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Early Microvascular Complications in Type 1 and Type 2 Diabetes: Recent Developments and Updates

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Abstract

The prevalence of youth-onset diabetes is progressing rapidly worldwide and poor glycemic control, in combination with prolonged diabetes duration and comorbidities including hypertension, has led to the early development of microvascular complications including diabetic kidney disease, retinopathy, and neuropathy. Pediatric populations with type 1 (T1D) and type 2 (T2D) diabetes are classically underdiagnosed with microvascular complications and this leads to both undertreatment and insufficient attention to the mitigation of risk factors that could help attenuate further progression of complications and decrease the likelihood for long-term morbidity and mortality. This narrative review aims to present a comprehensive summary of the epidemiology, risk factors, symptoms, screening practices, and treatment options, including future opportunities for treatment advancement, for microvascular complications in youth with T1D and T2D. We seek to uniquely focus on the inherent challenges of managing pediatric populations with diabetes and discuss the similarities and differences between microvascular complications in T1D and T2D, while presenting a strong emphasis on the importance of early identification of at-risk youth. Further investigation of possible treatment mechanisms for microvascular complications in

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youth with T1D and T2D through dedicated pediatric outcome trials is necessary to target the brief window where early pathological vascular changes may be significantly attenuated.

Keywords

Microvascular complications; type 1 diabetes; type 2 diabetes; youth; adolescents

Introduction

Diabetes, a global epidemic projected to affect 578 million people worldwide by 2030 [1], is associated with disease in both the small (microvascular) and large (macrovascular) blood vessels [2]. The most common microvascular complications include diabetic kidney disease (DKD), eye disease (retinopathy), and nerve disease (neuropathy). The pathogenesis of microvascular complications starts early in the course of diabetes and may be present in young people with type 1 diabetes (T1D) within a few years after diagnosis, or at diagnosis in people with youth-onset type 2 diabetes (T2D). Additionally, the incidence of microvascular complications accelerates during the transition to young adulthood, illustrating a serious clinical trajectory that could impact long-term health in people with youth-onset diabetes. Indeed, microvascular complications contribute to significant lifetime morbidity and mortality, including devastating outcomes such as kidney failure, blindness, and amputations. Efforts to mitigate the onset and progression of microvascular complications are complicated by the frequent presence of significant, well-established vascular injuries at the time of clinical manifestation which are oftentimes refractory to current therapeutic strategies in young people with T1D and T2D [3]. For example, the Natural History Study, a prospective 5-year observational study of kidney structure and function in youth with T1D, demonstrated that glomerular basement membrane thickening and mesangial expansion were present on kidney biopsy in youth with T1D who had normoalbuminuria, and these changes predicted subsequent progression to microalbuminuria [4]. Additionally, despite the grave sequelae, low rates of treatment for microvascular complications such as DKD have been documented in youth with diabetes [5]. Furthermore, there are limited therapeutic options available in pediatrics due to a paucity of outcome trials. This review seeks to provide a comprehensive appraisal of the epidemiology, risk factors, and current and future treatment options for microvascular complications in youth with T1D and T2D. We will also discuss unique challenges to managing microvascular complications in pediatric diabetes, and differences between T1D and T2D.

Diabetic Kidney Disease

Epidemiology

In conjunction with associated cardiovascular disease, DKD remains the greatest risk factor for all-cause morbidity and mortality in individuals with T1D [6] and T2D [7]. Epidemiologic studies have estimated that DKD affects over 25% of youth and adolescents with T1D of >10 years duration [8] and between 6.3 and 22.8% of adolescents with T2D of any duration [9,10]. Notably, a longer duration of diabetes has been associated with an increased prevalence of DKD in both T1D and T2D. The prospective, observational

Pittsburgh Epidemiology of Childhood-Onset Diabetes Complications Study reported a cumulative risk of 32% for developing DKD after having T1D for a total of 25 years [11]. Among individuals with T2D, the U.K. Prospective Diabetes Study (UKPDS) demonstrated a microalbuminuria prevalence of 25% after 10 years of diabetes, with further progression from no nephropathy to microalbuminuria at a rate of 2% for every year thereafter, thus correlating with an estimated cumulative DKD risk of 55% at 25 years post-T2D diagnosis [12]. Race/ethnicity has also been shown to play a strong role in the risk for developing DKD, particularly for individuals of Native American, Asian, or African Caribbean descent. Pima Indian adolescents are at an unusually high risk and have demonstrated a 27-40% likelihood of developing albuminuria after only 5 years of T2D [13,14]. However, when age, sex, race/ethnicity, diabetes duration, and HbA1c were accounted for, the SEARCH for Diabetes in Youth Study found that T2D had a 2.42 (95% CI 1.68-3.49) odds ratio for predicting an elevated albumin-to-creatinine ratio compared to T1D ($p<0.0001$) [9]. Youth-onset T2D is also associated with a 4-fold higher risk of progression to chronic kidney disease (CKD) compared to T1D (hazard ratio 4.03 (95% CI 1.64-9.95) [15]. Therefore, youth with T2D represent a population at particularly high risk for kidney failure and premature morbidity and mortality.

Risk Factors

DKD arises primarily from glomerular damage sustained from a combination of factors including hyperglycemia and glomerular hypertension which results in hyperfiltration, particularly in the setting of a prolonged duration of diabetes. Poor glycemic control and comorbid conditions drive pathophysiologic structural changes in the kidney including glomerular and tubular basement membrane thickening as well as mesangial and interstitial matrix expansion, tubular atrophy, and glomerular sclerosis [16]. In T2D, kidney structural lesions are initially more heterogenous than in T1D and may include a predominance of tubulointerstitial and vascular changes [17]. Histologic changes increase in prevalence with the development of albuminuria and impaired glomerular filtration rate (GFR) (<60 mL/min/1.73 m^2 in adults) [16,18]. The seminal Diabetes Control and Complications Trial (DCCT) and follow up Epidemiology of Diabetes Interventions and Complications (EDIC) studies have conclusively established that persistent hyperglycemia is directly associated with microvascular complications including DKD [19]. For the 195 participants aged 13-17 years with insulin dependent diabetes followed in the DCCT, intensive diabetes management targeting treatment of hyperglycemia resulted in a 55% risk reduction (95% CI 3-79%, $p=0.042$) in developing new onset microalbuminuria as compared to the conventional treatment group [20]. Notably, this reduction persisted for the duration of the EDIC study [21]. The Oxford Regional Prospective Study took this one step further and found that youth with T1D demonstrate a 30% increased risk for albuminuria for every 1% increase in HbA1c [22], while the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study demonstrated that youth with T2D have a 17% increased risk in albuminuria for every 1% increase in HbA1c [10]. In addition to persistent hyperglycemia, sub-optimally treated hypertension has been shown repeatedly to have a significant effect on the progression of albuminuria and impaired GFR [23]. Other previously reported risk factors for the development of DKD in youth and adolescents include elevated low-density lipoprotein and/or triglycerides [24], obesity [25], smoking [26], and family history of DKD [27].

Timely identification of individuals at risk for rapid decline is necessary to initiate treatment and possibly reverse the early stages of DKD.

Symptoms and screening

DKD can be challenging to detect as individuals will often remain asymptomatic until their GFR is significantly, and often irreversibly, compromised [28]. This highlights the importance of frequent screenings in asymptomatic individuals with diabetes, particularly in those with a history of severe and/or prolonged dysglycemia. Increased urine albumin-to-creatinine ratio (UACR) (i.e., a urine albumin >30 mg/g [3.4 mg/mmol] creatinine on 2 out of 3 separate screening occasions) remains the primary screening test for detecting youth at risk for DKD, as albuminuria is a marker of multiple pathologic findings fundamental to DKD including elevations in glomerular pressure, abnormalities of the glomerular basement membrane, and injuries to the endothelial cells and kidney tubules (Table 1). For youth with T1D, screening should be initiated either at puberty or >10 years of age, whichever is earlier, when a patient has had T1D for ≥5 years (American Diabetes Association [ADA] criteria) [29] or at ≥11 years of age or when the patient has had T1D for >2-5 years (International Society for Pediatric and Adolescent Diabetes [ISPAD] criteria) [3]. Screening should then be repeated annually. In contrast, youth with T2D should be screened at diagnosis and annually thereafter [29,3]. First morning urine samples should be obtained, whenever possible, to minimize benign, transient elevations secondary to orthostasis, stress, and/or exercise [30].

Accurate measurement of kidney function represents another critical aspect of screening for kidney disease in youth-onset diabetes [29]. This is particularly important because 29-41% of adults with diabetes and decreased kidney function have normal urinary albumin excretion [31,32]. Because direct measurements of GFR through clearance of exogenous filtration markers such as iohexol or inulin are both cumbersome and time-consuming secondary to repeat blood and urine sampling to calculate the clearance curve, direct measurements of GFR are rarely assessed outside of clinical research. Instead, GFR is mainly evaluated by indirect measurements through calculated equations assessing the clearance of endogenous filtration markers such as serum creatinine or cystatin C [33,34]. However, attention must be taken to ensure that the equations used to estimate GFR are validated in the population being screened. Specifically, these equations may underestimate kidney function in healthy children, so a mildly decreased GFR (i.e., 75-90 mL/min/1.73m^2) may not be indicative of early DKD [33]. Additionally, longitudinal follow up with repeat eGFR assessments has demonstrated better prognostic value in predicting future progression to chronic kidney disease than single eGFR assessments [35]. A new and promising direction for DKD screening is the use of timed dried blood spots for measured GFR by iohexol clearance, a method that has been shown to be more accurate than many estimating equations and less burdensome than traditional direct measurements [36]. Additionally, rapid determination of measured GFR via Visible Fluorescent Injectate (VFI), a new, well-tolerated exogenous biomarker with an excellent safety profile, has also been shown to have a close linear correlation with iohexol-based measured GFR and can be done at the bedside [37].

According to the ADA guidelines for children and adolescents, GFR estimation is recommended at diabetes diagnosis and then as clinically indicated for T1D and annually for T2D [29]. In those who develop macroalbuminuria, more frequent assessments of estimated GFR (eGFR) may be needed. In children, development of impaired kidney function (eGFR <90 mL/min/1.73m^2) before adulthood is rare. In addition to microalbuminuria, hyperfiltration has been found to represent the earliest indication of DKD in both youth-onset diabetes and adult-onset diabetes. In the TODAY cohort, hyperfiltration was present in 7% at baseline and increased to 13.3% at 5 years of follow-up [38]. Serial measurement of eGFR also permits the detection of a rapid decline in GFR, defined as >3-5 mL/min/1.73 m^2 per year, which is associated with an increased risk of cardiovascular disease and all-cause mortality [39]. Among adult patients with diabetes, rapid kidney function decline is associated with baseline hyperfiltration and predicts progression to incident impaired GFR (<60 mL/min/1.73 m^2 in adults) [40]. Therefore, serial GFR measurements in children may identify those at increased risk for progressive DKD, though long-term studies in the pediatric population are lacking.

Additionally, kidney biopsy may be considered as a method to improve diagnostic accuracy for suspected pediatric DKD, particularly when there is a concern for superimposed nondiabetic kidney disease. Kidney biopsy may also be used to further classify the stage of disease and prognosticate long term outcomes [41]. Proposed minor indications for kidney biopsy include rapid progression of proteinuria and/or unexplained renal insufficiency. A kidney biopsy should also be considered in the setting of clinical features of atypical DKD, such as gross hematuria, or the presence of nephrotic syndrome [42]. Given youth and young adults are less likely than adults to develop advanced DKD at baseline, a high index of suspicion for concurrent nondiabetic kidney disease is prudent with the development of these features. Yet, concurrent risk factors for complications associated with the kidney biopsy procedure must also be considered and these include the use of antiplatelet or anticoagulation medications that may increase the risk of bleeding and comorbid conditions that may place the patient at risk for morbidity including elevated blood pressure [43]. The decision to perform a biopsy should therefore be individualized after careful consideration of the risks and benefits of the procedure.

Treatment

Strict glycemic control, specifically targeting a HbA1c ≤7%, has been shown to prevent the progression to microalbuminuria and macroalbuminuria in both T1D and T2D [44]. Clinical strategies are employed to achieve this aim to increase time in goal glycemic range and reduce the frequency and duration of severe hypo-and hyperglycemic episodes [19,45]. Advanced diabetes technologies such as automated insulin delivery (AID) systems, technologies that combine a continuous subcutaneous insulin infusion pump, continuous glucose monitor (CGM), and control algorithm to modify the amount of background insulin delivered, are one possible method to achieve this goal, particularly in individuals with T1D. AID systems have been associated with improved time in goal glycemic range and reduced frequency, severity, and duration of hypoglycemia [46,47]; however, studies evaluating the impact of AID systems on kidney outcomes are lacking. Subcutaneous insulins with modified delivery profiles are another possible treatment mechanism for

targeting optimal glycemic control and improving DKD risk. Icodec, a once-weekly basal insulin, has been recently shown to exhibit a similar glucose-lowering and safety profile as once-daily glargine in youth with T2D [48]. Once weekly insulin administration may help facilitate treatment adherence and improve dysglycemia, although Icodec's effects on kidney outcomes is unknown.

Moving beyond treatments for hyperglycemia, renin-angiotensin blockade via angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARB's) remains the first line treatment for hypertension in the setting of T1D or T2D. Use of these agents in patients with diabetes has consistently prevented progression to albuminuria and decreased renal function [49,50]. Additionally, beneficial effects on kidney function and proteinuria have been demonstrated independent of blood pressure reduction [51], likely secondary to a reduction in intraglomerular pressure and an improvement in incident hyperfiltration. Blood pressure management should be in accordance with recent pediatric guidelines, targeting a blood pressure <130/80 mm Hg or <95th percentile, whichever is lower [52]. In adults, lower blood pressure targets have not been showed to prevent progression to macroalbuminuria or kidney failure. Therefore, among children with normal kidney function and normoalbuminuria, more strict blood pressure control is not currently indicated [53]. However, in those patients with impaired kidney function (GFR <90 mL/min/1.73 m^2 in children and adolescents and <60 mL/min/1.73 m^2 in adults), a more stringent blood pressure control targeting the 50th percentile may be beneficial, in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [54]. Additionally, confirmation of hypertension may be assisted by ambulatory blood pressure monitoring over a 24-hour period, with the added benefits of increasing diagnostic accuracy, assessing blood pressure variability, and identifying blunting of the normal nocturnal dip in blood pressure secondary to diabetes [3]. Indeed, the American Academy of Pediatrics' updated guidelines for the screening and management of high blood pressure in youth recommend strong consideration of ambulatory blood pressure monitoring in the setting of certain high-risk conditions, including pediatric diabetes, to improve both diagnostic accuracy and reproducibility [52]. More definitive data regarding long-term kidney outcomes in children with diabetes are needed to definitively establish ideal blood pressure targets.

Therapeutic strategies that go beyond glycemia and renin-angiotensin blockade are warranted as these derangements do not wholly describe DKD risk, including known pathologic features of early DKD development such as glomerular hyperfiltration. Recent promising developments in the treatment of DKD, particularly in T2D, include the sodium glucose cotransporter 2 inhibitors (SGLT2is) and the glucagon-like peptide 1 receptor agonists (GLP-1 RAs). A full review of these medications is beyond the scope of this review, but both have shown beneficial effects on the progression of DKD in adults with T2D. In randomized controlled trials, GLP-1 RA's have prevented the development of macroalbuminuria compared to placebo [55]. However, as of now, these medications have not prevented the development of more definitive long-term kidney outcomes, including a doubling of creatinine or progression to ESRD. Liraglutide, a GLP-1 RA administered as a once daily subcutaneous injection, has recently received FDA approval for use in pediatrics. Accordingly, the 2020 ADA guidelines recommend the addition of liraglutide in children ≥10 years of age who are not meeting glycemic targets on metformin (with or without

basal insulin) [29]. In contrast to GLP-1 RAs, SGLT2is have demonstrated a both beneficial effect in preventing the development of macroalbuminuria and progression to ESRD [56]. In the landmark Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, the risk of progression to ESRD was 32% lower in those treated with the SGLT2i canagliflozin vs. placebo [56]. These medications, therefore, represent a major advancement in the care of DKD in those with T2D. Although FDA approval in children has not yet been obtained, SGLT2is are currently recommended in adults with type 2 diabetic nephropathy. Phase 3 studies to investigate their use in children with T2D are currently ongoing.

Retinopathy

Epidemiology

Diabetic retinopathy is the most frequent microvascular complication of diabetes [57], and a common occurrence in adolescents with T1D and T2D. Epidemiological data in youth with T1D estimate the prevalence of diabetic retinopathy between 4.6 and 20.0% [58–60]. The SEARCH for Diabetes in Youth cohort reported an age-adjusted prevalence of diabetic retinopathy among young people with T1D of 5.6% [60]. The epidemiology of diabetic retinopathy in youth-onset T2D is more limited, but data suggest a prevalence between 4.0 and 42.0% [59,60]. The SEARCH for Diabetes in Youth study found an age-adjusted prevalence of diabetic retinopathy of 9.1% in youth-onset T2D [60,61]. The same study found that the absolute difference in diabetic retinopathy prevalence between young people with T1D and T2D was 3.5% (95% CI 0.4-7.7%), which translated to a 2.24-fold higher odds of retinopathy in T2D vs. T1D [60,61]. In the TODAY study and its follow-up study (TODAY2), 13.7% of participants with youth-onset T2D had retinopathy, all with very mild non-proliferative diabetic retinopathy (NPDR). In TODAY2 (2017-2018), after an additional 7 years of diabetes duration, 51.0% of participants had evidence of eye disease, including 8.8% with moderate to severe retinal changes and 3.5% with macular edema [62].

Symptoms and screening

Early diabetic retinopathy is usually asymptomatic although underlying structural and functional changes in the microvasculature and pericytes may lead to aneurysms, occlusions, leakiness, and hypoxic injuries [63]. Due to its silent onset, regular screening is needed to diagnose early disease. The classical screening of diabetic retinopathy relies on 7-standard field color fundus photography, and grading typically follows the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol [64] (Table 1). The four stages of diabetic retinopathy are classified as mild, moderate, and severe NPDR and proliferative retinopathy [64]. Fundus photography can be supplemented by optical coherence tomography (OCT), which is a non-invasive imaging test that provides highly detailed assessments of retinal morphonology, such as volume of the individual retinal nerve fiber layers, disorganization of the inner retinal layers, intraretinal fluid in the form of cysts, subretinal fluid, vitreoretinal interface abnormalities, or diffuse intraretinal thickening [65]. OCT angiography can also be used to identify early microvascular changes in the retina by creating high-resolution perfusion maps of the central retinal vasculature [66]. Electroretinography (ERG) is another non-invasive method that measures the electrical activity of the retina in response to a light

stimulus and can be used to demonstrate early abnormalities in retinal electrical signaling in the diabetic eye. Local changes in ERG implicit time have been shown to manifest prior to the onset of other diabetic retinopathy lesions such as microaneurysms [67].

Risk factors

Cohort studies have uncovered important risk factors for retinopathy in young people with T1D and T2D. For example, the risk of incident retinopathy is higher in people who were diagnosed with T1D before the age of 14 years compared to those diagnosed during adulthood [68]. Additionally, girls with T1D appear to be disproportionately impacted by diabetic retinopathy [69]. Loss of glycemic control and DKD are also significant risk factors for diabetic retinopathy [69]. Notably, the Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AdDIT) found that the greatest risk factor for progression of diabetic retinopathy was elevated albuminuria [70]. In TODAY and TODAY2, loss of glycemic control predicted progression of diabetic retinopathy, but not decreased retinal thickness in young people with T2D [71]. At the time of the follow-up fundus photo assessment (12 years diabetes duration), 58.5% of participants with microalbuminuria in TODAY2 had diabetic retinopathy (mild to severe) vs. 39.1% in those without microalbuminuria and 37.7% of participants with microalbuminuria had a 3-step progression on the ETDRS scale vs. 15.8% among participants without microalbuminuria [72]. Similar findings were found for macroalbuminuria, hyperfiltration, and rapid GFR decline [72] (Table 2). Likewise, the presence of moderate/severe NDPR conferred 2 to 4 fold greater odds of microalbuminuria, macroalbuminuria, hyperfiltration, and rapid GFR decline in young people with T2D in TODAY2 [72].

Treatment

Over the past decade, strategies for the evaluation and treatment of diabetic eye disease have advanced dramatically, including targeted therapies that result in remarkable restoration and maintenance of visual acuity. Targeted therapies include intravitreous anti-vascular endothelial growth factor (VEGF) injections [73], as well as laser photocoagulation and vitreoretinal surgery. Despite advances in treatment for diabetic retinopathy, >40% of patients do not fully respond to current therapy, including anti-VEGF injections [74], and little progress has been made in the prospective identification of individuals most likely to lose vision, or respond to currently known therapies. The ability to predict when treatments will be most beneficial or, conversely, when retinal damage has occurred that would limit visual potential despite therapy, would enable more effective decisions about treatment regimens, enhance patient counseling and inform decisions as to when to initiate or terminate therapy. Recently, SGLT2is have shown promise to mitigate progression of retinopathy, but large dedicated retinopathy outcomes trials are missing [75]. Furthermore, the majority of the trials to date have been limited to adults with T2D, and data in young people with T1D and T2D remain very limited. The effects of metabolic bariatric surgery, an emerging therapy for people with severe obesity and T2D, on diabetic retinopathy is inconclusive, yet there is a paucity of data on the long-term effects of metabolic bariatric surgery on diabetic eye disease [76].

Peripheral and autonomic neuropathies

Epidemiology

Microvascular complications involving the nervous system also present in youth with diabetes. Diabetic neuropathy (DN), including both peripheral and autonomic neuropathies, broadly encompasses the nerve dysfunction seen with T1D and T2D. The most common neuropathy among patients with diabetes is distal symmetric polyneuropathy, hereafter referred to as peripheral neuropathy. The prevalence of peripheral neuropathy is well documented in youth with T1D where estimates range between 7% [77] and 90% [78]. This large range in estimated prevalence among youth with T1D likely captures both symptomatic and asymptomatic peripheral neuropathy, as diverse measures are applied across studies that are differentially sensitive to clinical and sub-clinical symptoms of peripheral neuropathy. The prevalence of peripheral neuropathy in youth with T1D increases over time, more than doubling after 5 to 10 years of follow-up [79].

In youth with T2D, recent but limited evidence from the SEARCH for Diabetes in Youth study estimates the prevalence of peripheral neuropathy to be between 22% and 26% [77,2]. While not necessarily reflected in the prevalence values reported in the extant literature, in direct comparisons between youth with T1D vs. T2D the SEARCH for Diabetes in Youth study has found significantly greater prevalence of peripheral neuropathy in T2D vs. T1D (22-26% vs. 7%) [77,80,2]. These data are consistent with other comparisons of diabetes-related complications between youth T1D and T2D and provide further evidence of a more severe clinical trajectory for youth with T2D. Further follow-up and surveillance-based research is needed to more fully understand the burden of peripheral neuropathy in youth with T2D.

In addition to peripheral neuropathy, individuals with youth-onset diabetes also present with serious DN complications such as cardiac autonomic neuropathy (CAN) [81,82]. Owing to its effect on the autonomic nerves that innervate blood vessels and the heart, CAN is a major contributor to mortality risk from cardiovascular disease in diabetes [83]. Thus, CAN is of considerable concern for the clinical course and long-term health of people with youth-onset diabetes. In a systematic review of the literature in young people with T1D, Tang and colleagues (2013) estimated the prevalence of CAN to be between 28% and 42%, depending on the measure used to quantify CAN (cardiovascular nerve function tests vs. pupillometry, respectively) [81]. More recent data from the SEARCH for Diabetes in Youth study estimates CAN prevalence to be approximately 12% in young people with T1D and 17% in T2D using measures of heart rate variability [82]. These SEARCH data highlight, again, the increased burden of DN in youth with T2D.

Symptoms and screening

Across both T1D and T2D, peripheral neuropathy preferentially involves sensory neurons. Sensory disturbances begin with a “glove and sock” pattern where distal regions of the body like the hands and feet are affected first. Structural abnormalities of the nerve fibers underlie the symptoms of peripheral neuropathy (i.e., numbness, neuropathic pain) and, interestingly, the pattern of structural nerve damage and nerve lesions in people with T1D

differs compared to people with T2D [84]. These differential patterns of structural nerve damage are yet to be replicated in comparisons of youth with T1D and T2D.

While research studies often use advanced imaging methods including magnetic resonance imaging for the detection of nerve damage as a subclinical indicator of peripheral neuropathy, clinical screening techniques for peripheral neuropathy are more straightforward and can be conducted by noninvasive physical examination. Specifically, tests of peripheral sensation by pinprick of the foot, ankle reflexes, vibration sensation via tuning fork, and examination of proprioception, or awareness of body positioning, are the most common (Table 1). A position statement released in 2017 by the ADA recommends screening for peripheral neuropathy at least annually [85]. The physical screening tests that are applied in adults, such as the monofilament test and tuning fork test, however, are shown to have poor sensitivity in pediatric populations with diabetes [86,87]. For example, in a sample of children with T1D, Hirschfeld and colleagues (2014) found that the tuning fork test for vibration sensation yielded a sensitivity of 0% [87]. These data, among others, challenge the diagnostic utility of noninvasive screening tests in young people with diabetes and suggest that gold standard metrics such as nerve conductance tests be applied where peripheral neuropathy is suspected.

Screening for CAN is more involved than tests of peripheral neuropathy and can include measures of heart rate variability and quantification of the QT interval via electrocardiography. Unfortunately, despite the severity of CAN, its early stages are more often asymptomatic. Symptoms of CAN include resting tachycardia, loss of heart rate variability, exercise intolerance, and silent ischemia. In their position statement, the ADA recommend screening of patients with diabetes who demonstrate any microvascular or neuropathic complications [85]. Thus, young people with diabetes who present with symptoms of peripheral neuropathy should also be screened for CAN, when possible.

Risk factors

Poor glycemic control is a central and dominating risk factor in the development and progression of peripheral neuropathy in youth and adults with diabetes, particularly in T1D [77,88]. Additionally, peripheral neuropathy is closely linked with obesity [84,88] and the milieu of the metabolic syndrome [89], including hypertension and dyslipidemia in young people with T1D [77] and with T2D [90,77]. It is important to note that the major risk factors for peripheral neuropathy are distributed differently in youth with T1D as compared to youth with T2D, suggesting that the pathophysiology of peripheral neuropathy may also be different between diabetes types. Further, in a study conducted by Jende and colleagues (2018) where direct comparison was made between older adults with T1D and T2D, the researchers found distinct risk factor profiles for the differential patterns of nerve damage between the diabetes groups as poor glycemic control was associated with nerve lesions in T1D, while dyslipidemia was associated with nerve lesions in T2D [84].

Like peripheral neuropathy, SEARCH also found that the major risk factors for CAN in youth with diabetes included poor glycemic control and elevated triglycerides [82], suggesting that DN of all major types could co-occur in youth with suboptimal glucose and lipid profiles. However, the evidence in young people with T2D remains severely limited,

and research is urgently needed to build robust DN risk profiles in this group to better understand the disease processes and develop potential interventions to limit the progression of peripheral and autonomic neuropathies.

Treatment

To date, treatments have not been shown to successfully repair the nerve damage that underlies DN. However, pharmacologic interventions are prescribed to treat the risk factors for DN with the goal of stopping or slowing the progression of nerve damage. Major risk factors for DN such as poor glycemic control and dyslipidemia are managed by a variety of anti-diabetic therapies and lipid-lowering medications. Although, direct effects of such treatments on halting the progression of DN have not been studied in young people with diabetes (Table 2). Thus, treatment trials focused on DN as the primary outcome are needed to investigate the effectiveness of current glycemic and lipid management interventions on DN development and progression in youth with diabetes.

Conclusion and future directions

Microvascular complications in youth-onset diabetes are unique with respect to presentation, diagnosis techniques, and treatment when compared to complications seen in adults. While adults exhibit more “hard” clinical outcomes from diabetes-related microvascular complications including partial or complete kidney failure from DKD or amputations from diabetic peripheral neuropathy, these changes are typically not observed in pediatric populations with diabetes. Subclinical signs and symptoms of microvascular damage are more likely to be present in young people with diabetes and this could possibly explain the decreased sensitivity of some adult screening tools for microvascular complications in youth-onset diabetes. Additionally, youth-onset diabetes is uniquely impacted by hormonal changes secondary to puberty, the long-term effects of which we are only beginning to understand [91]. Thus, greater emphasis should be given to developing screening protocols with higher sensitivity for subclinical indicators of microvascular complications in youth with diabetes.

The advancement of our knowledge of microvascular complications and their treatments in youth with diabetes hinges on deepening our understanding of the phenotypic differences between youth and adults, and between individuals with T1D and T2D. First, to help expand our knowledge of DKD, studies that support an integrated approach assimilating data from functional imaging, clearance studies for intraglomerular hemodynamic function, and kidney biopsies for histopathological and molecular analysis could serve as the key to understanding the underlying mechanisms of DKD. Further therapeutic research studies that take these mechanisms into consideration, and possibly leverage the use of advancements in technology and/or adjunctive medications approved for adult-onset diabetes, are needed to prevent the development and progression of DKD in youth-onset diabetes. Second, potential considerations for further research in diabetic retinopathy include longitudinal studies and trials that leverage innovations in diagnostic tools by integrating fundus photography, OCT, and ERG to define the earliest changes in the neural and vascular architecture of the retina. Additional avenues include dedicated studies in young people with T1D and T2D

and retinopathy outcome trials evaluating novel therapies, including SGLT2is to mitigate progression of early diabetic eye disease. Lastly, due to the frequently asymptomatic presentation of diabetic neuropathy in pediatrics, the development of more highly sensitive screening methods is warranted, in addition to work establishing the effectiveness of current diabetes therapies in slowing the development and progression of peripheral and autonomic neuropathies. While the need for additional microvascular complications research studies in youth with diabetes is vast, improvements in long-term kidney, eye, and nerve disease outcomes in youth-onset diabetes are essential to reduce the high associated morbidity and mortality.

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Multiple Choice Questions:

1. You are seeing a 14-year-old female patient who has had type 1 diabetes for a total of 5 years in diabetes clinic. Your patient and her family are interested in learning more about the complications of diabetes. Which of the following do you advise the family is the most common microvascular complication of diabetes?

- **a.** Diabetic kidney disease
- **b.** Diabetic eye disease
- **c.** Diabetic nerve disease
- **d.** Cardiovascular disease

2. Which of the following most accurately describes the onset and progression of diabetic kidney disease in children with type 2 diabetes compared to children with type 1 diabetes?

- **a.** Diabetic kidney disease is more prevalent at onset in type 2 diabetes, but available evidence suggests it progresses at a slower rate.
- **b.** Diabetic kidney disease is more prevalent at onset in type 2 diabetes, and available evidence suggests it progresses at a faster rate.
- **c.** Although early diabetic kidney disease may exist at diagnosis in type 2 diabetes, the long-term risk of chronic kidney disease progression is similar to type 1 diabetes.
- **d.** It is extremely rare for early diabetic kidney disease to be present at diagnosis in either type 1 or type 2 diabetes, and the risk of long-term progression of chronic kidney disease is similar for both conditions.

3. You are caring for an 18-year-old male patient with type 2 diabetes who has recently developed worsening albuminuria, which has now progressed to macroalbuminuria. He is currently receiving treatment with metformin and lisinopril. His HbA1c is above target at 7.5% and he has a normal serum creatinine. Which of the following is the best option to improve his long-term kidney outcome?

- **a.** Initiation of long-acting insulin
- **b.** Addition of an angiotensin-receptor blocker (ARB)
- **c.** Initiation of a glucagon-like peptide 1 receptor agonist (GLP-1 RA)
- **d.** Initiation of a sodium-glucose co-transporter 2 (SGLT2) inhibitor

4. Which of the following most accurately describes the patient that is at highest risk for developing retinopathy?

a. A 16-year-old male patient with type 1 diabetes diagnosed at 15 years of age with an HbA1c of 7.5% and no microalbuminuria.

b. An 8-year-old male patient with type 1 diabetes diagnosed at 2 years of age with an HbA1c of 8% and no microalbuminuria.

c. A 16-year-old female patient with type 1 diabetes diagnosed at age 7 years with an HbA1c of 11% and microalbuminuria.

d. An 18-year-old female patient with type 1 diabetes diagnosed at age 15 years with an HbA1c of 9% and microalbuminuria.

5. You are evaluating a 16-year-old male with a 4-year history of very poorly controlled type 2 diabetes (HbA1c >14% now) on combination therapy with metformin and long-acting insulin who presents with numbness and tingling in his bilateral lower extremities. What is your next step for further evaluation and/or treatment of this finding?

a. Order cardiovascular reflex testing including heart rate variability and an EKG to evaluate the QT interval.

b. Start treatment with gabapentin.

c. Recommend improved glycemic control and increase the patient's long-acting insulin by 20%.

d. Start treatment with a glucagon-like peptide 1 receptor agonist (GLP-1 RA).

Summary Points

1. Microvascular complications including diabetic kidney disease, retinopathy, and neuropathy are widely prevalent in youth with type 1 and type 2 diabetes; yet, these complications are frequently underdiagnosed and undertreated, thus placing these individuals at significantly higher risk for diabetes-related morbidity and mortality.

2. Diabetic kidney disease arises primarily from glomerular and tubular damage sustained from a combination of factors including hyperglycemia and glomerular hypertension with associated hyperfiltration; thus, first-line treatments center on the normalization of glycemia and the use of renin-angiotensin system blockers to reduce intraglomerular pressure.

3. Retinopathy is the most common microvascular complication in youth with diabetes and loss of glycemic control and concurrent diabetic kidney disease remain the most significant risk factors for the development of retinopathy in youth with diabetes.

4. Distal symmetric polyneuropathy is the most common neuropathy associated with a diagnosis of diabetes in youth and it can co-exist with cardiac autonomic neuropathy, a significant risk factor contributing to morbidity and mortality related to cardiovascular disease.

5. Future large, prospective pediatric outcome trials are needed to investigate the use of singular and combination pharmacological therapies for the treatment of microvascular complications in youth with type 1 and type 2 diabetes.

Multiple Choice Question Answers:

1. B
2. B
3. D
4. C
5. A

Table 1.

Screening Recommendations for Microvascular Complications in Type 1 Diabetes and Type 2 Diabetes

Microvascular Disease Screening	Type 1 Diabetes		Type 2 Diabetes	
	Pediatrics [29,3]	**Adults [92]**	**Pediatrics [29,93]**	**Adults [92]**
Diabetic Kidney Disease				
Initiation	- At puberty or >10 years of age, whichever is earlier, when T1D duration is ≥5 years [29] - T1D for >2-5 years or ≥11 years of age, whichever is earlier [3]	T1D for ≥5 years	T2D diagnosis	T2D diagnosis
Frequency	Annually	*Normal kidney function:* - Annually *UACR >30 mg/g or eGFR <60 mL/min/1.73m^2*: - Twice annually	Annually	*Normal kidney function:* - Annually *UACR >30 mg/g or eGFR <60 mL/min/1.73m^2*: - Twice annually
Method	First morning UACR and based on 2/3 positive samples, eGFR via validated pediatric formula	UACR, eGFR via validated adult formula	UACR, eGFR via validated pediatric formula	UACR, eGFR via validated adult formula
Diabetic Eye Disease				
Initiation	- T1D for 3-5 years and at puberty or ≥11 years of age, whichever is earlier [29] - T1D for >2-5 years or ≥11 years of age, whichever is earlier [3]	Within 5 years of T1D diagnosis	T2D diagnosis	T2D diagnosis
Frequency	- Every 2 years [29,3] - At initiation of intensive anti-glycemic treatment, then every 3 months for 6-12 months thereafter [3]	*Normal eye exam:* - Every 1-2 years *Retinopathy:* - At least annually	Annually	*Normal eye exam:* - Every 1-2 years *Retinopathy:* - At least annually
Method	Dilated, comprehensive fundoscopic exam or retinal photography	Dilated, comprehensive fundoscopic exam	Dilated, comprehensive fundoscopic exam or retinal photography	Dilated, comprehensive fundoscopic exam
Diabetic Neuropathy				
Initiation	- T1D for ≥5 years and at puberty or ≥10 years of age, whichever is earlier [29] - T1D for >2-5 years or ≥11 years of age, whichever is earlier [3]	T1D for ≥ 5 years	T2D diagnosis	T2D diagnosis
Frequency	Annually	Annually	Annually	Annually
Method	- Comprehensive foot exam (inspection, pulses, determination of proprioception, vibration, assessment of symptoms of neuropathic pain) [29,3] - Orthostatic, heart rate variability [3]	Comprehensive foot exam (pinprick/temperature and 10-g monofilament sensation, vibration via a 128-Hz tuning fork)	Comprehensive foot exam (inspection, pulses, pinprick and 10-g monofilament sensation, vibration via a 128-Hz tuning fork, ankle reflexes)	Comprehensive foot exam (pinprick/ temperature and 10-g monofilament sensation, vibration via a 128-Hz tuning fork)

Abbreviations: T1D = type 1 diabetes, T2D = type 2 diabetes, UACR = urine albumin to creatinine ratio, eGFR = estimated glomerular filtration rate.

Table 2.

Intervention Trial Outcomes

	Population	Study Design	Intervention	Outcomes	Results
Medical Trials					
Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) [94]	Youth aged 10-16 years with T1D: - 4407 screened - 1287 with elevated UACR - 443 randomized	Minimum 2-year duration randomized, double-blind, placebo-controlled trial of Angiotensin Converting Enzyme (ACE) inhibitors and statins in the prevention of long- term complications in youth with T1D	- Atorvastatin 10 mg QD - Quinapril 5 mg QD x 14 days > 10 mg QD ARM 1: statin + placebo ACE inhibitor ARM 2: ACE inihibtor + placebo statin ARM 3: placebo ACE inhibitor + placebo statin ARM 4: ACE inhibitor + statin	Primary outcome: - ΔUACR (adjustments made for age, gender, and diabetes duration) Secondary outcomes: - ΔCVD markers (cIMT, FMD, EndoPAT, PWV, blood pressure, lipids, hsCRP) - ΔGFR - ΔRetinopathy (retinopathy scores and retinal microvascular structure - ΔQuality of life and health economics	Use of ACE inhibitor, statin, and/or a combination of the two did not affect UACR over time.
Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) [95,10]	Youth aged 10-17 years with T2D of <2 years duration - 699 randomized - 319 achieved primary outcome	Minimum 2-year duration randomized trial of Metformin, Rosiglitazone, and lifestyle management in the prevention of treatment failure based on glycemic control	- Metformin 1,000 mg BID - Rosiglitazone 4 mg BID - Lifestyle management ARM 1: Metformin alone ARM 2: Metformin + Rosiglitazone ARM 3: Metformin + Lifestyle management	Primary outcome: - Loss of glycemic control (HbA1c ≥8% x 6 months, inability to wean insulin within 3 months of initiation, or occurrence of a second episode within three months of discontinuing insulin) Secondary outcomes: - ΔInsulin sensitivity - Safety - ΔInsulin secretion - ΔBody composition (BMI, waist circumference, fat mass, bone density) - ΔHypertension - ΔDyslipidemia	Rates of glycemic failure were 51.7%, 38.6%, and 46.6% for metformin alone, metformin plus rosiglitazone, and metformin plus lifestyle intervention, respectively. ARM 2 was superior to ARM 1 (p=0.006) and ARM 3 was intermediate. Microalbuminuria increased over time regardless of study arm and was related primarily to degree of glycemia.
Effects of Metformin on Cardiovascular Function in Adolescents with Type 1 Diabetes (EMERALD) [96]	Youth aged 12-21 years with T1D - 52 randomized	3-month randomized, placebo-controlled trial of Metformin 1,000 mg BID	- Metformin 1,000 mg BID - Identical-appearing placebo ARM 1: Metformin ARM 2: Placebo	Primary outcome: - ΔInsulin sensitivity Secondary outcomes: - ΔADP time constant - ΔPulse wave velocity - ΔCentral arterial intimal medial thickness - ΔCardiac function on ECHO - ΔAortic wall sheer stress	Metformin improved insulin sensitivity, ascending aorta pulse wave velocity and wall sheer stress, and far wall diastolic carotid intima-media thickness. Metformin was associated with an increase in eGFR by serum creatinine but not by cystatin C. There was no change in UACR.
Liraglutide in Children and Adolescents with Type 2 Diabetes (ELLIPSE) [97]	Obese youth aged 10-17 years with T2D - 135 randomized - 118 completed 26 weeks - 109 completed 52 weeks	26-week randomized, double-blind, placebo-controlled trial of Liraglutide and Metformin with a 26-week extension period	- Liraglutide 1.8 mg subQ QD (or highest tolerated dose) - Metformin 1,000-2,000 mg QD ARM 1: Liraglutide + Metformin ARM 2: Placebo + Metformin	Primary outcome: - ΔHbA1c Secondary outcomes: - ΔFasting plasma glucose, other glycemia endpoints - Hypoglycemia, other adverse events - ΔHOMA-B, HOMA-IR - ΔBody composition (BMI), weight, blood pressure, pulse, lipids - ΔGrowth, Tanner stage, bone age	Liraglutide up to 1.8 mg QD plus metformin, with or without basal insulin, improved glycemic control over 52 weeks and was largely limited to gastrointestinal side effects.
Acute Effect of Empagliflozin on	Youth aged 10-17 years	Open-label, randomized,	- Empagliflozin 5, 10, or 25 mg	Primary outcome: - Pharmacokinetic and	Empagliflozin was associated with increased

	Population	Study Design	Intervention	Outcomes	Results
Fractional Excretion of Sodium and eGFR in Youth with Type 2 Diabetes [98]	with T2D - 27 randomized	parallel-group study of a single dose of Empagliflozin at 5, 10, or 25 mg		pharmacodynamic data to identify the safe-effective dose Secondary outcomes: - Δ24-hour urinary glucose excretion - ΔFasting plasma glucose - 8-point plasma glucose profile	natriuresis, as seen with an adjusted mean Fe_{NA+}, and a decrease in eGFR from baseline (p=0.006 and p=0.0006, respectively), suggesting a reduction in intraglomerular pressure.
Surgical Trials					
Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) [99]	Severely obese youth aged 12-19 years approved to undergo bariatric surgery - 242 included	3-year prospective, observational cohort study	Bariatric surgery: - Roux-en-Y gastric bypass - Sleeve gastrectomy - Adjustable gastric band	Primary outcomes: - ΔBMI - ΔNumber of participants achieving T2D remission - ΔNumber of participants achieving remission from hypertension Secondary outcomes: - Number of participants who develop hypoferritinemia and/or hypovitaminosis B12 - Number of occurrences of abdominal reoperations	Mean BMI decreased (50.5 kg/m^2 to 36.2 kg/m$^{2)}$ at 3-year follow up. Participants with baseline eGFR <90 mL/min/1.73m^2, mean±SD eGFR improved (76±12 mL/min/1.73m^2 to 102±28 mL/min/1.73m$^{2)}$ at 3-year follow-up (p<0.0001). Participants with baseline UACR ≥30 mg/g improved significantly after surgery: geometric mean (95% CI) 74 mg/g (45-121) to 17 mg/g (10-28) at 3 years (p<0.0001). Participants with normal kidney function and no albuminuria at baseline remained stable.
Combined Medical and Surgical Trial Analyses					
Teen-LABS vs. TODAY [100]	Obese youth of similar age and racial distribution - 30 from Teen-LABS with T2D at time of bariatric surgery (24 Roux-en-Y and 6 sleeve gastrectomy) - 63 from TODAY	Participants with T2D in TODAY (irrespective of treatment group) were frequency matched to the Teen-LABS participants with T2D using the following matching criteria: baseline age (13–18 years), race/ethnicity, sex, and baseline BMI (>35 kg/m^2)	ARM 1: Bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy, or adjustable gastric band) ARM 2: Medical management (Metformin alone, Metformin plus Rosiglitazone, or Metformin plus lifestyle management)	Primary outcomes: - ΔBMI, HbA1c, insulin sensitivity, triglycerides Secondary outcomes: - ΔeGFR, hyperfiltration - ΔUACR and elevated UAE	Youth from TODAY receiving medical management demonstrated increased rates of hyperfiltration, elevated UACR, and hypertension over the 5-year study duration, while youth from Teen-LABS demonstrated regression of each of these outcomes, despite exhibiting worse baseline markers of kidney health.

Abbreviations: T1D = type 1 diabetes, T2D = type 2 diabetes, UACR = urine albumin to creatinine ratio, GFR = glomerular filtration rate, eGFR = estimated glomerular filtration rate, ACE inhibitor = angiotensin converting enzyme inhibitor, CVD = cardiovascular disease, cIMT = carotid intima-media thickness, FMD = flow-mediated dilation, PWV = pulse wave velocity, hsCRP = highly sensitive c-reactive protein, HbA1c = hemoglobin A1c, BMI = body mass index, ADP = adenosine diphosphate, ECHO = echocardiogram, HOMA-B = homeostasis model assessment of beta-function, HOMA-IR = homeostasis model assessment of insulin resistance, Fe_{NA+} = fractional excretion of sodium, UAE = urinary albumin excretion.