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Pharmacological Management of Youth with Type 2 Diabetes and Diabetic Kidney Disease: A Comprehensive Review of Current Treatments and Future Directions

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Abstract

Introduction: Diabetic kidney disease (DKD) is a leading cause of mortality in people with type 2 diabetes (T2D) and over 50% of individuals with youth-onset T2D will develop DKD as a young adult. Diagnosis of early-onset DKD remains a challenge in young persons with T2D secondary to a lack of available biomarkers for early DKD while the injuries may still be reversible. Furthermore, multiple barriers exist to initiate timely prevention and treatment strategies for DKD including a lack of Food and Drug Administration approval of medications in pediatrics; provider comfort with medication prescription, titration, and monitoring; and medication adherence.

Areas Covered: Therapies that have promise for slowing DKD progression in youth with T2D include metformin, renin-angiotensin-aldosterone system inhibitors, glucagon-like peptide-1 receptor agonists, sodium glucose co-transporter 2 inhibitors, thiazolidinediones, sulfonylureas, endothelin receptor agonists, and mineralocorticoid antagonists. Novel agents are also in development to act synergistically on the kidneys with the aforementioned medications. We comprehensively review the available pharmacologic strategies for DKD in youth-onset T2D including mechanisms of action, potential adverse effects, and kidney-specific effects, with an emphasis on published pediatric and adult trials.

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Expert Opinion: Large clinical trials evaluating pharmacologic interventions targeting treatment of DKD in youth-onset T2D are strongly needed.

Keywords

Diabetic kidney disease; pediatrics; therapies; treatments; youth-onset type 2 diabetes

1. Introduction

Global rates of type 2 diabetes (T2D) are persistently rising and remain closely tied to rising rates of metabolic syndrome features including insulin resistance and associated glucose intolerance, central obesity, hyperlipidemia, and hypertension [1]. In comparison to adult-onset T2D, youth-onset T2D exhibits a more severe and progressive phenotype with increased β-cell destruction and insulin resistance [2, 3], which not only results in a decreased life expectancy but also a more significant risk for micro- and macro-vascular complications. Diabetic kidney disease (DKD) develops from a complex interplay of pathophysiologic factors in T2D including upregulation of intracellular and metabolic pathways, increased production of reactive oxygen species, inflammatory and epigenetic changes, dysregulated autophagy, and end-organ hypoxia which culminate in increased intraglomerular pressure and hyperfiltration in the early phases of DKD and subsequently lead to disease progression [4]. DKD is strongly associated with cardiovascular disease and both conditions serve as the leading causes for morbidity and mortality in T2D [5], with metabolic, morphologic, and molecular features occurring early in the disease course, long before laboratory evidence such as albuminuria or changes in glomerular filtration rate (GFR) are evident. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth Follow-Up Study (TODAY2), DKD exhibited a 15-year cumulative incidence of greater than 50% [5-9] in youth-onset T2D, direct evidence of a significantly underrecognized and undertreated complication. Yet, recommendations for the evaluation and treatment of early DKD in youth with T2D are limited by a paucity of dedicated pediatric trials (Table 1) and are formulated based on data that are inferred from studies completed in adults. In this review, we comprehensively appraise the currently available pharmacologic management strategies for DKD in youth and adult-onset T2D, with an emphasis on therapies that are approved by the United States Food and Drug Administration (FDA) for use in youth with T2D, as well as therapies that are currently being used off label or are in development.

2. Therapeutic Agents for Management of DKD in T2D

2.1 Metformin

Metformin, a dimethylbiguanide, is an antihyperglycemic agent first synthesized in the 1950's that remains a first line therapy for T2D in nearly all adult and pediatric guidelines.

2.1.A Mechanism and Clinical Effects—Metformin exerts its insulin sensitizing and blood glucose lowering effects primarily through inhibition of gluconeogenesis and opposition of glucagon-mediated signaling in the liver [20]. It inhibits the liver mitochondrial respiratory chain and enhances insulin sensitivity through modulation of lipid metabolism, as well as reduction of gluconeogenic enzymes [21] and improvements

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in skeletal muscle glucose uptake [20]. Metformin may also exert renoprotective effects through a variety of mechanisms including attenuation of inflammation and oxidative stress [22, 23], apoptosis [24], tubular injury [25], and fibrosis [26], and inducing autophagy [27], lipid availability [28], glucagon-like peptide 1 (GLP-1) receptor activation [29], and urinary sodium excretion [30]. The positive effects of metformin are complex and require further study, particularly in individuals across the age spectrum with T2D.

2.1.B Adverse Effects—Metformin is frequently associated with gastrointestinal side effects including abdominal discomfort, nausea, vomiting, and diarrhea, particularly with the use of immediate-release formulations [31]. Approximately 50% of metformin remains unabsorbed in the gut and accumulates in the distal small intestine mucosa, with concentrations that exceed 30 to 300 times that achieved in the plasma [31], thereby contributing to the high rates of side effects. Proposed mechanisms for the gastrointestinal side effects of metformin include delays in intestinal glucose absorption [32], effects on bile acid metabolism or the intestinal microbiome [33, 34], augmentation of enterocyte lactate production [32], or enhancements of GLP-1 secretion [35]. Side effects are attenuated through a combination of a month-long gradual titration to goal dose and the use of extended-release formulations.

Metformin use in the setting of chronic conditions such as kidney or liver disease must also be considered. In conditions that disrupt the processes of lactate production or clearance, metformin is associated with increased plasma concentrations of lactate secondary to inhibition of liver mitochondrial respiration [36], a process called “metformin-associated lactic acidosis (MALA)”. MALA carries an almost 50% mortality rate and thus metformin has been classically contraindicated in the setting of moderate to severe kidney impairment. However, there is a growing movement to liberalize the use of metformin in individuals with kidney disease, as the incidence of MALA remains exceedingly low (i.e., <10 cases per 100,000 patient-years) and the known benefits of treatment with metformin in people with T2D are high [37].

2.1.C Metformin and DKD—As the most frequently prescribed therapy in T2D, metformin has been shown to have positive effects on glycemia, cardiovascular disease risk, and possibly mortality risk in people with T2D, although this finding has not been extensively corroborated. In the “United Kingdom Prospective Diabetes Study (UKPDS)”, overweight people with new onset T2D were randomized to treatment with metformin vs. conventional therapy with diet alone and these individuals demonstrated significant risk reductions in any diabetes-related endpoint, diabetes-related death, and all-cause mortality as a result of metformin therapy (all $p<0.05$) [38]. Notably, metformin’s therapeutic effects persisted 10 years post study completion despite differences in hemoglobin A1c being lost between groups after the first year [39]. While these positive effects may be attributed to a short period of glycemic lowering due to metformin use, other potential physiologic effects warrant further investigation including changes in insulin sensitivity and/or alterations of kidney physiology. No differences in microvascular disease relative risk (a composite score of vitreous hemorrhage, retinal photocoagulation, or kidney failure) were seen between the metformin and conventional therapy groups after 10 years [39].

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Despite widespread use of metformin in T2D, large-scale clinical trials with DKD-specific primary endpoints are lacking and current data are mixed. In a trial of 51 normotensive adults less than 65 years of age with T2D and nephropathy who received 12-weeks of either the sulfonylurea glibenclamide or metformin, metformin was associated with a decrease in urine albumin excretion (mean reduction of 24.2 mg/day, p=0.008) [40]. In contrast, the "Hyperinsulinemia: The Outcome of its Metabolic Effects (HOME)" study found no significant difference in urine albumin excretion with metformin therapy vs. placebo with insulin; however, endothelial function was significantly improved and this effect was unrelated to changes in glycemia or generalized inflammation [41]. Additionally, in the "A Diabetes Outcomes Prevention Trial (ADOPT)", 4,351 recently diagnosed, drug naïve adults with T2D were randomized to treatment with metformin, thiazolidinedione rosiglitazone, or sulfonylurea glyburide for 4 years and urine albumin to creatinine ratio was noted to slowly rise over the course of the study with metformin therapy. Relative to treatment with either rosiglitazone or glyburide, metformin was associated with the highest change in urine albumin excretion from baseline over time (+20.9% [95% CI: 13.3-28.9%] with metformin, +2.1% [95% CI: −4.2-8.8%] with rosiglitazone, and +6.1% [95% CI: −1.2-14.0%] with glyburide, p<0.001 for metformin vs. rosiglitazone). Changes in estimated GFR via the Modification of Diet in Renal Disease (MDRD) Study equation from baseline were +1.4% [95% CI: 0.0-2.9%] with metformin, +5.1% [95% CI: 3.6-6.7%] for rosiglitazone, and −0.4% [95% CI: −2.0-1.2%] for glyburide (p=0.0005 for metformin vs. rosiglitazone). There were no differences between groups in incident microalbuminuria, hypertension, or GFR <60 mL/min/1.73m^2 [42]. It is evident that our knowledge of metformin's effects on kidney function in adults with T2D is currently inconclusive and this necessitates future study with DKD-specific primary endpoints.

Furthermore, studies evaluating treatment specific DKD outcomes in youth with T2D are even more limited. In the "Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)" study, incidence rates of microalbuminuria increased across all treatment groups (metformin vs. metformin plus lifestyle vs. metformin plus rosiglitazone) over time (overall incidence rate of 6.3% at baseline to 16.6% at study completion) [43]. Interestingly, hemoglobin A1c as a time-dependent covariate was the only factor which associated with microalbuminuria risk (p=0.03), with a 17% increased risk of microalbuminuria for every 1% increase in hemoglobin A1c [43]. Further studies of kidney specific outcomes in youth-onset T2D are also necessary.

2.2 Renin-angiotensin-aldosterone system (RAAS) inhibitors

There are two primary categories of RAAS inhibitors, angiotensin converting enzyme inhibitors (ACE-is) and angiotensin receptor blockers (ARBs). ACE-is and ARBs are largely equivalent in their clinical effects and efficacy. Both classes of medications have been studied comprehensively in DKD and represent a mainstay treatment for those with active DKD. Ample evidence in pediatric and adult DKD exists demonstrating their utility and limitations [44, 45]. Extensive reviews outlining their general mechanisms and clinical effects have been published previously [46].

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2.2.A Clinical Evidence of ACE-is/ARBs in DKD—Evidence for efficacy of ACE-is/ARBs is strongest for individuals with macroalbuminuria related to DKD [47]. Treatment with ACE-is/ARBs reduces progression of DKD in both T2D and T1D [48, 49]. For persons with DKD without macroalbuminuria, ACE-is/ARBs reduce worsening of albuminuria [44]. However, pre-emptive treatment with ACE-is/ARBs in the absence of albuminuria or DKD does not appear effective in reducing risk of developing DKD [50]. Both ACE-is and ARBs are teratogenic, so women of childbearing potential should be counseled accordingly, and contraception advised. Rare side effects of ACE-is include angioedema and cough. If individuals receiving treatment with an ACE-i present with a chronic dry cough or swelling while on therapy, they should be switched to an ARB which is not associated with this side effect. Given that ACE-is/ARBs are well tolerated and have demonstrated efficacy for improving cardiovascular and kidney outcomes across a wide spectrum of diseases, they should be a first consideration for young people with diabetes presenting with albuminuria and/or hypertension.

2.2.B Mechanisms and Intermediate Effects of ACE-is/ARBs—Glomerular hyperfiltration is a manifestation of intraglomerular hemodynamic dysfunction in individuals with diabetes, even without overt DKD. Studies suggest that hyperfiltration may be the result of inappropriate and chronic activation of RAAS, and a potential mediator of albuminuria and DKD development [51]. Treatment with ACE-is/ARBs both targets direct hormonal effects and attenuates glomerular hyperfiltration through relaxation of the efferent arteriole [46]. In simplest terms, reduced intraglomerular pressure secondary to treatment with ACE-is/ARBs improves glomerular size selectivity and reduces filtered albumin. While long term implications of improving or preventing worsening albuminuria remains under investigation, at this point it remains a valid indication for use of ACE-is/ARBs in young persons with diabetes.

2.3. Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

GLP-1RAs are a burgeoning area of study for the treatment of T2D in youth and are currently available in once daily injections, once weekly injections, and once daily pills. At present, there are a total of ten GLP-1RAs that are approved for the treatment of T2D in adults including albiglutide (once weekly injection, “TANZEUM”, GlaxoSmithKline), beinaglutide (three times daily injection, Benemae Pharmaceuticals), dulaglutide (once weekly injection, “TRULICITY”, Eli Lilly), exenatide (twice daily injections, “BYETTA”; and once-weekly injections, “BYDUREON”, both Amylin & Eli Lilly), liraglutide (once daily injection, “VICTOZA”, Novo Nordisk), lixisenatide (once daily injection, “LIXUMIA”, Sanofi), PEG-ioxenatide (once weekly injection, “FU LAIMEI”, Hansoh Pharmaceuticals), and semaglutide (once weekly injection, “OZEMPIC”; and once daily oral pill, “RYBELSUS”, both Novo Nordisk). To date, the FDA has approved only two GLP-1RAs for the treatment of T2D in youth aged 10 to 17 years including liraglutide 1.8 mg/day and exenatide extended-release injections.

2.3.A Mechanism and Clinical Effects—Glucagon-like peptide-1 (GLP-1) is a peptide hormone that is released from the L-cells of the distal ileum following an oral glucose load that subsequently causes post-prandial insulin secretion by the incretin effect

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[52]. GLP-1 receptor agonists (RAs) act at the level of the 7-transmembrane G-protein coupled GLP-1 receptor to activate adenylate cyclase and stimulate a cascade resulting in the post-prandial release of insulin as well as numerous additional downstream effects including increased β-cell proliferation, somatostatin release, natriuresis and diuresis, glucose uptake in the muscle and adipose tissue, skeletal muscle perfusion, lipolysis, and satiety, and decreased β-cell apoptosis, glucagon secretion, gastric emptying, gastrointestinal motility, gluconeogenesis, steatosis, and generalized inflammation [53]. Post-prandial insulin secretion due to the incretin effect is significantly attenuated in T2D [54] while the glucagonostatic effects of GLP-1 remain largely intact [55]. Postulated mechanisms for the modulation of DKD risk in T2D include improvements in insulin resistance, hyperglycemia, blood pressure, obesity, dyslipidemia, inflammation, and potentially renal hypoxia [56]. Notably, the 2022 American Diabetes Association Standards of Care for Children and Adolescents with Diabetes also recommends consideration of GLP-1RAs (i.e., high dose liraglutide) as adjunctive therapy to lifestyle modification for weight loss in adolescents with T2D and obesity [57].

2.3.B Adverse Effects—The most commonly reported adverse effects of GLP-1RAs are gastrointestinal in nature and include nausea, vomiting, and diarrhea [58]. Rarely, hemodynamic side effects due to excessive fluid losses and dehydration may result in pre-renal acute kidney injury, particularly in the setting of treatment with exenatide [59]. Kidney biopsies in adults with T2D and concern for exenatide-associated kidney failure and have identified ischemic glomeruli along with tubular atrophy, moderate to severe interstitial fibrosis, and early diabetic nephropathy [59]. In combination with insulin sensitizing agents such as metformin and/or thiazolidinediones, one unique benefit of GLP-1RAs is a lack of reported hypoglycemia [60, 61]. When combined with a sulfonylurea and/or insulin, use of GLP-1RAs may necessitate a decrease in dosage of either the concomitant sulfonylurea or insulin due to an increased risk of hypoglycemia [60]. Other common side effects include headaches, injection site reactions, particularly with extended-release formulations, and/or nasopharyngitis; however, these side effects are typically mild, often do not result in therapy discontinuation, and improve over time.

2.3.C Effects on the Kidney—GLP-1RAs undergo renal clearance; thus, kidney effects of GLP-1RAs remain difficult to evaluate. Preliminary results are promising; however, studies are largely limited to soft kidney function outcomes including changes in estimated GFR (eGFR) or urinary albumin to creatinine ratio [62-64], new onset macroalbuminuria [65, 66], time to new onset macroalbuminuria [67], or persistent macroalbuminuria [68] in lieu of gold standard measures. Additionally, most kidney outcomes data in GLP-1RA studies comes from large, placebo-controlled safety and cardiovascular outcome trials in adults with T2D and pre-existing cardiovascular disease or risk, a population that only allows for pediatric inferences.

In the “Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with T2D (SUSTAIN-6)”, 3,297 individuals with T2D and cardiovascular disease or risk were randomized to semaglutide 0.5 mg or 1 mg once weekly vs. placebo and semaglutide was associated with improvement in glycemia, body weight, and risk for

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new or worsening nephropathy (HR=0.64 [95% CI: 0.46-0.88], p=0.005) after 2 years of therapy [68]. Additionally, the "Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)" trial also showed a significant difference in HbA1c, weight, and worsening nephropathy (−22%, HR=0.74 [95% CI: 0.60-0.91]) in participants with T2D on liraglutide vs. placebo for a median of 3.8 years [69]. However, both the SUSTAIN-6 and LEADER trials utilized a pre-specified composite kidney outcome [68, 69] rather than direct assessments of kidney function. The "Exenatide Study of Cardiovascular Event Lowering (EXSCEL)" trial also used a kidney function composite score and found significant improvement in kidney outcomes with extended release exenatide when compared to placebo in adults with T2D (HR 0.85 [95% CI: 0.73-0.98, p=0.027). Dedicated kidney outcomes trials, particularly in individuals with known kidney disease, are limited but support the positive effects of GLP-1RAs seen in safety and efficacy trials. In the "Study Comparing Dulaglutide with Insulin Glargine on Glycemic Control in Participants with Type 2 Diabetes and Moderate or Severe Chronic Kidney Disease (AWARD-7)", dulaglutide reduced albuminuria by 39% (10-69%) and attenuated eGFR decline vs. glargine alone in adults with T2D and moderate to severe chronic kidney disease [63].

GLP-1RA therapy remains a promising avenue for the prevention and treatment of DKD; however, gold-standard assessments of kidney function are lacking and have exhibited mixed results to date. In a study of 10 overweight men, an infusion of exenatide was associated with an acute increase in measured GFR by inulin clearance, renal plasma flow by *p*-aminohippurate clearance, and estimated glomerular pressure, as well as decreased renal vascular resistance [70]. In a cohort of 52 overweight men and post-menopausal women with T2D, an exenatide infusion was not associated with changes in intraglomerular hemodynamic function but it did increase proximal tubule sodium excretion [71]. No studies evaluating the effects of GLP-1RAs in youth with T2D using gold standard methods have yet been published.

GLP-1RA treatment effects on kidney oxygen bioavailability must also be considered. Diabetes-induced kidney microvascular injury has been shown to result in excessive energy expenditure due to hyperfiltration, hypoxia, inflammatory changes with deposition of excess extracellular matrix, and late stage fibrosis [72]. Treatment with GLP-1RAs in obese rat models has resulted in restoration of kidney energy homeostasis, as well as a reduction in reactive oxygen species, inflammation, and fatty kidney [73]. Further evaluation of the effects of GLP-1RAs on intraglomerular hemodynamic function and kidney oxygen availability in youth and adults with T2D is necessary to help attenuate DKD, particularly in the early stages of disease.

2.3.D Combination GLP-1 and glucagon-dependent insulinotropic polypeptide (GIP) RAs—Dual GLP-1/GIP RAs further expand on the armamentarium of potential targetable receptors within the body for the treatment of T2D and integrate the downstream actions of incretin hormones GLP-1 and GIP to improve glycemia and potentially modify kidney function. In the Study of Tirzepatide (LY3298176) Once a Week Versus Insulin Glargine Once a Day in Participants with Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4), a randomized, open-label, parallel group, multi-site

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Phase 3 study in adults with T2D, a BMI ≥25 kg/m^2, and either high risk or known CVD, a median duration of 85 weeks of Tirzepatide was associated with a slowed rate of eGFR decline (−1.4 [74] mL/min/1.73 m^2 vs. −3.6 mL/min/1.73 m^2) and a reduced UACR versus treatment with the insulin glargine (36.9% [74] vs. −6.8% [95 CI: −14.1 to 1.1%] [74]. While direct comparisons between GLP-1RAs and dual GLP-1/GIP RAs have yet to be done to evaluate primary kidney outcomes, dual GLP-1/GIP RAs remain a promising avenue for future treatment of DKD associated with T2D.

2.4 Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2is)

SGLT2is have transformed cardiovascular and kidney outcomes in adults with T2D [75, 76]. SGLT2is that have achieved FDA approval for the treatment of T2D in adults include canagliflozin (“INVOKANA”, Janssen), dapagliflozin (“FARXIGA”, AstraZeneca), and empagliflozin (“JARDIANCE”, Lilly/Boehringer Ingelheim Pharmaceuticals). There appears to be a class-effect in terms of efficacy and safety of SGLT2is [77, 78]; yet currently no SGLT2is are approved by the FDA for use in persons younger than 18 years of age.

2.4.A Mechanism and Clinical Effects—SGLT2 is almost exclusively expressed in the proximal tubule of the kidney. Glucose is freely filtered at the glomerulus and 90% of filtered glucose is reabsorbed in the apical membrane of the proximal tubule by SGLT2 [79, 80]. The clinical effects and tolerability of SGLT2is were demonstrated in families with autosomal recessive familial glycosuria related to mutations in SGLT2 [81]. SGLT2is have only modest efficacy for lowering hemoglobin A1c. Accordingly, the positive benefit of SGLT2 inhibition likely derives from mechanisms outside of tighter glycemic control [82].

Treatment with SGLT2is induces favorable metabolic effects. At the tissue level, treatment with SGLT2is results in diminished adiposity and reduced intracellular lipid accumulation [83]. Shifts in cellular metabolism observed with inhibition of SGLT2 results from a combination of macro-effects (i.e., negative total-body glucose flux) and direct cellular effects in cells that express SGLT2 [83]. SGLT2is shift metabolism away from glucose oxidation and towards ketone and fatty acid oxidation, increase the efficiency of oxygen utilization, and reduce free radical generation [84-86].

While SGLT2i is almost exclusively expressed in the proximal tubule, cellular effects of SGLT2i are more widespread in the kidney. In a recent study by *Schaub et al.*, metabolomic profiling performed on human kidney biopsy tubular cells in youth with T2D and healthy controls showed that T2D was associated with perturbations in mechanistic target of rapamycin complex 1 (mTORC1) signaling and altered metabolomics in kidney tubular cells from all segments [87]. Individuals with T2D treated with SGLT2is demonstrated metabolic profiles that were more similar to healthy controls. Interestingly, SGLT2i use was strongly associated with reduction in mTORC1 signaling in both the proximal and distal tubular cells. Further research is needed to understand how SGLT2is induce metabolic shifts in tubular cells that do and do not express SGLT2.

SGLT2i may also stimulate erythropoietin production in the kidney [88], thereby improving anemia, a well-established risk factor for progression of CKD and cardiovascular disease [89, 90]. Erythrocytosis and increases in red blood cell counts have been noted in studies of

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SGLT2is [91], but the exact cellular mechanisms remain under debate. SGLT2is may exert either direct or indirect effects on hypoxia-inducible factors (HIF), HIF-1α and HIF-2α [92].

The hemodynamic and natriuretic effects of SGLT2 inhibition are also postulated as protective mechanisms. Treatment with SGLT2is results in decreases in blood pressure, weight, and N-terminal of prohormone of brain natriuretic peptide (NT-proBNP) [93, 94]. Kidney-glomerular hyperfiltration is common in people with diabetes and is postulated to contribute to DKD [95]. SGLT2is induce a drop in the GFR, primarily by reactivating tubuloglomerular feedback mechanism [95]. Participants randomized to SGLT2is in all large clinical trials experienced an acute drop in GFR [96]. Despite this, it is well documented that SGLT2is slow the long-term decline in eGFR associated with DKD [97]. Relatedly, SGLT2 inhibition reduces proteinuria and protects against incident or worsening albuminuria.

In sum, the potential of SGLT2is to greatly improve long-term kidney outcomes further supports their use in youth with diabetes, a population with a significant lifetime risk of developing progressive kidney disease.

2.4.B Adverse Effects—Overall, extensive research demonstrates SGLT2is have an outstanding safety profile. Nonetheless, there are several considerations with their use in pediatric populations. Initial trials in populations with diabetes have raised the concern that SGLT2i-induced glucosuria increases the risk for urinary tract infections (UTIs). However, subsequent analyses have not supported an increased risk of UTIs with SGLT2i use [98, 99]. The incidence of mycotic genitourinary infections is increased with SGLT2 inhibition, so patients must be monitored and treated accordingly [100].

Another important safety consideration with SGLT2is is the risk for diabetic ketoacidosis. Euglycemic ketosis is a hallmark of SGLT2 inhibition, and in low concentrations is not necessarily harmful [101]. However, development of ketoacidosis, a dangerous and potentially life-threatening complication if severe, was found to occur in 0-1% of participants randomized to treatment with SGLT2is in major clinical trials [102, 103]. The risk for ketoacidosis is highest in persons with T1D and the cumulative incidence of ketoacidosis in persons with T1D treated with SGLT2is in major clinical trials was 3-6%, leading the FDA to not extend approval of SGLT2is to T1D [104]. Several risk factors in persons with T1D increase the relative risk of developing ketoacidosis with SGLT2is, including relative insulin deficiency, dehydration, and/or illness [102].

2.4.C Landmark Trials in Adults—Multiple large, randomized controlled trials have demonstrated the efficacy of SGLT2is to improve kidney outcomes in adults with T2D and/or DKD. The “Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG)” trial enrolled 7,020 participants greater than 18 years of age with T2D and eGFR >30mL/min/1.73m^2 to assess the cardiovascular safety of empagliflozin [105]. A secondary analysis of trial data noted that individuals randomized to treatment with empagliflozin had a 39% reduction in their risk for worsening nephropathy (incident macroalbuminuria, doubling of serum creatinine, or need for dialysis/transplant) [106]. The “Canagliflozin Cardiovascular Assessment Study (CANVAS)” and “Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical

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Evaluation (CREDENCE)" trials demonstrated similar efficacy of canagliflozin, and enrolled adults with T2D and an eGFR >30mL/min/1.73m^2 [107, 108]. Of note, CREDENCE excluded persons with an eGFR >90mL/min/1.73m^2. Both trials demonstrated a 30-40% reduction in risk for most adverse kidney outcomes including worsening albuminuria, greater than 40% decline in eGFR, and dialysis dependence. "Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD)" was the only trial not to exclusively enroll participants with diabetic nephropathy [109]. Nonetheless, this trial demonstrated the efficacy of dapagliflozin to improve kidney outcomes for those with CKD with or without T2D. The "Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY)" shared a similar study design, and nearly identical results, to DAPA-CKD [110]. Taken together, these trials demonstrate the class-effect of SGLT2is for treatment of DKD and non-diabetic CKD.

2.4.D Studies in Pediatrics—Evidence on the tolerability and efficacy of SGLT2is in pediatric populations is limited. However, the positive efficacy and safety results demonstrated in adults has led to increasing off-label use of SGLT2is in pediatrics and this will lead to new opportunities for research. A recent study of 9 young individuals with heart failure (mean age 14.2 years) receiving dapagliflozin did not observe any adverse effects, including UTIs, ketoacidosis, fracture, or hypovolemia after a mean treatment duration of 30 days with SGLT2is [17].

There has also been several mechanistic studies of SGLT2is in youth with diabetes. *Laffel et. al* performed a pharmacokinetic study of empagliflozin by administering a single dose to youth aged 10-17 years with T2D [18]. There was a dose-dependent increase in urinary glucose excretion. Importantly, the pharmacokinetics were similar to those observed in studies of adults. A secondary analysis revealed that a single dose of empagliflozin resulted in an increase in the fractional excretion of sodium and a modest decrease in eGFR (−5.5 mL/min/1.73m^2) [19]. The drop in eGFR was most significant in those with hyperfiltration at baseline.

There is growing interest to expand the benefits of SGLT2is to young persons with T1D [111]. The "Adolescent Type 1 Diabetes Treatment with SGLT2i for Hyperglycemia and Hyperfiltration (ATTEMPT)" trial (Clinicaltrials.gov identifier: NCT04333823) is actively recruiting to study the efficacy of dapagliflozin versus placebo in modulating glomerular hyperfiltration and metabolic parameters in adolescents with T1D. These results will add a pediatric perspective to recent studies of SGLT2is in adults with T1D [16, 112]. SGLT2 inhibition may demonstrate future efficacy and feasibility in youth with T1D, albeit with an informed approach and implemented strategies to reduce the risk for ketoacidosis, such as continuous ketone monitoring.

3. Other drugs

3.1 Thiazolidinediones

Thiazolidinediones (TZDs) contribute to glycemic control by activating the peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ activation is linked to improvements in peripheral insulin sensitivity and β-cell function [113, 114]. TZDs are not

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approved for youth with T2D but are often used off-label due to their beneficial effects on insulin sensitivity and glycemic control. Indeed, in the TODAY study, glycemic failure rates decreased by 13% in adolescents with T2D when adding rosiglitazone, a TZD, to metformin compared to metformin alone [10]. However, rates of albuminuria did not differ among the metformin plus rosiglitazone, metformin plus lifestyle, or metformin alone groups in TODAY.

Although TZD therapy has been associated with adverse events including fractures, fluid retention, and heart failure in adults [115], these side effects were not observed in the TODAY study. In adults with T1D and T2D, the TZD pioglitazone has been used in combination with SGLT2is, as the diuretic properties of SGLT2is are thought to mitigate the fluid retention conferred by the TZD. Additionally, murine models suggest that combination therapy of an ACEi plus rosiglitazone provides synergy in attenuating diabetic kidney injury that is not simply additive of either monotherapy alone [116].

3.2 Sulfonylureas

Sulfonylureas are among the oldest class of hypoglycemic agents, and work by stimulating insulin secretion by closing ATP-sensitive K^+ channels in the pancreatic β-cell plasma membrane. There are few studies on sulfonylureas in youth with T2D. One study showed that the sulfonylurea glimepiride reduced HbA1c similarly to metformin in youth with T2D, but larger weight gain and a higher rate of hypoglycemia were documented in the glimepiride group [117]. To our knowledge, there are no studies in youth with T2D that have evaluated the effects on diabetic kidney disease. Accordingly, sulfonylureas are rarely used in adolescents with T2D.

3.3 Endothelin receptor agonists

Endothelin receptor antagonists (ERA) primarily target the endothelin A (ET_A) receptor, which have demonstrated kidney protective effects. The ERA atrasentan attenuated DKD progression in adults with T2D in the “Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR)” trial [118]. Unlike SGLT2 inhibitors, ERAs increase sodium and fluid retention, leading to increased body weight and hemodilution (decreased hematocrit and hemoglobin), as well as edema and a higher risk of developing heart failure [119, 120]. This has limited the development and widespread use of agents in this class, especially in people who are predisposed to volume overload, including individuals with DKD. Indeed, a large randomized controlled trial in people with T2D and DKD using a relatively non-selective ERA avosentan was terminated early because of an increased frequency of heart failure [119]. In addition, despite the precautionary approach taken in the SONAR trial with atrasentan, including the use of diuretics and exclusion of people with heart failure or high BNP concentrations, there was a higher rate (3.5% versus 2.6%) of heart failure hospitalizations with atrasentan [118]. There are no ERA trial data in young persons with T2D. Although ERA holds promise as a therapy for T2D and DKD, it is unclear whether benefits would outweigh risks, and it is likely best used in combination with a natriuretic or diuretic agent.

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3.4 Mineralocorticoid antagonists

T2D has been linked to inappropriate mineralocorticoid receptor (MR) activation with resultant inflammation and fibrosis [121]. Indeed, murine MR knockout models document protection against kidney inflammation and fibrosis [122]. In the “Chronic Renal Insufficiency Cohort (CRIC)”, higher serum aldosterone concentrations independently predicted greater risk of chronic kidney disease progression in adults with and without T2D [123]. These data provide mechanistic support for mineralocorticoid antagonism in mitigating CKD progression. In the “FInerenone 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)” clinical trials, finerenone, a nonsteroidal MR antagonist (MRA), attenuated risk of DKD progression and kidney failure in adults with T2D and DKD [124]. Albuminuria lowering was also observed with esaxerenone, another nonsteroidal MRA, in Japanese people with T2D. In these trials, tolerability of MRA was reassuring, but hyperkalemia was found to be more common compared to placebo. Thus, combination with a potassium lowering agent such as an SGLT2i holds promise and warrants further study. There are no data yet in young persons with T2D, but it is plausible that these agents will be used off-label in combination with SGLT2is in individuals with DKD not responsive to monotherapy.

3.5 Novel agents

Other therapeutic interventions that may hold promise to mitigate DKD risk in young persons with T2D include serine/threonine kinase, apoptosis signal–regulating kinase 1 (ASK1) inhibitors, and JAK-STAT inhibitors that attenuate inflammation, apoptosis, and fibrosis [125, 126]. Soluble guanylyl cyclase (sGC) activators have also been proposed to mitigate DKD as low cyclic guanosine monophosphate (cGMP) concentrations have been implicated in DKD progression [127]. However, a randomized, placebo-controlled trial in 156 adults with T2D, impaired GFR, and albuminuria ≥200 mg/g, failed to demonstrate attenuation of albuminuria following 12 weeks of praliciguat treatment [128]. Finally, interventions that improve renal substrate metabolism such as mitochondrial peptides and bioavailable-small molecule activators of AMPK and mTORC1 inhibitors offer promise as even small enhancements in fuel utilization may translate into large improvements in kidney function and ultimately clinical outcomes [90, 129-134].

4. Conclusion

DKD is common and occurs early in the course of youth-onset T2D. Therapeutic options to mitigate DKD risk in youth with T2D are currently limited to insulin, metformin, GLP-1RAs and RAASis. Other agents such as SGLT2is, MRAs and ERAs hold promise, but have limited data in youth with T2D and are considered off label. To address the scarce therapeutic options to prevent and treat DKD in youth with T2D, we need more dedicated pediatric trials.

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5. Expert Opinion

Current projections predict that 50-70% of people with youth-onset T2D will develop DKD during adolescence and young adulthood. Despite these grave projections, pharmacological interventions are scarce, which is ascribed to a paucity of trial data in youth-onset T2D (Figure 1). Accordingly, recommendations are formulated based on data extrapolated from trials performed in adults with T2D, which may not be effective in youth. Additionally, due to limited efficacy and safety data, several drugs available to adults with T2D are not approved for the treatment of youth with T2D. Indeed, the only medications for the treatment of youth with T2D approved by the United States Food and Drug Administration, the European Medicines Agency, and Health Canada are metformin and insulin, with the recent addition of a GLP-1-RA.

In addition to the constrained armamentarium of approved medications, we also contend that the management of DKD in youth-onset T2D is challenged by therapeutic inertia. The reluctance to prescribe these medications during adolescence may be ascribed to the unfamiliarity of pediatric providers with newer adjunctive medications to mitigate the risk of DKD, and concerns about poor medication adherence and safety. A misguided dependence on lifestyle modifications prior to starting pharmacotherapy, and primarily focusing on glycemic control, in lieu of starting kidney protective therapies early and in parallel with targeting glycemia, also contributes to a lack of therapeutic inertia. Additionally, the typical busy clinician may find it difficult to allocate sufficient time for DKD risk management in part due to their lack of training and in part due to unwillingness of the adolescent to accept the initiation of additional therapies. Finally, reluctance to follow existing guidelines may relate to the limited number of trials in youth with T2D and the inferential nature of the evidence from adult studies.

To address the limited therapeutic options to prevent and treat DKD in youth with T2D, we need more dedicated pediatric trials, and to address the therapeutic inertia, professional societies must work together to train clinicians and reach consensus on the guidelines to minimize conflicting recommendations.

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Article Highlights

- Diabetic kidney disease (DKD) and strongly associated cardiovascular disease are the leading causes for morbidity and mortality in youth-onset type 2 diabetes (T2D), with metabolic, morphologic, and molecular features occurring early in the disease course, long before laboratory evidence such as albuminuria or changes in glomerular filtration rate are evident.
- Therapeutic options to mitigate DKD risk in youth with T2D are currently limited to insulin, metformin, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and renin-angiotensin-aldosterone system inhibitors (RAASis).
- Other agents such as sodium-glucose co-transporter 2 inhibitors (SGLT2is), mineralocorticoid receptor antagonists (MRAs) and endothelin receptor antagonists (ERAs) hold promise but have limited data in youth with T2D and are considered off label.
- Limitations in approved medications for the treatment of DKD in youth-onset T2D have directly inhibited therapeutic inertia for clinicians which could possibly be addressed through coordination of professional societies to reach consensus on the guidelines and thereby minimize conflicting recommendations.
- Additionally, to address the limited therapeutic options to prevent and treat DKD in youth with T2D, we need more dedicated pediatric trials.

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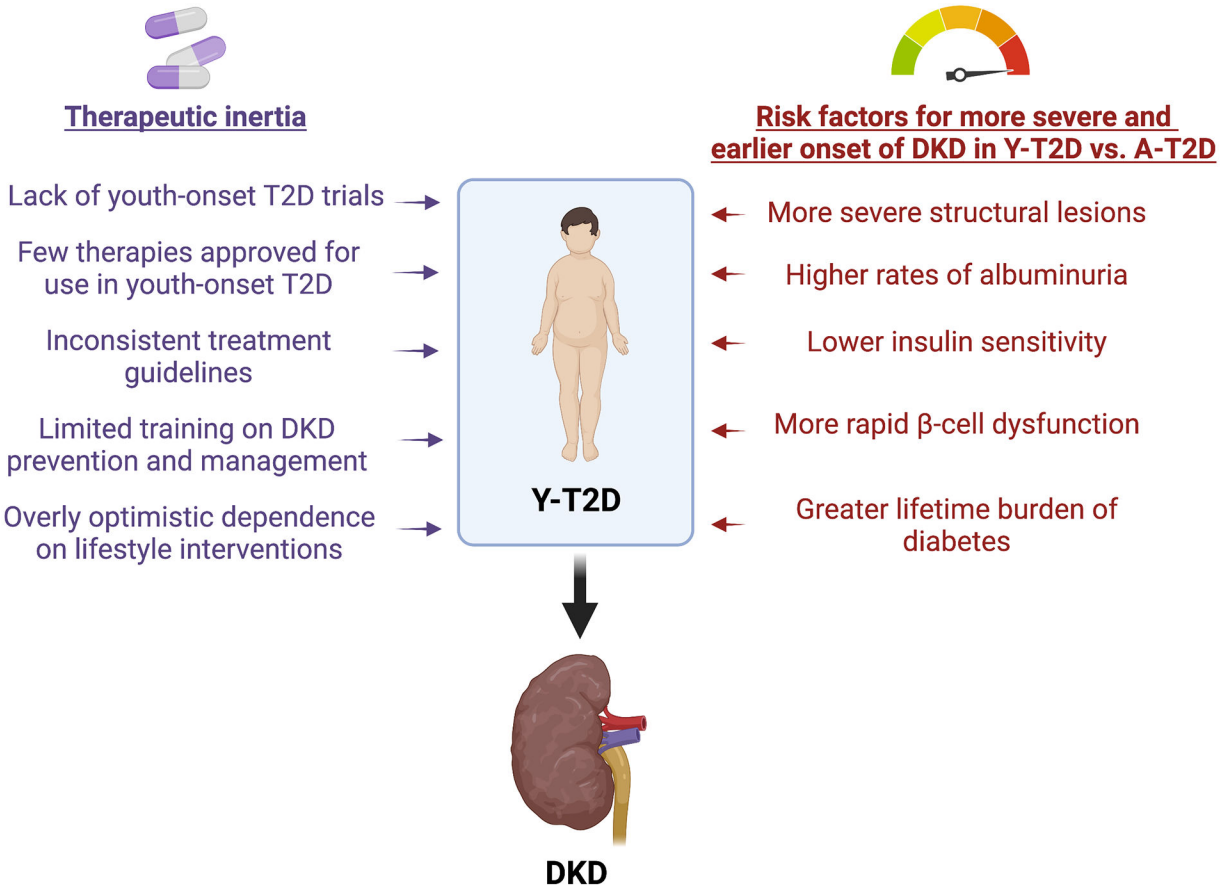

Figure 1. Challenges for the Timely Management of Diabetic Kidney Disease in Youth with Type 2 Diabetes

Key: A-T2D – adult-onset type 2 diabetes; DKD – diabetic kidney disease; T2D – type 2 diabetes; Y-T2D – youth-onset type 2 diabetes.

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Table 1.

Published Pediatric Clinical Trials in Youth

Medication class	Trial (Reference)	Agent	Number of participants	Condition	Phase	Design	Duration of treatment (weeks)	Outcomes
Metformin TZD	NCT00081328 [10]	Metformin Rosiglitazone	699	T2D	3	Randomized, parallel assignment, quadruple blinded	6 months	Loss of glycemic control
GLP-1RA	NCT01541215 [11]	Liraglutide	135	T2D	3	RCT, double blind	26 weeks and 26 weeks open extension	Changes in hemoglobin A1c, fasting blood glucose
	NCT00943501 NCT00993304 [12, 13]	Liraglutide	21	T2D	1	RCT, double blind	5 weeks and 3 weeks adverse event follow up	Pharmacokinetics
	NCT00254354 [14]	Exenatide	13	T2D	2	RCT, single blind	1 day x 3	Pharmacokinetics
SGLT2i	NCT01525238 [15]	Dapagliflozin	20	T2D	1	Randomized open label	2 days	Pharmacokinetics, safety, glycemia
	NCT01498185 [16]	Dapagliflozin	62	T1D	2	RCT, double blind	14 days	Glycemia, pharmacokinetics
	[17]	Dapagliflozin	9	Heart failure	N/A	Observational, retrospective analysis	30 days	Safety
	NCT02121483 [18, 19]	Empagliflozin	27	T2D	1	Randomized open label	3 days	Pharmacokinetics, fasting plasma glucose, urinary glucose excretion

Key: GLP-1RA – glucagon-like peptide-1 receptor agonist; RCT – randomized controlled trial; SGLT2i – sodium glucose co-transporter 2 inhibitors; T2D – type 2 diabetes; T1D – type 1 diabetes; T2D – type 2 diabetes; TZD – thiazolidinedione.

NOTE: All pediatric trials have been conducted pursuant to the *pediatric rule* which is a mandate by the Food and Drug Administration that states that all medications approved for use in adults must undergo safety and efficacy testing in pediatrics.