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# Youth versus Adult-Onset Type 2 Diabetic Kidney Disease: Insights into Currently Known Structural Differences and the Potential Underlying Mechanisms

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## Abstract

Type 2 diabetes (T2D) is a global health pandemic with significant humanitarian, economic, and societal implications, particularly for youth and young adults who are experiencing an exponential rise in incident disease. Youth-onset T2D has a more aggressive phenotype than adult-onset T2D and this translates to important differences in rates of progression of diabetic kidney disease (DKD). We hypothesize that youth-onset DKD due to T2D may exhibit morphometric, metabolic, and molecular characteristics that are distinct from adult-onset T2D and develop secondary to inherent differences in renal energy expenditure and substrate metabolism, resulting in a central metabolic imbalance. Kidney structural changes that are evident at the onset of puberty also serve to exacerbate the organ's baseline high rates of energy expenditure. Additionally, the physiologic state of insulin resistance seen during puberty increases the risk for kidney disease and is exacerbated by both concurrent diabetes and obesity. A metabolic mismatch in renal energetics may represent a novel target for pharmacologic intervention, both for prevention and treatment of DKD. Further investigation into the underlying molecular mechanisms resulting in DKD in youth-onset T2D using metabolomics and RNA sequencing of kidney tissue obtained

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at biopsy is necessary to expand our understanding of early DKD and potential targets for therapeutic intervention. Furthermore, large scale clinical trials evaluating the duration of kidney protective effects of pharmacologic interventions that target a metabolic mismatch in kidney energy expenditure are needed to help mitigate the risk of DKD in youth-onset T2D.

**Keywords**

Youth; type 2 diabetes; diabetic kidney disease; albuminuria

## Introduction:

Type 2 diabetes (T2D) is a growing health pandemic that is closely tied to multiple predisposing factors including central obesity, glucose intolerance, hypertension, and dyslipidemia, with a significant emphasis on insulin resistance (IR) as an underlying etiology for pathogenesis [1]. The National Health and Nutrition Examination Survey (NHANES), a large cross-sectional survey of youth and adults in the United States, has demonstrated persistent rising rates of obesity in youth aged 12-19 years (16.0% in 1999-2002 to 20.9% in 2015-2018, $p<0.001$) [2], in conjunction with rising rates in adults >20 years of age (33.7% in 2007-2008 to 39.6% in 2015-2016, $p<0.001$) [3]. In parallel with this drastic change in weight over time, adolescents in the United States are increasingly diagnosed with T2D and from 2002-2003 to 2014-2015 have demonstrated an annual increase of incident T2D of 4.8% [4]. Race/ethnicity is also a significant risk factor for T2D diagnosis as the incidence of T2D among non-Hispanic Whites (0.6%) is lower than Hispanics (3.1%), non-Hispanic Blacks (6.3%), Asian or Pacific Islanders (8.5%), and Native Americans (8.9%) ($p<0.05$ for all comparisons) [5].

Youth-onset T2D displays a more extreme phenotype when compared to adult-onset T2D, including significantly greater IR and subsequent β-cell destruction [6,7], thus resulting in higher rates of dysglycemia and an increased risk for micro- and macro-vascular complications including retinopathy, neuropathy, cardiovascular disease, and diabetic kidney disease (DKD) [7-11]. Differences in the age of presentation and ensuing characteristics of incident DKD are of particular interest as DKD remains a leading cause of morbidity and mortality in both youth and adults with T2D [12]. Indeed, based on data from the UK Prospective Diabetes Study (UKPDS) Cohort, adolescents who develop T2D will have a life expectancy that is 15 years shorter than adolescents who do not develop T2D [13]. We present a comprehensive review of the morphologic, metabolic, and molecular characteristics of DKD in both youth and adults with T2D, with a focus on further examination of potential underlying mechanisms for these age of onset-based differences (Figure 1).

## Epidemiology of DKD:

Diabetes affects 536.6 million adults (10.5%) aged 20-79 years globally [14] and represents a worldwide health burden that is only worsening in severity. Global diabetes-related costs were estimated to be 966 billion USD in 2021 and projections estimate an increase to 1,054 billion USD by 2045 [14]. DKD-associated complications contribute largely to the morbidity and mortality attributed to diabetes and the health-related costs. In 2019, there

were 2.62 million incident cases of chronic kidney disease secondary to diabetes worldwide with a prevalence of 134.58 million affected individuals who experienced 13.09 million disability-adjusted life years and 405.99 thousand deaths [15]. The societal impact of DKD continues to rise exponentially and presents an economic and humanistic burden to both youth and adults with diabetes, particularly as the average age of diabetes onset gradually declines. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth Follow-Up Study (TODAY2), the 15-year cumulative incidence of DKD was >50% [12,16-19], a sobering statistic as DKD represents a severe and chronic health issue that has the potential to adversely impact an individual's ability to live a productive and fulfilling life. Notably, DKD appears to differentially affect racial and ethnic minority populations and individuals from low to middle-income countries [15].

## Prevalence of DKD in T1D vs. T2D:

DKD is consistently more aggressive in youth-onset T2D than T1D [20-24]. However, whether this is secondary to an inherent difference in the progression of disease or other predisposing factors such as concurrent metabolic and/or vascular complications, a longer duration of diabetes, or a delay in diagnosis resulting in a prolonged period of hyperglycemia before diagnosis of T2D is unknown. The SEARCH for Diabetes in Youth study (SEARCH), a large, multi-center study involving youth diagnosed with either T1D (n=1,746) or T2D (n=272) before the age of 20 years and with a mean diabetes duration of 7.9 years, has demonstrated a significantly higher prevalence of DKD, as defined by either an estimated glomerular filtration rate ≤60 mL/min/1.73 $m^2$ or a first morning urine albumin-to-creatinine ratio ≥30 mg/g, in youth with T2D (20%) than youth with T1D (6%) [8]. While youth with T2D exhibited higher rates of other vascular complications including retinopathy, peripheral neuropathy, hypertension, and arterial stiffness in addition to DKD, when compared to youth with T1D, the odds of developing DKD in individuals with T2D were almost triple that seen in people with T1D, even after multivariable adjustment for age, sex, duration of time from diabetes diagnosis to onset of diabetes-related complication, clinical site, and body mass index [8]. These findings suggest an inherent difference in the underlying mechanisms of DKD between T2D and T1D and warrants further study to help tailor future treatment strategies to mitigate the progression of chronic kidney disease in T2D.

## High Risk Populations for the Development of DKD:

In large, multicenter studies throughout the United States, race/ethnicity plays a consistent role in the development and progression of DKD due to T2D [5,25]. Populations at particular risk for youth-onset T2D include racial and ethnic minority groups such as non-Hispanic Blacks, Hispanics, and Indigenous populations [5]. We have demonstrated that youth-onset T2D, as defined by absent/low T1D autoantibodies, absent maturity-onset diabetes of youth (MODY) loci, persistent insulin secretion, and lack of insulin dependence, continues to increase in prevalence in the Pima Indian population [26]. Contributing factors include rising rates of youth-onset obesity resulting in significantly elevated rates of IR as well as a higher incidence of intrauterine exposure to diabetes [27]. Gestational diabetes is often associated with a low birth weight which may result in a lower total number of nephrons [28]. Additionally, the hyperglycemic milieu may also negatively affect the development of nephrons in the fetus [29]. Each of these factors is likely associated with a younger average

age of diagnosis of T2D and thus an earlier age of DKD development. Furthermore, Pima Indians with confirmed youth-onset T2D demonstrated a higher incidence of morbidity with a 5-fold increased risk of kidney failure secondary to diabetes in people 25-54 years of age, as well as increased mortality when compared to individuals with adult-onset T2D [30]. While the Pima Indian population represents a particularly aggressive phenotype of youth-onset T2D, global rates of youth-onset T2D are rising [5] in parallel with consequent DKD.

## Hemodynamics and Energetics of DKD:

T2D-associated alterations in kidney hemodynamic function are closely tied to rising rates of DKD and occur secondary to a multitude of metabolic factors that result in inflammatory changes, fibrosis, and hypertrophy of the kidneys [31,32]. These factors include hyperglycemia, glomerular hyperperfusion, and hyperfiltration, complications that are further compounded by obesity, IR, and systemic hypertension [32,33].

In the kidneys, the complex physiologic combination of hematologic perfusion, filtration, and reabsorption results in a high metabolic rate and increased energy requirement [34]. Diabetes then leads to increased glucose reabsorption from the proximal tubule via the sodium-glucose cotransporter 2 and decreased distal solute delivery, thereby resulting in decreased tubuloglomerular feedback and dilation of the afferent arteriole with increased glomerular perfusion [32,35]. Elevated production of angiotensin II from the efferent arteriole also results in vasoconstriction and the combination of increased glomerular perfusion and efferent arteriolar vasoconstriction produces elevated intraglomerular pressure and glomerular hyperfiltration [32,35]. Each of these diabetes-related complications consumes a greater amount of $O_2$ and thereby increases the organ's baseline energy requirement [36]. When the kidneys are unable to compensate fully for the increased $O_2$ consumption secondary to the negative effects of diabetes, IR, and hyperglycemic cellular toxicity, a progressive state of hypoxia and ischemic kidney injury ensues [37,38]. IR is strongly correlated with hyperfiltration in youth with T2D in both the TODAY and Resistance to Insulin in Type 1 and Type 2 Diabetes (RESISTANT) cohorts [12,18], providing support for the more aggressive impact of T2D on DKD in youth than adults. Hyperfiltration predisposes the nephron to progressive damage by increasing glomerular pressure and leads to an increase in transcapillary convective flux of ultrafiltrate including the macromolecule albumin [39]. Further kidney function decline is accelerated in remnant nephrons that are compensating for a reduction in total nephron mass through hyperfiltration which leads to increased urine albumin excretion in youth with T2D [40,41].

In the UKPDS Cohort, a randomized, non-blinded study of 5,102 adults aged 25-65 years with new onset T2D which investigated intensive blood glucose and blood pressure management on the progression of vascular complications in T2D from 1977 to 1997, the prevalence of microalbuminuria rose from 7.3% at diabetes diagnosis to 17.3% at 5 years, 24.9% at 10 years, and 28.0% at 15 years post-diagnosis [42]. Microalbuminuria was found to transition to macroalbuminuria at a rate of 2.8% per year and then to kidney failure at a rate of 2.3% per year, with a loss of GFR occurring more rapidly in the setting of greater urine albumin excretion [42]. Notably, both the Restoring Insulin Secretion (RISE) consortium, a study evaluating approaches to maintaining insulin secretion in children and adults with

either prediabetes or newly-diagnosed T2D, and Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated a more aggressive phenotypic pattern of dysglycemia and loss of β-cell function in youth vs. adult-onset T2D [6,7]. This also translated to important differences in kidney physiology in youth and adult-onset T2D. Indeed, in the TODAY cohort of individuals with youth-onset T2D, the prevalence of elevations in urine albumin excretion increased from 6.3% at baseline to 16.6% at 3.9 years follow up and 18% at 5 years follow up [12,43]. Rates of progression of DKD in youth-onset T2D, as evidenced by a higher cumulative prevalence of microalbuminuria, were significantly higher than those seen in both adult-onset T2D and adult-onset T1D [44].

Of note, adults with T2D also experience a higher rate of regression of microalbuminuria to normalbuminuria than similar populations of youth with T2D. Araki *et al.* demonstrated a 51% rate of remission and a 54% rate of regression of elevated urine albumin excretion over a 6 year follow up period in a population of 216 Japanese adults with type 2 diabetes and microalbuminuria [45]. For comparison, Kyung Son *et al.* demonstrated a 37.5% rate of regression and a 20% rate of progression of microalbuminuria in a small pilot study of 18 adolescents with T2D [46]. In the adults, multiple important factors were associated with increased rates of remission of microalbuminuria including shorter duration of microalbuminuria, use of renin-angiotensin aldosterone system blockade, lower hemoglobin A1c, and lower systolic blood pressure [45], elements that all warrant future consideration for optimization in youth and adults with T2D to help mitigate DKD progression.

### Hemodynamics and Energetics of DKD in T1D vs. T2D:

DKD morphology is strongly impacted by both type of diabetes exposure and age of diabetes onset. T2D-associated pathological changes in kidney structure have demonstrated similarities to T1D, likely secondary to overlapping features including hyperglycemia exposure, IR, and duration of diabetes. Yet, the presentation of DKD in T2D displays a significantly higher degree of variability, potentially due to inherent differences in underlying diabetes pathology [47]. In the Oxford Regional Prospective Study, a natural history study following youth with youth-onset T1D starting within 3 months of diabetes diagnosis, the cumulative prevalence of microalbuminuria in youth-onset T1D was 50.7% (95% CI: 40.5-60.9%) after 9.8 ± 3.8 years of diabetes duration which was significantly higher than a similar cohort of individuals with adult-onset T1D (33.6% [95% CI: 27.2-40.9%]) after 18 years of follow-up and similar glycemic exposure [44]. SEARCH subsequently compared outcomes in youth with T1D vs. youth with T2D and individuals with youth-onset T2D demonstrated 3-fold odds of developing DKD vs. youth with youth-onset T1D [8]. In the TODAY study, a prospective and longitudinal study of >500 youth with T2D of <2 years duration evaluating the time to treatment failure with either metformin, metformin plus rosiglitazone, or metformin plus lifestyle modification, DKD was demonstrated to have a much more aggressive and early-onset phenotype in youth with T2D, with >50% of study participants developing elevated urine albumin excretion by 15 years post-T2D diagnosis [16]. Additionally, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, a large study of 10,251 adults aged 40-79 years with T2D and risk factors for cardiovascular disease, declines in estimated GFR were most rapid in both the youngest group of T2D-onset and the group with the longest duration of T2D [48]. In

individuals with similar diabetes duration, those diagnosed with T2D at <40 years of age demonstrated the fastest declines in estimated GFR of all groups [48]. These data suggest that T2D age at onset and diabetes duration help determine future risk for DKD in people with T2D.

### Structural lesions:

Pathological lesions in T2D-associated DKD are complex and warrant continued study with state-of-the-art kidney biopsy morphometrics to help expand our knowledge of their structural and functional associations. Known lesions in T2D include thickening of the glomerular basement membrane, mesangial expansion due to cellular enlargement and matrix secretion, podocyte loss with hypertrophy of the residual podocytes, nodular glomerulosclerosis, arterial hyalinosis, tubular epithelial atrophy, capillary rarefaction, and accumulation of inflammatory cells, atypical collagen, and activated myofibroblasts [49]. While kidney structural lesions in T2D share many common features with lesions seen in T1D, they are significantly more heterogeneous and are less directly associated with the current clinical picture of T2D [50]. The underlying causes of variation in kidney structural lesions in T2D have not been fully elucidated but may be secondary to inherent heterogeneity in diabetes pathology or the effects of comorbid metabolic conditions including systemic hypertension, atherosclerotic changes, and IR.

Arguably the most comprehensive evaluation of structural lesions associated with youth-onset DKD to date has come from studies involving kidney biopsies in the Pima Indian population with T2D. As with other race/ethnicities, the most common structural kidney injuries seen in Pima Indians with youth-onset T2D include glomerular basement membrane thickening and mesangial expansion, lesions that both show extensive associations with declining kidney function [51]. Pima Indians demonstrate a unique form of DKD with relatively homogenous structural lesions that are largely present before the onset of clinically evident disease [51-53]. These lesions are entirely attributable to T2D and represent a pattern that is not typically seen in other populations with T2D [54,55], making this population a prime target for DKD research. Indeed, Pima Indians with diabetes but normal GFR and no evidence of microalbuminuria have a greater glomerular basement membrane thickness and higher mesangial fraction volume than healthy donors without diabetes [52]. Youth-onset T2D in Pima Indians is consistently associated with a more severe profile of kidney structural lesions than adult-onset T2D, and even mild lesions occur in conjunction with a higher median urine albumin to creatinine ratio and hemoglobin A1c [51]. Indeed, in a cohort of Pima Indians including 52 individuals aged 39.1±9.9 years with youth-onset T2D and 109 people aged 51.4±10.2 years with adult-onset T2D of similar diabetes duration, mean urine albumin to creatinine ratio was higher in the youth-onset group (58 [56] vs. 27 [25$^{th}$-75$^{th}$ percentile 13-73], $p$=0.02) [56]. Additionally, a multitude of structural lesions including glomerular basement membrane width, mesangial fraction volume, glomerular volume, and percentage of glomerular sclerosis were inversely associated with age at diabetes onset [56]. Although Pima Indians represent a single racial and ethnic group, findings present in this population have been consistently demonstrated in other groups as well. Evidence strongly indicates that youth-onset T2D carries significantly greater risk of DKD than adult-onset T2D of a similar duration across populations [12,17,57].

## Metabolic and Molecular Mechanisms of DKD:

Underlying causes for the increased severity of structural lesions in DKD associated with youth-onset T2D have not been fully explained; however, metabolic dysregulation has been repeatedly shown to have a long-term effect on programming future risk for DKD development. The developmental phenomenon known as “metabolic programming” plays an important role in promoting future DKD risk [58], as pediatric disease factors including brief periods of poor glycemic control in childhood can significantly increase future risk for DKD despite a prolonged period of excellent glycemic control as an adult [59]. Furthermore, when combined with environmental factors, epigenetic mechanisms including DNA methylation, chromatin histone alterations, and non-coding RNAs mediate the persistent and long-term expression of DKD-related genes induced by historical glycemic exposure as a feature of metabolic memory [60]. These features contribute to the early onset and aggressive evolution of DKD due to youth-onset T2D and subsequently places these individuals at higher risk of severe disease than people who present later in life with adult-onset disease.

Studies leveraging important advanced techniques including metabolomics and kidney tissue-level RNA sequencing will help us further understand the metabolic and molecular determinants of structural kidney lesions in youth-onset T2D and their worsened phenotype in comparison to adult-onset T2D. In fact, kidney-specific epigenome maps and tissue-specific expression quantitative trait loci maps are in development to help isolate kidney disease genome-wide association study (GWAS) loci to better identify and treat young persons at particularly high risk for DKD progression [61,62]. Improvements in our understanding of the molecular and metabolic mechanisms underlying kidney disease may thus lead to the development of novel therapeutic strategies for mitigation of DKD in youth-onset T2D.

Additionally, gestational diabetes has been hypothesized to have an adverse effect on kidney morphogenesis in offspring. In mice models, maternal diabetes is associated with apoptosis of the glomerular podocytes, thus resulting in nephron collapse, dysmorphogenesis, and small kidneys in the offspring [63]. Hyperglycemia *in utero* is also associated with persistent upregulation of angiotensinogen and renin messenger RNA, particularly in the proximal tubule, as well as upregulation of nuclear factor-κB, a key transcription factor upregulated in the setting of stress and generalized inflammation [63]. Taken together, these factors place the kidneys of offspring of mothers with a history of gestational diabetes at higher risk for injury in the setting of a future diabetes diagnosis and warrant further mechanistic study.

### Puberty may amplify risk of kidney injury in youth with obesity and diabetes:

A nation-wide screening program in Denmark found that urinary albumin excretion increased transiently during puberty in all adolescents, evidence that puberty places stress on the kidneys [64]. However, the rise in albumin excretion was higher in those with elevated body mass index (BMI) and persisted after puberty in those with diabetes, arguing that puberty may induce irreversible kidney injury in youth with obesity and diabetes [64-66]. Puberty has also been linked with increased biomarkers of oxidative stress and excessive kidney growth by ultrasound in youth with T1D [67-70] A correlation between growth hormone, which is physiologically elevated in puberty, and albuminuria has been observed

in adolescents with T1D [71,72]. Additionally, epidemiological data from Finland found that the cumulative risk of kidney failure was highest in youth with peripubertal onset of T1D compared to diagnoses of T1D in early childhood or after puberty [66]. Finally, we and others have established that youth-onset T2D, which typically manifests during or shortly after puberty, carries significantly greater risk of DKD than T1D and adult-onset T2D of similar disease duration [12,17,73-76]. Taken together, these data suggest that developing T2D during puberty amplifies the risk of kidney injury, yet the mechanisms by which reproductive maturation amplifies kidney disease remain elusive.

Puberty is associated with significant changes in physiology that may predispose to kidney hypoxia in individuals with obesity and/or diabetes. The kidneys are highly metabolically active and susceptible to oxidative stress and hypoxia [77,78]. The high $O_2$ demand is necessary to maintain adequate adenosine triphosphate (ATP) production for the $Na^+/K^+$-ATPase, as 95% of the ATP produced in the kidney is through aerobic metabolism [77,79]. During puberty, the kidneys almost double in size (total kidney volume, TKV) [68], which likely increases the kidneys' already high energy expenditure. Higher concentrations of growth hormone and insulin-like growth factor 1 (IGF-1) during puberty are also thought to exacerbate the tubular workload by increasing glomerular filtration rate (GFR) and the filtered $Na^+$ load [80-83]. The elevated GFR may be further magnified in pubertal adolescents with obesity and diabetes [12,17,70,74,84]. Additionally, there is evidence that hyperinsulinism associated with obesity and T2D can stimulate $Na^+$ reabsorption [85-92]. Renin-angiotensin-aldosterone system (RAAS) and vasopressin, which are activated in diabetes, also stimulate $Na^+$ reabsorption [93-102]. In parallel, puberty is associated with IR that impairs substrate metabolism and ATP generation [89,103-105]. The pubertal increase in IR is attributed to rises in fat mass, sex steroids, and growth factors [103-107]. Although insulin sensitivity naturally decreases during puberty [89-91,108], the decline is accentuated by obesity and diabetes [91,92,108]. IR shifts renal fuel utilization towards free fatty acid (FFA) oxidation [109-111], which has a lower ATP yield per $O_2$ consumed compared to other substrates [112-114]. Further, IR results in impaired oxidative phosphorylation and ATP synthesis by inhibition of adenosine monophosphate kinase [115,116], increased mechanistic target of rapamycin complex 1 (mTORC1) activity, and mitochondrial dysfunction [117-119]. Accordingly, we posit a metabolic imbalance between renal energy expenditure and substrate metabolism during puberty in youth with obesity and/or diabetes. We postulate that the resultant metabolic mismatch predisposes to relative kidney hypoxia. In turn, the relative kidney hypoxia may result in loss of glomerular charge and size selectivity, with increased transglomerular transport of protein and kidney injury. Supporting these hypotheses, we recently published cross-sectional data showing that pubertal adolescents with T1D exhibit relative kidney hypoxia compared to controls without diabetes and that the degree of hypoxia was related to IR and BMI [70]. The role puberty plays in the pathogenesis of DKD in youth with T2D, who exhibit a greater degree of IR and hyperfiltration than those with T1D, is unknown.

## Therapeutic Strategies for Treatment of DKD:

**Pharmacology:** Employing medical strategies to prevent and treat DKD in youth-onset T2D presents a significant challenge to diabetes providers due to a combination of pharmacologic and social factors. Adolescents and young adults exhibit a characteristic

pattern of poor adherence to medication administration which is compounded by unique factors inherent to T2D including a high prevalence of diagnosis in racial/ethnic minority groups, a strong genetic influence and high prevalence of family history of diabetes, and low socioeconomic status [120]. Additionally, youth with T2D exhibit a particularly suboptimal response to our available medical therapies for DKD [121] when compared to adults with T2D and this fact, in combination with a significantly lower number of U.S. Food and Drug Administration (FDA)-approved pharmacologic therapies for DKD in youth with T2D, results in a less successful treatment profile overall. Current medications for the management of DKD are largely targeted to strict glucose management (i.e., insulin, metformin, and select glucagon like peptide-1 receptor agonists [GLP-1RAs]) and renin-angiotensin-aldosterone system blockade through angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) [122]. Sodium-glucose co-transporter 2 inhibitors (SGLT2is), medications which effectively block the sodium-glucose co-transported in the proximal tubule of the nephron from reabsorbing sodium and glucose, and GLP-1 RAs, agents aimed at increased insulin secretion and decreased glucagon secretion, serve as mainstay therapies for the mitigation of DKD, yet all SGLT2is and the majority of GLP-1RAs are not currently FDA approved in pediatrics [123-125].

Achieving approval to expand pharmacologic indications for medications beyond blood glucose or blood pressure control remains challenging in pediatrics for multiple reasons. First, achieving recruitment goals for clinical trials involving youth with T2D is difficult due to the relatively small population of youth who meet criteria for pancreatic autoantibody-negative diabetes, an over-representation of disadvantaged populations with confounding complications including psychiatric conditions requiring antipsychotic medications which may be diabetogenic, and strict requirements for pivotal trials which in some cases required drug-naïve participants [126]. Requirement of drug-naïve participants for clinical trials is in direct contradiction to treatment guidelines by the American Academy of Pediatrics which currently recommends immediate treatment with metformin and/or insulin following a T2D diagnosis [127]. Poor general adherence with treatment regimens and follow up visits for adolescents and young adults with T2D also compounds the issues surrounding completion of clinical trials in youth with T2D.

Medications targeting renal-specific pathophysiology beyond glycemia and blood pressure control may represent the future of advanced treatment for youth-onset DKD. We assert that a metabolic mismatch in renal oxygen availability and consumption may play a pivotal role in the development of youth-onset DKD, and targeted treatments may mitigate the progression of DKD in these individuals. One potential treatment mechanism to achieve this goal is through activation of mitochondrial-derived peptides, a type of peptide that targets the skeletal muscle which serves as a large disposal site for ingested glucose [128]. Mitochondrial-derived peptides induce pentose phosphate pathway glucose uptake, improve insulin resistance, decrease liver gluconeogenesis and generalized inflammation, and promote adenosine monophosphate-activated protein kinase (AMPK) activation and glucose transporter type 4 (GLUT-4) expression in muscle tissue in preclinical trials [128-130], all mechanisms that may independently improve the risk for DKD. Activators of the sirtuin-1 (SIRT1)/AMPK pathway may serve as another potential mechanism for DKD mitigation due to downstream phosphorylation of proteins that positively regulate insulin

sensitivity and increase fatty acid oxidation [131], factors that play an important role in kidney disease. Lastly, the mechanistic target of rapamycin pathway is a third potential targetable pathway for the treatment of DKD. Amino acids and growth factor stimulation of mTORC1 stimulates generalized cellular growth and proliferation [132] and activation of this pathway has a pivotal role in both physiologic and pathologic kidney hypertrophy [133], an initial kidney structural change with the development of DKD. Inhibition of this pathway may thus mitigate the risk of DKD progression. In conclusion, targeted therapies against factors contributing to a metabolic mismatch in kidney physiology may serve as optimal treatments for DKD in youth with T2D.

**Metabolic Surgery:** One potential mechanism for future treatment of DKD in pediatrics that moves beyond pharmacotherapy and negates the challenges related to large-scale, randomized, placebo-controlled trials is bariatric surgery. Bariatric surgery is used extensively in adult populations for management of weight and refractory T2D, but emerging data demonstrates similar positive benefits in adolescent populations with obesity and T2D including weight reduction, remission of T2D, and improvements in insulin resistance and DKD risk marker profiles [134,135]. In the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, a longitudinal cohort of 22 obese youth and young adults without T2D undergoing laparoscopic Roux-en-Y gastric bypass surgery, a 38% reduction in BMI (61±12.3 kg/m$^2$ to 39±8.0 kg/m$^2$) with a concurrent 300% increase in the insulin sensitivity index and a 2-fold increase in the disposition index (both $p$<0.01) were demonstrated after a 1 year post-surgery follow up [135]. In a subsequent multicenter study involving 5 U.S. weight-loss surgery centers involving 242 obese adolescents, Roux-en-Y gastric bypass surgery was associated with remission of T2D in 95% (95% CI: 85 to 100%) of participants and remission of abnormal kidney function as defined by low GFR or proteinuria in 86% (95% CI: 72 to 100%) of participants at 3 years post-procedure. When compared to medical management strategies employed in the TODAY study, the Teen-LABS cohort demonstrated significant improvements in both glycemia and markers of DKD. Teen-LABS participants exhibited a decrease in mean hemoglobin A1c from 6.8% (95% CI: 6.4-7.3%) to 5.5% (95% CIL 4.7-6.3%) at 2 years post-bariatric surgery follow up, while participants in the TODAY cohort who received pharmacologic management only demonstrated an increase in hemoglobin A1c from 6.4% (95% CI: 6.1-6.7%) to 7.8% (95% CI: 7.2-8.3%) [136]. Similarly, albuminuria was present in 17% (39/230) of participants at baseline in the Teen-LABS cohort and this decreased to 11% (19/173) at 3 years post-bariatric surgery follow up ($p$<0.06) and individuals with albuminuria demonstrated a significant improvement in albumin to creatinine ratio over time (i.e., 74 mg/g [45-121 mg/g] to 17 mg/g [10-28 mg/g], $p$<0.0001) [137]. In contrast, the prevalence of elevated albumin excretion in the TODAY cohort did not change over time [136]. Further studies evaluating the effects of bariatric surgery vs. medical therapy on more advanced measures of kidney function including intraglomerular hemodynamic function, hyperfiltration, and renal oxygenation in youth and young adults with T2D are critical to elucidate the underlying treatment mechanisms and thereby optimize future surgical and non-surgical approaches for DKD management in youth with T2D.

## Conclusion:

Current projections estimate that 50-70% of people with youth-onset T2D will develop DKD during adolescence and young adulthood. Data summarized in this review document that despite the high prevalence and severity of DKD in youth-onset T2D, the underlying mechanisms are poorly understood, and effective treatment options are lacking. Based on preliminary findings appraised in this review, we posit that youth-onset T2D may exhibit a distinct morphometric and molecular phenotype of DKD that stems from a metabolic imbalance between renal energy expenditure and substrate metabolism. We also contend that developing T2D during puberty amplifies the risk of kidney injury, as the kidneys almost double in size during sexual maturation, likely increasing the kidneys' already high energy expenditure. In parallel, puberty is associated with physiologic IR, which is accentuated in obesity and diabetes.

If perturbed renal energetics plays an important role in the pathogenesis of DKD in youth-onset T2D, determinants of the metabolic mismatch could serve as promising therapeutic targets to mitigate their high burden of DKD (e.g., mitochondrial peptides and activators of AMPK and SIRT1, and mTORC1 inhibitors) [116,118,138,139]. Additionally, increased uptake of bariatric surgery in the adolescent population with obesity and T2D may also result in significant improvements in weight and IR, remission of T2D, and reduction in DKD risk profiles. Even temporary efforts to correct the metabolic imbalance may translate to durable protection against DKD.

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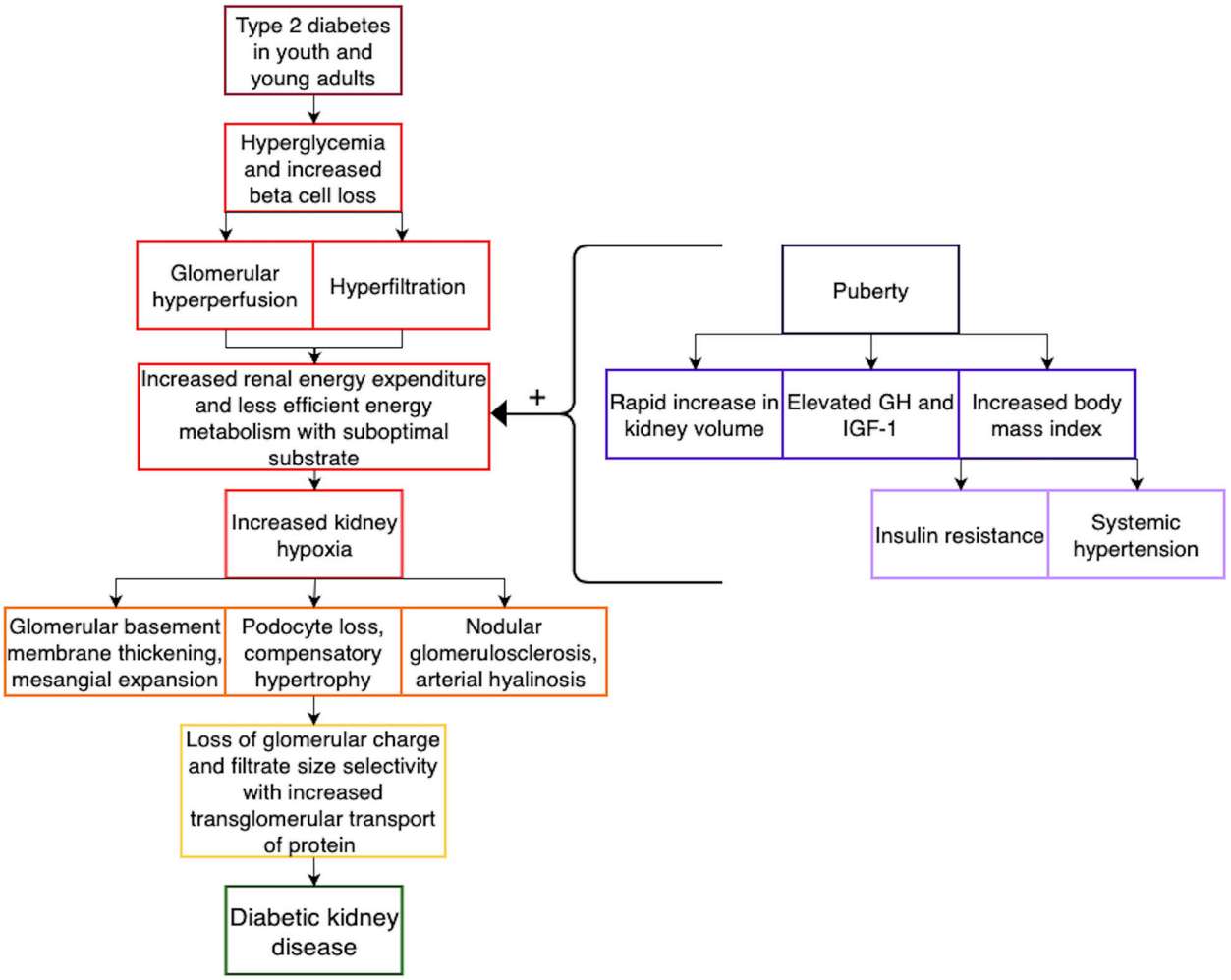


**Figure 1: Proposed Kidney Structural and Functional Changes Underlying the Development of Diabetic Kidney Disease in Youth-Onset Type 2 Diabetes**

Abbreviations: GH – growth hormone; IGF-1 – insulin-like growth factor-1.