeutic adjustments, which may reduce cumulative renal stress and delay nephron injury (Tuttle *et al*., 2021; American Diabetes Association, 2024). Because intermittent deficits in insulin administration could accelerate cumulative nephron burden, treatment compliance in teens remains a key determinant of biochemical stability (Tuttle *et al*., 2021).

Individualized insulin titration is particularly important in the setting of development and puberty and in times of changing insulin sensitivity because hormonal shifts can impact renal hemodynamics and the glycemic response. Hormonal variations during adolescence can exacerbate insulin resistance and alter glomerular dynamics, thereby influencing both metabolic control and renal outcomes (Bjornstad *et al*., 2021). For long-term preservation of renal function, integrated metabolic management that includes medication, diet and systematic monitoring is required.

Renin–angiotensin system blockade as foundational renoprotection

The most proven medication to sustain the functionality of the kidney in diabetes mellitus-related renal disease is that of renin-angiotensin system blockade. This class of drug reduces albumin excretion, lowers intraglomerular pressure and lessens the resistance in the efferent arteriole (Rossing *et al*., 2022).

Commonly used agents in adolescents include lisinopril, ramipril and enalapril. These medications are initiated when early hypertension or persistent albuminuria is observed.

There will be a transient increase in serum creatinine post-initiation of therapy due to decreased filtration pressure. This is normally stable; however, it does not indicate kidney injury (Cherney *et al*., 2021).

Losartan is a similar agent but from angiotensin receptor blockers. Angiotensin receptor blockers provide comparable renoprotective effects and are particularly useful in patients who are intolerant to angiotensin-converting enzyme inhibitors (Rossing *et al*., 2022).

Following initiation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, included studies consistently reported reductions in albuminuria and a slower rate of estimated glomerular filtration rate decline.

Significant effects on the kidneys include:
The decrease in albuminuria

- A slower rate of creatinine progression
- Maintaining the filtering reserve
- Enhanced hemodynamic stability throughout time

Sodium-glucose cotransporter-2 inhibitors and emerging pediatric relevance

The benefits of sodium-glucose cotransporter-2 inhibitors for the kidneys go beyond only reducing blood sugar levels, making them a significant therapeutic advancement.

These substances decrease glomerular hyperfiltration, restore tubuloglomerular feedback and prevent proximal tubular reabsorption of glucose and salt (Heerspink *et al*., 2020). Additionally, hemodynamic investigations demonstrate better renal oxygen use during therapy and decreased afferent arteriolar vasodilation (Cherney *et al*., 2021).

Numerous investigations reported that sodium-glucose cotransporter-2 inhibitors improved glomerular hemodynamic stability and slowed the rate of renal function decline.

Among their main renal effects are:

- A decrease in intraglomerular pressure
- A reduction in tubular oxygen demand
- Reduced release of inflammatory mediators
- A slower progression of fibrosis

Dehydration, vaginal infection and the danger of euglycemic ketoacidosis are among the safety concerns (Portalatin *et al*., 2025). Although long-term renal safety still needs to be confirmed, early pediatric findings using dapagliflozin have demonstrated positive reductions in albuminuria (Choi *et al*., 2024).

Estimated glomerular filtration is reliably preserved during long-term treatment, according to adult renal outcome trials (Hannouneh *et al*., 2025).

Mineralocorticoid receptor antagonism and anti-fibrotic renal protection

As diabetic kidney disease progresses, fibrosis becomes more important in predicting biochemical decline. Non-steroidal mineralocorticoid receptor antagonists, such as finerenone, reduce inflammatory signals and block profibrotic pathways (Bakris *et al*., 2020). Further evidence suggests that finerenone may slow the progression of interstitial fibrosis once renin-angiotensin inhibition has reached its peak (Kanumilli *et al*., 2024). Steroidal mineralocorticoid receptor antagonists such as spironolactone and eplerenone have also demonstrated efficacy in reducing proteinuria, although their clinical use may be limited by the risk of hyperkalemia. Mineralocorticoid receptor antagonism is increasingly being considered as an important therapeutic strategy when persistent inflammatory activity is associated with progressive renal deterioration (Agarwal *et al*., 2023). This therapeutic approach appears to be particularly useful when albuminuria persists despite stable blood pressure and adequate glycemic management.

These drugs lessen collagen buildup, mesangial growth and long-term cellular damage in the renal interstitium by preventing mineralocorticoid receptor overactivation. Clinical studies have demonstrated that this mechanism contributes to reduced albuminuria and slowing of chronic kidney disease progression (Bakris *et al*., 2020; Agarwal *et al*., 2023). Finerenone-based therapy was linked to decreases in inflammatory and fibrotic indicators, especially in adult patients with chronic albuminuria despite normal renin-angiotensin system suppression.

They also have an anti-inflammatory effect by suppressing oxidative stress pathways that lead to endothelial dysfunction and chronic nephron loss. This anti-inflammatory activity plays a critical role in preserving microvascular integrity and reducing long-term renal injury (Kanumilli *et al*., 2024). Non-steroidal antagonists differ from previous steroidal drugs in this wider biological effect, especially because they provide better selectivity and a decreased risk of endocrine side effects. Patients who have persistent biochemical progression despite typical nephroprotective medication seem to benefit most clinically, particularly when residual albuminuria suggests ongoing intrarenal damage. Because decreased renal clearance may increase susceptibility to hyperkalemia, especially when paired with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, careful potassium monitoring is still crucial during treatment.

Treatments that target inflammatory and structural pathways may help postpone the development of advanced chronic kidney disease in adolescents with persistent diabetic renal stress, as fibrosis increasingly defines long-term renal outcome.

GLP-1 receptor agonists in obese adolescent diabetic kidney disease

Glucagon-like peptide-1 receptor agonists assist the kidneys indirectly by increasing metabolism and lowering body weight. Their role is particularly relevant in obese adolescents because inflammation linked to obesity greatly exacerbates endothelial dysfunction (Mann *et al*., 2024). Liraglutide and semaglutide reduce systemic inflammation, improve insulin sensitivity and suppress appetite. These effects contribute to improved metabolic control and indirectly support renal protection by reducing hemodynamic and inflammatory stress on the kidneys (Mann *et al*., 2024; Mlynarska *et al*., 2024). For renal benefit, improved metabolic circumstances appear to be more significant than direct nephron action (Mlynarska *et al*., 2024). Current evidence suggests that the renoprotective effects of glucagon-like peptide-1 receptor agonists are predominantly indirect, mediated through metabolic improvement, weight reduction and anti-inflammatory pathways rather than direct nephron-specific mechanisms. According to published research, glucagon-like peptide-1 receptor agonist therapy improved metabolic regulation, decreased obesity-related renal stress and slightly slowed the evolution of renal risk factors. Additionally, these drugs help minimize insulin demand and postprandial glucose excursions, which, over time, may lessen chronic metabolic stress on glomerular structures. Because excess adipose tissue encourages the production of pro-inflammatory mediators that exacerbate renal microvascular damage, decreases in visceral adiposity are especially important. Glucagon-like peptide-1 receptor agonists may promote endothelial integrity preservation and enhance overall renal hemodynamic stability by reducing these pathways.

Modest drops in systolic blood pressure and better lipid management, both of which affect long-term nephron preservation in adolescents with several metabolic risk factors, may provide further benefits. In order to increase adherence and reduce treatment interruption, gastrointestinal tolerability and progressive dose escalation are still crucial factors, particularly at the beginning.

Supportive pharmacological strategies

Blood pressure regulation

Hypertension significantly accelerates nephron destruction in adolescents with diabetes. Even small variations in blood pressure enhance glomerular stress and protein leakage (Flynn *et al*., 2022). Other antihypertensive drugs, such as calcium channel blockers, may be required when renin-angiotensin blocking is insufficient. Combination antihypertensive therapy is often necessary to achieve optimal blood pressure targets and reduce progressive glomerular damage in adolescents with diabetic kidney disease (Flynn *et al*., 2022). In addition to preserving endothelial function, sustained blood pressure regulation lessens the long-term mechanical strain on glomerular capillaries, which delays the structural degradation of delicate renal tissue. By detecting disguised hypertension and early nocturnal irregularities, ambulatory blood pressure measurement may further enhance treatment decision-making in adolescents with fluctuating metabolic control.

Chronically high systolic pressure can hasten mesangial expansion and encourage the glomerular basement membrane to gradually thicken, both of which lead to a gradual decrease in filtration efficiency. Therefore, when repeated blood pressure readings are above target despite lifestyle modification and glycemic optimization, early pharmaceutical adjustment is crucial. In certain patients, combination antihypertensive medication may be necessary to minimize further renal stress and establish stable hemodynamic control. In younger people, careful dose titration is especially crucial since too much blood pressure lowering can impair renal perfusion and result in symptomatic hypotension.

Frequent follow-up also aids in identifying treatment response variability, particularly throughout adolescence when blood pressure trends may be influenced by growth, hormonal changes and irregular adherence.

Lipid correction

In addition to statins, other lipid-lowering agents such as fibrates and niacin may be considered in selected patients to improve lipid profiles and reduce vascular complications. Furthermore, additional antidiabetic agents including dipeptidyl peptidase-4 inhibitors, sulfonylureas and thiazolidinediones may contribute to glycemic control, although their direct renoprotective effects are less well established compared to newer pharmacological agents.

Dyslipidemia aggravates endothelial damage and glomerular sclerosis. Effective lipid control using statins and related agents has been associated with improved vascular function and reduced progression of renal disease (De Ferranti *et al*., 2023). Statins may improve vascular stability and reduce microvascular inflammation (De Ferranti *et al*., 2023). These substances may enhance nitric oxide bioavailability and lessen oxidative damage in the renal microcirculation in addition to decreasing cholesterol. Because vascular damage frequently advances concurrently with decreased filtration reserve, early treatment of aberrant lipid profiles is especially important in diabetic kidney disease.

Frequent follow-up also aids in identifying treatment response variability, particularly throughout adolescence when blood pressure trends may be influenced by growth, hormonal changes and irregular adherence. A more thorough evaluation of the course of the disease and the efficacy of treatment can be obtained by combining blood pressure management with renal biochemical monitoring.

Correction of metabolic acidosis

As renal impairment increases, bicarbonate administration may stabilize blood urea nitrogen and reduce catabolic nitrogen production (Wesson *et al*., 2025). In adolescent patients suffering from chronic metabolic stress, improvement of nutrient composition and decrease in muscle protein breakdown can be achieved by addressing acidosis. Chronic acidosis causes nephron damage because of stimulation of ammoniagenesis and inflammation in tubular cells. Persistent metabolic acidosis accelerates renal injury by promoting inflammatory signaling and fibrosis within the tubular interstitium (Wesson *et al*., 2025).

Through inhibition of complement activation and slowing down the progression of fibrosis, regulation of acid-base balance may be beneficial in maintaining tubular cell function. In view of the fact that reduction of renal reserve capacity, accompanied by reduced bicarbonate reabsorption, results in aggravation of protein breakdown and metabolism, timely adjustment of acidosis is even more necessary.

In the case of using bicarbonate for a long period of time, special care should be taken into account among teenagers due to potential hazards associated with an increased sodium intake and elevated blood pressure level. Gut microbiota dysbiosis was also reported as a factor contributing to increased renal inflammation and changes in nitrogen metabolism in diabetic individuals (Dai *et al*., 2022). Emerging evidence suggests that gut-derived uremic toxins play a significant role in endothelial dysfunction and chronic inflammatory activation in diabetic kidney disease (Dai *et al*., 2022). There are many chronic kidney disease pathways leading to the formation of diabetes related to oxidative stress and impaired mitochondrial function (Hou *et al*., 2022).

As revealed by recent studies, uremic toxins produced by bacterial fermentation in the gut may lead to endothelial dysfunction and chronic inflammation in the kidneys.

Table 1: Major pharmacological classes in adolescent diabetic kidney disease.

Drug class	Principal mechanism	Renal biochemical effect	Important caution
Insulin	Glycemic stabilization	Delays onset and slows progression of microvascular damage	Hypoglycemia
ACE inhibitors	Lowers intraglomerular pressure (efferent dilation)	Induces acute functional eGFR dip; stabilizes long-term filtration decline	Hyperkalemia; monitor for acute eGFR dip at initiation
ARBs	Blocks AT1 receptors (efferent dilation)	Induces acute functional eGFR dip; slows structural nephron loss	Hypotension; monitor for acute eGFR dip at initiation
SGLT2 inhibitors	Restores tubuloglomerular feedback (afferent constriction)	Induces initial acute hemodynamic eGFR dip; preserves long-term filtration rate	Euglycemic DKA risk (type 1 diabetes); pediatric approval is for T2D glycemic control only
Finerenone	Non-steroidal MR antagonism	Attenuates inflammatory and tissue fibrotic pathways to slow nephron loss	Potassium elevation; no adolescent DKD trials
GLP-1 agonists	Incretin mimetic/Metabolic improvement	Indirect cardiorenal protection; reduces podocyte stress via weight and glycemic control	Gastrointestinal effects; no adolescent renal outcome trials

Note: Data summarized from KDIGO (2022), ADA (2024) and recent clinical trials (Bakris *et al*., 2020; Mann *et al*., 2024).

Table 2: Monitoring strategy during pharmacological treatment.

Parameter	Recommended interval	Clinical purpose
Serum creatinine	1–2 weeks after initiating RAS blockers or SGLT2 inhibitors, and every 3–6 months routinely	Assess estimated glomerular filtration rate (eGFR) and monitor for the expected acute functional dip (<30%) versus toxic injury
Blood urea nitrogen	With renal follow-up	Assess nitrogen clearance
Urine albumin-creatinine ratio	Every 3–6 months	Early treatment response
Potassium	1–2 weeks after initiation or dose escalation, then every 3–6 months routinely	Detect electrolyte imbalance
Blood pressure	Every visit	Hemodynamic control

Note: Monitoring recommendations adapted from pediatric nephrology guidelines (ADA, 2024; Flynn *et al*., 2022). Frequent reevaluation promotes safer long-term dose modification and early progression identification.

This highlights the emerging role of gut–kidney axis interactions in the progression of diabetic kidney disease (Dai *et al*., 2022). The interconnection between metabolism and renal damage shows the importance of the combination of biochemical restoration with broader strategies aimed at the preservation of metabolic balance within the whole organism. The main pharmacological groups employed for biochemical normalization and renoprotection in adolescent diabetic nephropathy are described in table 1 below.

Proposed therapeutic sequencing

A stepwise pharmacological approach is recommended for managing adolescent diabetic kidney disease. Initial management should focus on optimization of glycemic control using insulin or metformin. This should be followed by early initiation of renin–angiotensin system blockade in patients with albuminuria or hypertension.

In patients with persistent renal stress, sodium-glucose cotransporter-2 inhibitors may be introduced to reduce intraglomerular pressure and improve tubular feedback mechanisms. Mineralocorticoid receptor antagonists such as finerenone may be considered in cases of ongoing inflammatory and fibrotic activity.

Glucagon-like peptide-1 receptor agonists may be incorporated in obese adolescents to improve metabolic control, reduce systemic inflammation and support long-term renal protection. This sequential approach allows targeted intervention at different stages of disease progression.

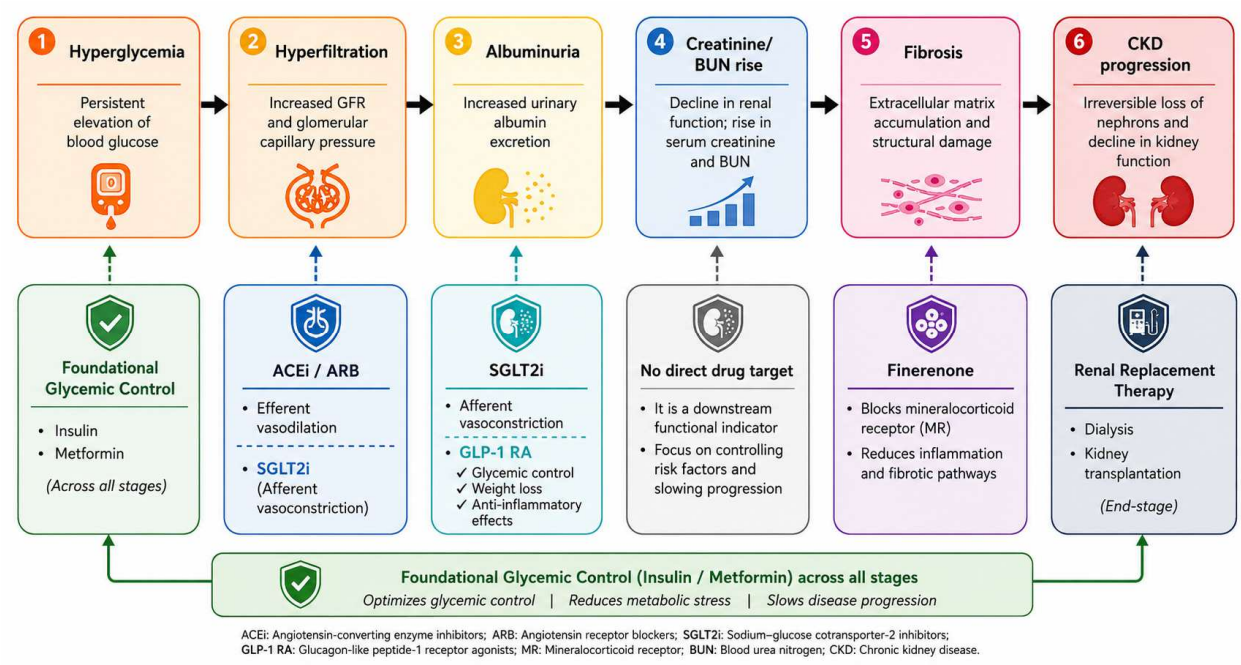

Fig. 2: Adolescent diabetic kidney disease: pharmacological therapeutic pathway.
Note: Insulin operates during hyperglycemia; ACE inhibitors and ARBs act during hyperfiltration; SGLT2 inhibitors act during the tubular-glomerular phase; finerenone acts during the advancement of fibrosis; and GLP-1 receptor agonists alleviate metabolic burden. This framework highlights how different drug classes act at distinct stages of renal injury progression.

The mechanism, biochemical impact and safety profile of these medicines vary, necessitating customized selection based on metabolic condition and illness severity. Because therapeutic response and adverse effects evolve during follow-up, structured biochemical monitoring is essential during treatment, as outlined in table 2.

Frequent reevaluation promotes safer long-term dose modification and early progression identification. The sequence of renal injury progression and pharmacological intervention targets in adolescent diabetic kidney disease is illustrated in Fig. 2.

Clinical translation challenges in adolescents

Despite the existence of various pharmacologic interventions that have shown protective effect on the kidneys in adults, the ability to directly apply those medications in adolescents is quite challenging. Renal maturation, hormonal variations and insulin sensitivity play an important role in influencing pharmacotherapy efficacy and safety.

There is very little data on the benefits of use of SGLT2 inhibitors, mineralocorticoid receptor antagonists, including finerenone and GLP-1 receptor agonists in adolescents because most of the data is based on adult studies. Thus, any assumptions regarding the beneficial outcomes of pharmacotherapy in adolescents cannot be generalized. As a result, some conclusions about newer pharmaceutical treatments should be understood as contextual rather than adolescent-specific findings because they are based on adult evidence, so their use in teenagers is mostly dependent on extrapolation from adult data.

Additionally, some early molecular abnormalities, including mitochondrial dysfunction and injury to the endothelial glycocalyx layer, may occur even before changes in traditional biomarkers become evident. Such emerging markers like neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 can be used for detecting kidney damage at early stages in adolescents. Therefore, extrapolation of adult clinical trial data to adolescent populations should be performed with caution, considering differences in renal physiology, hormonal status and disease progression patterns. Heterogeneity in trial design, patient groups, outcome measures and the preponderance of adult-derived findings hindered direct quantitative comparison across pharmacological classes.

Future directions

Early intervention in renal injury prior to an increase in serum creatinine levels or loss of glomerular function will play an essential role in the future management of diabetes mellitus nephropathy. Apart from conventional strategies for managing hypertension and hyperglycemia, novel medications currently being researched include those that can target fibrotic signals, inflammation and endothelial dysfunction (Zou *et al*., 2025). Ongoing clinical trials investigating endothelin receptor antagonists

and biologic therapies in pediatric populations may provide further insight into emerging treatment options and their applicability in adolescent diabetic kidney disease.

By modifying cytokine activity, macrophage recruitment and oxidative stress pathways, some experimental drugs are being assessed for their potential to reduce intrarenal inflammation and prevent increasing structural damage in the glomerulus and tubulointerstitium. Because transforming growth factor-β, nuclear factor-kappa B signaling and chemokine-mediated cellular damage play a significant role in nephron loss and chronic fibrogenesis, treatments that target these pathways are thought to be especially promising.

Stem cell-based treatments and extracellular vesicle therapies, which may aid in renal repair by enhancing microvascular integrity and lowering cellular apoptosis, have also drawn attention due to advancements in regenerative medicine. Simultaneously, proteomic and genomic profiling are making it easier to identify high-risk phenotypes, which enables earlier therapy intensification in people who are expected to undergo rapid disease progression.

While new molecular evaluations indicate that combining metabolic and anti-inflammatory targets may offer the most successful long-term renal preservation strategy, precision medicine methods may enable tailored medication sequencing based on molecular risk profiles (Downie *et al*., 2023). Therefore, it is anticipated that future treatment frameworks would incorporate biomarker panels and clinical characteristics to enable dynamic therapy modification based on disease activity, response to treatment and anticipated renal trajectory. Continued expansion of high-quality clinical evidence, particularly from pediatric-focused studies, is essential to strengthen the scientific foundation of pharmacological management in adolescent diabetic kidney disease. Patients with diabetic kidney disease may eventually benefit from such multifaceted approaches in terms of both cardiovascular protection and kidney outcomes.

CONCLUSION

With regard to adolescents who have been diagnosed with diabetic nephropathy, an increase in BUN and serum creatinine indicates that their kidneys are already experiencing serious malfunctioning and require a quick introduction of multifactorial pharmacotherapy. In addition to biochemical markers, long-term clinical endpoints such as progression to advanced stages of chronic kidney disease and the requirement for renal replacement therapy should also be considered when evaluating treatment effectiveness. While newer medications like finerenone, SGLT2i drugs, or GLP-1RAs are considered to be more beneficial for the renoprotective effect, inhibition of renin-angiotensin axis still needs to be applied. Overall, optimal renoprotection is expected to result from individualized and timely treatment.

Albuminuria is controlled, glomerular filtration rate is stabilized and the progression of tubulointerstitial damage is slowed down. In adolescents with diabetes, besides the high level of hyperglycemia and related complications, the progression of diabetic nephropathy depends on inflammatory activation, endothelial dysfunction and mineralocorticoid signaling. Hence, combining several different treatments is likely to yield better outcomes.

When introducing medication into therapy, it is necessary to carefully monitor blood pressure, electrolyte content in blood and kidney function in adolescents. For effective prevention of further nephron injury, drug therapy has to be supplemented with insulin regulation, nutritional counseling and prevention of cardiovascular diseases. The concept of early intervention even in the absence of any apparent symptoms has received considerable attention, particularly among high-risk patients who have developed microalbuminuria, raised creatinine levels and hypertension. In such susceptible patients, this early therapeutic intervention approach will help delay the onset of chronic renal failure. It should be mentioned that a large portion of the data supporting more recent treatment drugs, such as GLP-1 receptor agonists, finerenone, and SGLT2 inhibitors, comes from adult populations. Therefore, until more pediatric-specific efficacy and safety data are available, their use in teenagers should be interpreted cautiously.

Author' contributions

Daoman Xia was responsible for conceptualization, literature collection, data interpretation, drafting of the manuscript and preparation of tables and figure. Jiana Zang contributed to study design, critical revision of scientific content, supervision and final approval of the manuscript for publication. Both authors approved the final submitted version and agree to be accountable for all aspects of the work.

Funding

This work was not supported by any funding.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this paper.

Supplementary data

https://www.pjps.pk/uploads/2026/07/SUP1783770430.pdf

REFERENCES

Agarwal R, Filippatos G and Pitt B (2023). Mineralocorticoid receptor antagonists in diabetic chronic kidney disease. *Kidney Int Rep*, **8**(2): 177–188.

American Diabetes Association (2024). Children and adolescents: Standards of care in diabetes. *Diabetes Care*, **47**(Suppl. 1): S258–S281.

Bakris GL, Agarwal R and Anker SD (2020). Finerenone in chronic kidney disease associated with type 2 diabetes. *N Engl J Med*, **383**(23): 2219–2229.

Bjornstad P, Drews KL and Caprio S (2021). Early diabetic kidney disease in youth-onset diabetes. *Curr Diab Rep*, **21**(2): 15.

Cherney DZI, Dekkers CCJ and Barbour SJ (2021). Renal oxygenation effects of SGLT2 inhibition. *Lancet Diabetes Endocrinol*, **9**(12): 845–854.

Chiarelli F and Marcovecchio ML (2022). Renal biomarkers in pediatric diabetes. *Horm Res Paediatr*, **95**(2): 101–112.

Choi N, Warady BA, Furth SL (2024). Dapagliflozin use in children with kidney disease. *Pediatr Nephrol*, **39**(8): 2141–2152.

Dai Y, Li J and Wang L (2022). Gut microbiota and diabetic kidney disease progression. *Ren Fail*, **44**(1): 157–168.

DCCT/EDIC Research Group (2021). Intensive diabetes treatment and renal outcomes in young patients. *N Engl J Med*, **384**(3): 189–199.

De Ferranti SD, Steinberger J and Ameduri R (2023). Dyslipidemia management in adolescents with metabolic disease. *Circulation*, **147**(21): 1634–1651.

Downie ML, Dumont T and McCarthy HJ (2023). Precision medicine approaches in diabetic kidney disease. *Can J Kidney Health Dis*, **10**: 20543581231124561.

Flynn JT, Kaelber DC and Baker-Smith CM (2022). Clinical practice guideline for pediatric hypertension. *Pediatrics*, **150**(3): e2022057990.

Graham GG, Punt J and Arora M (2022). Clinical pharmacokinetics of metformin. *Clin Pharmacokinet*, **61**(5): 655–670.

Hannouneh ZA, Wiegley N and Fathallah-Shaykh S (2025). SGLT2 inhibitors in diabetic kidney disease review. *Kidney Med*, **7**(1): 100912.

Heerspink HJL, Stefansson BV and Correa-Rotter R (2020). Sodium-glucose cotransporter-2 inhibitors in diabetic kidney disease. *N Engl J Med*, **383**(15): 1436–1446.

Hou YC, Zheng CM, Yen TH (2022). Chronic kidney disease progression pathways in diabetes. *Int J Mol Sci*, **23**, 4567.

Kanumilli N, Das S and Reddy M (2024). Finerenone and diabetic renal protection: Emerging evidence. *Diabetes Ther*, **15**(5): 1033–1047.

Kidney Disease: Improving Global Outcomes Diabetes Work Group (2022). KDIGO clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*, **102**(Suppl. 5): S1–S127.

Levin A, Stevens PE and Bilous RW (2024). KDIGO executive summary on chronic kidney disease evaluation and management. *Kidney Int*, **105**(4), 889–902.

Liao X, Wang X and Zhang H (2022). Serum cystatin C and diabetic nephropathy meta-analysis. *BMC Endocr Disord*, **22**, 101.

Lopez LN, Shah A and Reidy KJ (2021). Diabetic kidney disease in children and adolescents: An update. *Pediatr Nephrol*, **36**(6): 1387–1399.

Mann JFE, Hansen T and Idorn T (2024). GLP-1 receptor agonists and renal outcomes in diabetes. *Lancet Diabetes Endocrinol*, **12**(3): 221–232.

Marcovecchio ML, Dalton RN and Chiarelli F (2021). Microalbuminuria and renal decline in adolescence. *Pediatr Diabetes*, **22**(8): 1124–1133.

Mlynarska E, Franczyk B and Rysz J (2024). Novel insights into diabetic kidney disease treatment. *Int J Mol Sci*, **25**: 10222.

Muntean C, Chiriac S and Balgradean M (2022). Diabetic kidney disease in pediatric patients: Current perspectives. *Children (Basel)*, **9**(9): 1321.

Portalatin GM, Niaz T and Weaver DJ (2025). SGLT2 inhibitors in pediatric nephrology: Current evidence. *Front Pediatr*, **13**: 1521425.

Rossing P, Caramori ML and Chan JCN (2022). Renin–angiotensin system blockade in diabetic kidney disease. *Kidney Int*, **101**(1): 112–121.

Tuttle KR, Alicic RZ and Duru OK (2021). Clinical features of diabetic kidney disease in youth. *Clin J Am Soc Nephrol*, **16**(10): 1602–1613.

Uwaezuoke SN (2020). Diabetic kidney disease in childhood and adolescence: Conventional and novel renoprotective strategies. *EMJ Nephrol*, **8**(1): 78–86.

Wesson DE, Mathur V and Tangri N (2025). Metabolic acidosis in chronic kidney disease. *Clin J Am Soc Nephrol*, **20**(2): 220–231.

Zou LX, Zhao Y and Zhang Q (2025). Biomarkers for prediction of diabetic kidney disease progression. *Front Med*, **12**: 1492483.