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Nephropathy in Youth and Young Adults with Type 2 Diabetes

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Abstract

The occurrence and progression of nephropathy associated with early onset type 2 diabetes is a consequence of the ongoing epidemic of childhood obesity. Minimal evidence regarding treatment effectiveness of renovascular comorbidities in youth with early onset T2D is available, due to the relatively recent emergence of T2D in youth and young adults. Extrapolation of adult therapy guidelines is not an ideal approach to making therapeutic decisions in this population. Evolving management and intervention strategies are based on accumulating longitudinal data from cohorts of well characterized youth and young adults with T2D. The degree of similarity in histologic findings and disease specific characteristics of kidney disease in patients with early onset T2D and albuminuria compared to affected adults is not well characterized. Early aggressive therapies to minimize the impact of nephropathy are indicated as the evidence for best therapies in youth with T2D are further explored.

Keywords

Nephropathy; Type 2 Diabetes; Youth; Young adults; Microalbuminuria

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Conflict of Interest

Carolina Solis-Herrera, Curtis L. Triplitt, and Jane L. Lynch declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Type 2 diabetes and hypertension are the two leading causes of end-stage renal disease; with risks for developing diabetic nephropathy further increased by co-existing risk factors of hyperlipidemia and/or obesity. Youth and young adults with type 2 diabetes (T2D) have increased risk for earlier onset and accelerated progression of albuminuria when compared to both their type 1 diabetes (T1D) counterparts and adults with T2D of similar duration. [1–9] Furthermore, youth and young adults with T2D have an extended lifetime exposure to these risk factors. Pubertal hormone driven extremes of insulin resistance likely contribute to the observed risk for accelerated β -cell failure and circulating growth factors may have a negative impact on nephropathy progression. [10–13] In addition, reports of worse glycemic control among teens and young adults with diabetes portend both earlier and increased cumulative microvascular complications. [2, 14–19]

Type 2 diabetes in youth is a relatively new phenomenon, attributed to the significantly increased prevalence of childhood obesity over the past three decades. The rise in T2D incidence of less than 3% to nearly 45% of all cases of new-onset diabetes in adolescents in the US over the past two decades is alarming, with T2D disproportionately diagnosed in minority youth. [20–23] Clinicians have minimal longitudinal data regarding the epidemiology and natural history of renovascular comorbidities of T2D in youth to guide therapy decisions. [24] Longitudinal data from the Type 2 Diabetes in Adolescents and Youth (TODAY) study predict that children and adolescents diagnosed with T2D may have a much more aggressive course of disease with an increased risk for early hypertension and nephropathy when compared to adolescents with T1D. [5, 25] A higher prevalence of hyperlipidemia, non-alcoholic fatty liver disease and inflammatory markers further contributes to the concern for cumulative lifetime nephropathy risk in youth and young adults with T2D. [26–30]

Sustained motivation of youth with T2D to adhere to simultaneous dietary restrictions of sodium, fat and calories is difficult. Compliance with medical therapy and lifestyle recommendations is often hampered by a multitude of contributing psychosocial, medical and physiologic factors. [31, 32] Effectively addressing underlying factors that contribute to deteriorating glycemic control, hypertension, and obesity during teen and young adult years is critical to reducing renovascular disease risk.

Renovascular findings in youth with diabetes

The prospective observational Pittsburgh Epidemiology of Childhood-Onset Diabetes Complications Study has tracked the rates of overt nephropathy and reported a cumulative nephropathy rate of 32% at 25 years duration of T1D [33,34] The Diabetes Control and Complications (DCCT) study established the robust relationship between intensive glycemic control and microvascular complications in T1D. Adolescent DCCT participants randomized to the intensive arm of therapy in the DCCT experienced significantly reduced rates of MA during their average of 6.5 years of participation. Year 16 data from the subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) trial, during which original intensive and conventional therapy arm cohorts maintained similar time-averaged glycemic levels in community care, found persistent benefits for the original

intensive therapy cohort in both the use of antihypertensive therapy (56.2% vs. 59.3%) and MA occurrence (19.4% vs. 22.6%). The implication that there is an enduring effect of initial glycemic control on the rate and extent of eventual nephropathy in genetically predisposed patients with diabetes is worrisome for adolescent outcomes. [19, 35,36]

The SEARCH for Diabetes in Youth study is an on-going population based multi-center study designed to identify and characterize a geographically and ethnically diverse cohort of youth <20 years with diabetes in the United States youth since 2001. The SEARCH study observed that teenage youth with T1D or T2D were at greatest risk for poor glycemic control; less than one third of youth met ADA-recommended A1c targets and one fourth of SEARCH patients >12 years of age had poor glycemic control with an A1c >9.5%. [37] Comparison of T2D and T1D youth in SEARCH found the T2D cohort to be older (average age 14.8 vs. 11.4), more likely female (63% vs. 51.5%) and more frequently obese (81% vs. 13.2%). The majority (74.5 %) of T2D youth were more likely to be from minority ethnic/racial families compared to T1D youth (20.5%). SEARCH cross sectional data analysis found a 4-fold higher prevalence of elevated BP among T2D youth (20.2–23.7% vs. 5.0–5.9%) despite shorter diabetes duration, slightly better A1C levels, and more frequent use of anti-hypertensive medication. T2D youth were also more likely than T1D youth to have elevated first AM MA (30.4% vs. 5.5%). [8, 15, 21, 37]

There is limited comparable longitudinal data regarding nephropathy outcomes for youth diagnosed with T2D. Accumulating cross-sectional and epidemiologic data reveal both increased and earlier risk for MA as well progression to nephropathy in youth and young adults with T2D. [1–3, 38–39] The TODAY Study provides unique prospective longitudinal data regarding HTN and MA in a large multi-ethnic cohort of well characterized youth with T2D (ages 10–17 years). Participants were enrolled within two years of their T2D diagnosis and provided comprehensive diabetes care that included aggressive protocol-driven treatment of confirmed HTN and MA. The incidence of hypertension rose from 11.6% at baseline to 33.8% within only 3.9 years average duration of TODAY study participation. Consistent with adult T2D findings, males had a significantly higher risk for developing hypertension. The risk for hypertension increased by 14% per additional year of age and by 6% per additional unit of BMI at baseline. In contrast, the risk for microalbuminuria was similar between genders with a prevalence of 3% at baseline rising to 16.6%. The only significant factor influencing MA progression in TODAY participants was glycemic control; there was a 17% increased risk of developing MA for every 1% rise in A1C. Overall, 8% of participants developed macroalbuminuria and one-third of those advanced to proteinuria during the duration of the study. [5]

Similar to adults, the prevalence of nephropathy is higher among individuals of Asian, African Caribbean or Native American descent and highest among the Pima Indian population. Early onset T2D (<age 20) in the Pima Indian youth has been associated with near fivefold increased incidence of end stage renal disease (ESRD) between 25 and 54 years of age compared to those diagnosed later in life. Pima Indian youth diagnosed with T2D were found to have prevalence rates of 18% HTN and 22% MA at T2D diagnosis, with estimated prevalence rates of MA of 60% and proteinuria of 17% before 30 years of age. [40–43] A retrospective review of renovascular complication rates of individuals who were

diagnosed with either T1D or T2D in youth was done in Manitoba, the province in Canada which has a predominantly minority/first nation population and the highest rate of T2D in Canada. Patients with a diagnosis of T1D or T2D were identified using International Classification of Diseases Ninth Revision (ICD9) codes, with subjects matched for age, sex, and postal code. When compared to T1D youth, the T2D cohort had a fourfold risk of renal failure with a lower mean age of MA (14.9 vs. 15.3 years) despite a lower mean duration (1.6 vs. 6.3 years) of diabetes and 6.7% of the T2D youth developed renal failure at a mean duration of 9.1 years. Youth with T2D had a 23-fold risk of renal failure and 39-fold risk of dialysis when compared to nondiabetic controls. [44,45] It is important to note that the Canadian First Nation population, at least until 40 years of age, has a poorly understood high risk for glomerulonephritis. Renal biopsy on ten Canadian First Nation youth with T2D and persistent macroalbuminuria at or within 8 years of developing diabetes found that nine of the 10 showed immune complex disease or glomerulosclerosis and none showed classic diabetic nephropathy. [46] These findings suggest a role for renal biopsy in this population to avoid missing a coexisting diagnosis. However, it is unlikely that this finding is generalizable to any other population of youth with T2D

In contrast to T1D, renal biopsy histology in adults with T2D with early nephropathy show a mix of typical diabetic glomerulopathy (glomerular expansion and basement membrane thickening) and hypertensive/structural lesions. Renal alterations in T2D include glomerular endothelium stressed by hyperfiltration and hypertension, angiotensin II overproduction, exposure to reactive oxygen/nitrogen species, inflammation and advanced glycation end products. These insults lead to increased intraglomerular pressure and extracellular matrix proteins that expand the mesangium of the glomerulus. Persistent microalbuminuria suggests incipient nephropathy and precedes the findings of macroalbuminuria and the decline of glomerular filtration rate seen with diabetic nephropathy and ESRD. [47] There is a poorly understood but significant risk for MA in obese youth prior to a diagnosis of T2D. [48–52] Obesity and hypertension are independent contributors to renal hyperperfusion, increased filtration fraction and albuminuria. Massive obesity-related renal disease may show the unique findings of focal segmental glomerular sclerosis; however there are many overlapping renovascular findings in obesity and T2D nephropathy. [53–55]

Puberty has an impact on many factors that may accelerate the progression of renovascular complications. An possible protective effect on MA occurrence prior to puberty in T1D has been described, which suggests that pubertal growth factors and hormonal changes impact nephropathy risks. [1, 50,56,57] Despite evidence that estrogens are protective against the development and progression of non-diabetic chronic kidney disease, there is no similar evidence for such an effect on diabetes-induced kidney damage. [58] The majority of youth with T2D have pubertal findings at the time of diagnosis. Earlier and more exaggerate rates of insulin resistance in girls lead to a twofold risk for T2D during adolescence when compared to pubertal boys who have a later and lower peak in insulin resistance. [56,59] Insulin resistance leads to increased renal reabsorption of sodium and increased sympathetic nervous system changes, sustained hypertension and accelerated atherosclerosis of the renal microvasculature.

Nephropathy and Hypertension Management

Current youth and young adult management strategies to prevent diabetic nephropathy are based on adult experience. Coexisting hyperglycemia, hypertension, and hyperlipidemia predisposes the patient with T2D to a markedly increased risk of renovascular disease. The degree and duration of glycemic exposure has been repeatedly shown to be the best predictor of the onset of albuminuria and progression to nephropathy in patients with both T1 and T2 diabetes. The DCCT/EDIC and UKPDS found that successful glycemic control reduced the rate and extent of eventual nephropathy, though the degree of renovascular protection waned as the stage of diabetic nephropathy advanced. The UKPDS reported a MA prevalence of 25% at 10 years following T2D diagnosis, with progression from microalbuminuria to macroalbuminuria occurring at an annual rate of 2.8% and further progression to end stage renal failure occurring at an annual rate of 2.3% in a cohort of over 5000 patients. [60] The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study studied intensive glycemic control (achieved mean HbA1C 6.5%) versus less intensive (achieved mean HbA1C 7.3%) in T2D. New or worsening diabetic nephropathy was decreased 21% in the intensive-glucose-control group compared with the standard treatment group ($P = .006$). There was also a 9% reduction in new microalbuminuria ($P = .02$). [61] Meta-analysis review of glycemic control support these studies, finding a non-significant trend to decrease end-stage-renal disease (0.69 [0.46–1.05]) and no reduction in risk of death from renal disease. [62]

Treatment goals for BP in adults with diabetes and HTN have been in flux due to recent evidence. It should be understood that as a person ages, the SBP becomes a more important goal for therapy, whereas both SBP and DBP are important in younger individuals. DBP goals have been stable and are currently recommended to be $<80\text{mmHg}$. Multiple studies, though often a diabetes subset, have achieved a $\text{DBP} < 80\text{mmHg}$ in conjunction with lower risks of CV disease. Historically, HTN trials have started with higher baseline values for SBP and few have achieved currently recommended BP goals. For example, in the UKPDS, every 10mmHg reduction in SBP reduced the hazard ratio for diabetes-related death by 17%, yet the achieved mean SBP in the trial was above 140mmHg . More recent trials, such as INVEST and ACCORD have achieved BP goals and give us insight into appropriateness of current goals. INVEST (International Verapamil-SR Trandolapril Study) enrolled subjects with HTN and coronary artery disease. A sizeable subset (>6000 subjects) of T2D subjects were enrolled. The primary outcome of first occurrence of all-cause mortality, nonfatal myocardial infarction, or non-fatal stroke was not different between an atenolol or verapamil sustained release strategy for HTN control. Upon post-hoc analysis, it was noted that subjects with an attained SBP $<130\text{mmHg}$ and subjects with a SBP 130 to $<140\text{mmHg}$ had similar outcomes. Only subjects with a SBP $>140\text{mmHg}$ had a higher risk of the primary outcome. In addition, there was evidence of a “J-curve” or higher risk with lower BP levels achieved in subjects >70 years old. Of interest, an achieved SBP $<110\text{mmHg}$ was associated with an increased in all-cause mortality. [63–65] ACCORD enrolled subjects on up to three BP medications, a SBP up to 180mmHg , which was dependent on the number of current BP medications, and urine protein <1 gram. Mean enrollment BP was $139/76\text{mmHg}$, which is substantially lower than “older” trials. Over a more than 5 year follow-up, the SBP was 119.3mmHg in the intensively treated versus 133.5mmHg in the standard treatment group

and the DBP met goals in both groups. The primary composite cardiovascular outcome was not significantly lower in the intensively treated group. There was a significantly lower risk of stroke in the intensively treated group versus standard treatment. In contrast, adults with diabetic nephropathy achieving a SBP <120mmHg in the Irbesartan Diabetic Nephropathy Trial (IDNT) had a higher risk of all-cause mortality. [66] It is unclear if the lower blood pressure is a marker of “sicker” patients, or truly represents morbidity associated with the lower BP goal. The additional BP medication needed to achieve the lower SBP in the ACCORD increased the risk of side effects and adverse reactions such as hyperkalemia and acute renal failure. In adults, the evidence for the reduction of BP lower than 130/80mmHg may be appropriate for patients at high risk for stroke or progressing nephropathy.. The American Diabetes Association (ADA) recommends that lower systolic targets, such as <130 mmHg, may be appropriate for younger patients, if it can be achieved without significant side effects or adverse events.

Although preliminary T2D outcome data is limited at this time, the known relationship between nephropathy and cardiovascular morbidity predicts youth and young adults diagnosed with T2D may experience severe, chronic complications of Type 2 diabetes by their 40s with a loss of approximately 15 years from average remaining life expectancy. [67] In general, all major classes of BP medications have been proven to provide CV protection when adequate BP control is achieved. In contrast, special renoprotection is seen with blockade of the RAAS, which is the cornerstone of treatment for the prevention and progression of renal disease in diabetes patients. Though the level of evidence may be stronger for ACE inhibitors in T1D and ARB's in T2D, either can be used. Head to head data are not robust, but in one underpowered trial, GFR change over 5 years was not different between an ACE inhibitor or ARB. Combination therapy with RAAS drugs is not recommended as additional renal or CV protection has not been documented and potential harm from adverse reactions may be increased. [68] Timing of dosing can also be important. In an adult group with CKD, taking at least one BP drug at bedtime improved BP control and “dipping” of blood pressure as measured by 24 hour ambulatory blood pressure monitoring. Importantly, it also decreased the composite risk of CV death, MI, and stroke (adjusted HR, 0.28; 95% CI, 0.13–0.61; $P<.001$). This is a simple intervention with potentially important implications to patients. [69] This advice is likely relevant to youth and young adults with T2D who are already at risk for impaired nocturnal “dipping” of both systolic and diastolic BP, early left ventricular hypertrophy, posterior and septal wall thickening and increased arterial stiffness. [51,70,71]

Racial/ethnic variances in T2D nephropathy are described in the adult literature. The MicroAlbuminuria Prevalence (MAP) study has found up to 60% of Asian patients with T2D had microalbuminuria compared to 30–40% in the Western population. [72] In terms of nephropathy, the African American study of kidney disease and hypertension (AASK) trial demonstrated a renoprotective effect of angiotensin-converting enzyme inhibitor and slower decline of GFR in a hypertensive African American population compared to the CCB therapy. [73] There is also evidence of ethnic group and age variations in response to hypertension therapy regimens. Persons of African and Asian descent, as well as women, may have a higher incidence of cough and angioedema with angiotensin converting enzyme (ACE) therapy. [74] Calcium channel blocker agents (CCB) and diuretics are considered

more effective in the elderly and African American patients. [75] Most trials have used half-maximum to maximum dosing of RAAS blockade drugs. It is recommended that this dosing be used as a guide for nephropathy. In African-American patients and the elderly with nephropathy, a RAAS blockade drug in combination with either a calcium channel blocker or diuretic is recommended, if necessary to achieve the current BP goal of 130/80mmHg.

Aggressive multidrug therapies targeting known risk factors of hyperglycemia and hypertension are critical to limit renal function loss even before the onset of overt nephropathy in T2D [47] The Steno-2 trial randomized 160 T2D patients to intensive glycemic, lipid, and blood pressure goals. At the end of thirteen years of follow-up, 30% of intensive compared to 50% of standard therapy had died ($p=0.02$). Intensive therapy also significantly decreased the risk of nephropathy, retinopathy, and neuropathy. Importantly, it reduced the risk of nephropathy (relative risk, 0.44; 95% CI, 0.25 to 0.77; $P=0.004$) over a 13 year follow-up period. [76]

Early Detection of Hypertension and Microalbuminuria

Youth with T2D should be carefully monitored at quarterly visits for glycemic control, weight gain, and blood pressure (BP) with annual screenings of urinary microalbuminuria (MA) and serum lipids. [77,78] Unfortunately, hypertension in youth is frequently overlooked due to the complexity of the BP% calculation requirements, inappropriate cuff size use, and vague hypertensive symptoms. [79–81] Target systolic (SBP) and diastolic BP (DSP) should be less than the 95 percentile based on age, gender and height using the “Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” tables. [82]

Either random AM urine albumin: creatinine ratios or timed overnight urine collections for albumin excretion rate are acceptable options for the recommended screening for early nephropathy. Referral to nephrology is indicated when the clinical evaluation detects nephrotic range proteinuria, significant hematuria or renal structural abnormality on ultrasound. Otherwise, persistent urine albumin-to-creatinine ratios of >30 ug/g on three occasions performed at least one month apart (ideally collected from a first AM void) are useful as a surrogate clinical marker for early diabetic nephropathy changes when no other cause for kidney disease is evident.

Early detection and confirmation of hypertension and/or MA in the normotensive youth is followed by efforts to reduce salt intake for hypertension and improve glycemic control for MA. Blood pressure lowering and RAAS blockade are critical early interventions to delay or prevent progression of MA and preserve kidney function. [77,78,48,83–86] Other factors that are independently associated with increased MA risk include cigarette smoking, hyperlipidemia and genetic susceptibility. [4, 87] Although data for youth with T2D is limited, stable MA or regression to normoalbuminuria in up to half of affected adults and youth with T1D can occur with aggressive management of glycemia, hyperlipidemia and RAAS blockade therapy. [14, 88–90] Reassessment of microalbuminuria after puberty can be considered, however evidence to accurately predict which patients with MA will continue to progress to is not available. Thus, youth with T2D typically remain on prolonged RAAS

blockade therapy once it is initiated. Serum creatinine can be used to calculate creatinine clearance as a practical estimate to monitor glomerular filtration rates. An abnormal creatinine clearance of < 70 mL/min. is seen with advancing nephropathy [91,92]

Medical Management Challenges in youth and young adults

The alarm which accompanies the initial diagnosis of diabetes and possible ketoacidosis in a youth or adolescent demands that families rally with concern to mobilize time and resources for their child's health and welfare. However, the confirmed diagnosis of T2D (vs. T1D) is often viewed as a relief in families familiar with T2D who are hopeful that their child can maintain or transition to oral monotherapy in lieu of insulin. Unfortunately, motivating youth with T2D to adhere to low sodium, low fat diets simultaneous with glycemic restriction to achieve weight loss goals is challenging. Hectic schedules and increased independence make supervision more difficult at an age when increasing fast food access and school meals often coincide with decreased physical activity. The motivation and ability to comply with recommended lifestyle changes and medications often wane within months to a year following initial education and therapy, particularly among families with members who have been reluctant or unable to meet these goals for their own T2D disease. Struggles with T2D treatment attrition and noncompliance have been described regardless of culture or geographic location. [31, 93,94]

Diabetes management may become a lower priority in families with limited resources or a high family burden of disease and medical needs. The disproportionate prevalence of T2D among youth from home environments of low socioeconomic status (SES) influences access to affordable medications and care. Rescheduled or missed appointments and gaps in care when transitioning to an adult provider often further compromise clinical care. The TODAY study cohort demographics typify the extent of economic and psychosocial barriers that often exist. Participant families reported low SES (42% with household income $< \$25,000$) with the majority of the TODAY participants in single-parent households. [32]. Canadian registry data from Manitoba revealed that 59.1% of youth with T2D were in the lowest SES quintile. [44] Young adults with T2D can become overwhelmed when balancing health care priorities with financial realities of work schedules, school schedules and the need for multidisciplinary care. An increased incidence of depressive symptoms adds to the vulnerability of adolescents and young adults with T2D. [32, 95]

Several adolescent aspects of therapy should be anticipated when treating youth with T2D. Hypertension may be aggravated by weight gain, sleep apnea, stimulant or illicit drug use, smoking and contraceptive pills. Evidence suggests a continuous relationship between BMI and SBP with a steeper gradient of this relationship in adolescent boys, compared with girls not taking oral contraceptives [96] Weight gain may be associated with antipsychotic or antidepressant medication use. Weight gain and insulin resistance are associated with fatty liver and fluctuations of liver enzymes that may be difficult to differentiate from the much less common cholestatic hepatotoxicity associated with ACE or ARB therapy. Irregular menses and polycystic ovary disease are common among young women with obesity or T2D. Contraceptive counseling should reinforce the risk for first trimester congenital malformations associated with ACE and ARB therapies and the need to switch immediately

to alternative safer therapy during pregnancy. [97,98] Young women who have uncontrolled hypertension or MA are at increased risk for preeclampsia, premature delivery and lower infant birth weight in addition to the increased pregnancy complications and congenital anomalies related to diabetes in their offspring. [99,100]

Conclusion

Type 2 diabetes in youth is a relatively new disease. Limited outcome data are available to predict the risk for developing nephropathy in these patients who will likely be exposed to a higher degree and duration of glycemic exposure over their lifetime. Pubertal hormones can exacerbate existing insulin resistance to accelerate β -cell failure rates and may impact renal physiology as well in youth and young adults at genetic risk for T2D. Attempts to maintain glycemic control in youth and young adults with T2D frequently coincide with medical management of obesity, hypertension, fatty liver and hyperlipidemia. Dietary and medication compliance may be limited by issues related to supervision, maturity, depression and socioeconomic circumstances. Racial/ethnic minority youth are not only at higher risk for T2D risk but may also differ in their future patterns for renovascular disease risk and therapeutic response to ACE. Evidence suggests there may be a more heterogeneous spectrum of renal pathology among Canadian First Nation youth with early onset MA and T2D to suggest vigilance for accurately diagnosing coinciding renal disorders in this population. Emerging data is consistent with fears for accelerated development and progression of microalbuminuria in youth with T2D.

Clinical advances and more aggressive diabetes care guidelines following the publication of the Diabetes Control and Complications Trial (DCCT) outcomes have coincided with advances in blood pressure medication and diabetes metabolic monitoring technology. Treatment of hypertension and MA in patients with T2D is focused on early therapy interventions to reduce or reverse the progression of microalbuminuria and postpone the development of proteinuria. If diabetic nephropathy is present, optimized use of a RAAS blockade drug should be implemented, and then use of additional BP agents to treat to goal is recommended, with individualization of these BP choices as necessary. Glycemic control and hypertension control for prevention of nephropathy is paramount.

Longitudinal data is needed to determine the value of MA as a surrogate marker for underlying renal structural damage and risk for progression from proteinuria to diabetic nephropathy in the setting of aggressive RAAS blockade in youth and young adults with early onset T2D. Early interventions are critical to effectively alter or delay the anticipated several decade trajectory of diabetes complications. The development of diabetic MA and nephropathy at an earlier age likely confers a high risk for to cardiovascular morbidity and mortality and significant reduction in life expectancy. Further characterization of the microalbuminuria progression and predictors of nephropathy in T2D youth are urgently needed to optimize therapy strategies and reduce renovascular as well as cardiovascular complications in this high risk population.

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