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ISPAD GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2022: Microvascular and macrovascular complications in children and adolescents with diabetes

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1 | WHAT IS NEW OR DIFFERENT

1. Addition of screening and treatment recommendations for vascular complications in type 2 diabetes (T2D)
2. Update of urinary albumin/creatinine ratio (ACR) thresholds for the diagnosis of increased albuminuria
3. Recommendation for eGFR monitoring in young people with diabetes
4. Change in frequency of retinopathy screening for type 1 diabetes (T1D)

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

Screening for and prevention of complications (Table 1).

2.1 | Prevention

- Children and adolescents with diabetes should receive intensive education and treatment to prevent or delay the onset and progression of vascular complications. **A**
- Achievement of glycemic targets will reduce the risk for onset and progression of diabetes vascular complications. **A**
- Screening for vascular complications should be performed preconception and in each trimester of pregnancy. **B**

2.2 | Albuminuria

- Screening for increased albuminuria in T1D should start at puberty or from age 11 years, whichever is earlier, with 2–5 years diabetes duration, and repeated annually thereafter. **B**

- Screening for increased albuminuria in T2D should start at diabetes diagnosis and repeated annually thereafter. **B**
- Consider confirming persistently increased albuminuria by first morning urine sample for urinary albumin/creatinine ratio (ACR) to rule out orthostatic proteinuria. **E**
- Because of biological variability, it is recommended to use 2 of 3 urine samples over a 3–6-month period as evidence of increased albuminuria. Confounders are exercise, menstrual bleeding, urinary tract infections, fever, non-diabetic kidney diseases and marked hyperglycemia. It is advised to repeat abnormal screening tests because elevated albuminuria may be transient. **E**
- Consider screening of eGFR in T1D at puberty or from age 11 years, whichever is earlier, with 2–5 years diabetes duration. **E**
- Consider screening of eGFR starting at diabetes diagnosis in youth with T2D. **E**
- Consider work-up for non-diabetic kidney disease in all children and adolescents with T2D and T1D with Chronic Kidney Disease (CKD) stage A3 (UACR >300 mg/g or 30 mg/mmol) or G2-5 (eGFR <90 ml/min/1.73m^2) including urinalysis, renal ultrasound and immune work-up. **E**
- Optimize glycemia to prevent the onset and progression of albuminuria. **B**
- Optimize blood pressure (BP) to prevent the onset and progression of albuminuria. **B**
- Consider angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in adolescents with persistently elevated albuminuria to prevent progression to proteinuria. **E**
- Monitoring for changes in BP, serum creatinine and potassium within 2 weeks of initiation of an ACE inhibitor or ARB, and annually thereafter. **E**
- Consider holding ACE inhibitors or ARB during episodes of dehydration and DKA. **E**
- Contraception counseling is required in post-pubertal females with diabetes that are treated with an ACE inhibitors or ARB due to potential teratogenicity. **E**

2.3 | Retinopathy

- Screening for diabetic retinopathy (DR) should start at puberty or from age 11 years with 2–5 years diabetes duration. **B**
- Screening for DR in T2D should start at diabetes diagnosis. **C**
- Screening for DR should be performed by an ophthalmologist, optometrist, or a trained experienced observer through dilated pupils via bio-microscopy examination or fundal photography. **B**
- For those with diabetes duration less than 10 years, mild non-proliferative DR (NPDR, i.e., microaneurysms only) and optimal glycemic targets, biennial screening assessment is recommended. The frequency of retinopathy screening can be reduced to 3 years if there is no retinopathy at first assessment but needs to be more frequent if there are high-risk features for visual loss. **E**
- Because of potential worsening of DR in people with diabetes with long-standing suboptimal glycemia that subsequently rapidly improves, ophthalmological monitoring is recommended before initiation of intensive treatment and at 3-monthly intervals for 6–12 months thereafter, particularly if moderate NPDR or worse at the time of intensification. **E**
- Prompt referral of young people with diabetes with vision threatening retinopathy (severe NPDR or worse and/or diabetic macular edema [DME]) to an ophthalmologist with experience in the management of DR is recommended. **A**
- Laser treatment and intravitreal injections of anti-VEGF agents reduce the rate of visual loss for individuals with vision-threatening stages of retinopathy (severe NPDR or worse and/or DME). **A**

TABLE 1 Screening recommendations for vascular complications

	When to commence screening?	Screening methods
Nephropathy	**T1D:** at puberty or age 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Urinary ACR Confirm with 1st morning urine sample Frequency: annually
Retinopathy	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Fundus photography or mydriatic ophthalmoscopy Frequency: every 2–3 years
Neuropathy	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	History Physical examination Clinical tests Frequency: annually
Macrovascular disease	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Lipid panel every 3 years BP at least annually; ideally at every clinic visit

2.4 | Other ocular conditions

- A comprehensive eye examination is also recommended to detect cataracts, major refractive errors, or other ocular disorders at the time of retinopathy screening or earlier if there are any visual disturbances. **E**

2.5 | Neuropathy

- Screening for peripheral neuropathy in young people with T1D should start at puberty or from age 11 years with 2–5 years diabetes duration and be repeated annually thereafter. **B**
- Screening for diabetic neuropathy in T2D should start at diabetes diagnosis and be repeated annually thereafter. **B**
- Screening for peripheral neuropathy includes assessment of temperature or pinprick sensation, vibration and ankle reflexes.

Screening for cardiac autonomic neuropathy includes assessment of orthostasis and heart rate variability (HRV). **E**

2.6 | Blood pressure

- Measure BP at least annually and preferably at every clinic visit from diagnosis of T1D or T2D. **E**
- For people with diabetes <13 years of age hypertension is defined as average systolic (SBP) and/or diastolic BP (DBP) ≥ 95th percentile for sex, age, and height on three or more occasions. For people with diabetes ≥13 years of age, hypertension is defined as average SBP and/or DBP ≥130/80 mm Hg. **B**
- Consider use of 24 h ambulatory BP measurements for screening and especially confirmation of hypertension. **E**
- Initial treatment of hypertension consists of weight loss, limitation of dietary salt, and increased physical activity. **E**
- If unable to achieve normal BP after 6 months of lifestyle interventions, an ACE inhibitor or other BP lowering agent is recommended. **E**
- ACE inhibitors have been effective and safe in children in short-term studies **A**, but are not safe during pregnancy, which needs to be discussed with young women of childbearing potential. **B**

2.7 | Lipids

- Screening for dyslipidemia is recommended soon after diagnosis (when glycemia is stabilized) in all young people with T1D from age 11 years. **E** If lipid levels are normal, repeat screening every 3 years. If there is a family history of hypercholesterolemia, early cardiovascular disease (CVD) or if the family history is unknown, start screening as early as age 2 years. **E**
- Screening for dyslipidemia in T2D should start at diabetes diagnosis (when glycemia is stabilized) and repeated annually. **C**
- Screening with a fasting lipid profile is ideal but often not practical in youth with diabetes. Non-fasting lipids screening may be obtained and if triglycerides or LDL levels are elevated, a fasting lipid profile would then be indicated. A fasting sample is required to monitor therapy. **E**
- High LDL cholesterol is defined as >2.6 mmol/L (100 mg/dL). **E** If this is present then interventions to improve glycemia, dietary changes and increased exercise should be instituted. Dietary interventions should restrict saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day and around 10% of calories from monounsaturated fats.
- If the above interventions do not lower LDL cholesterol <3.4 mmol/L (130 mg/dL), statins may be considered in children from age 10 years (Table 2). **E**
- Contraception counseling is required in post-pubertal females with diabetes who are treated with statins due to their potential teratogenicity. **E**

TABLE 2 Recommended threshold values for different parameters for intervention and primary prevention of microvascular and CVD in children and adolescents with T1D

Threshold value	Type of intervention
<13 years: BP >90th percentile for age, sex and height ≥13 years: BP >120/80 mm Hg	Lifestyle intervention: exercise, diet and less screen time
<13 years: BP >90th percentile despite lifestyle intervention ≥13 years: BP >120/80 mm Hg despite lifestyle intervention	ACE inhibitor or other BP lowering agent If elevated albuminuria is present: ACE inhibitor or ARB
<13 years: BP >95th percentile for age, sex and height ≥13 years: BP > 130/90 mm Hg	Lifestyle intervention and ACE inhibitor or other BP lowering agent If elevated albuminuria is present: ACE inhibitor or ARB
LDL-cholesterol >2.6 mmol/L (100 mg/dL)	Dietary and lifestyle intervention
LDL-cholesterol >3.4 mmol/L (130 mg/dL)	Statin

2.8 | Lifestyle

- Prevention or cessation of smoking will reduce progression of albuminuria and cardiovascular disease. **B**

2.9 | Macrovascular disease

- Screening of BP and lipids is recommended, as above. The benefit of routine screening for other markers of macrovascular complications outside the research setting is unclear. **E**

2.10 | Type 2 diabetes

- Screening for all complications should commence at diagnosis. Attention to risk factors should be escalated because of the increased risk of complications and mortality. **B** (See also the ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes).

3 | INTRODUCTION

The long-term vascular complications of diabetes include diabetic kidney disease (DKD), retinopathy, neuropathy, and macrovascular disease. The outcomes are:

- Kidney failure and hypertension due to DKD.

- Visual impairment and blindness due to DR.
- Pain, paresthesia, and loss of sensation due to peripheral neuropathy.
- Postural hypotension, gastroparesis, diarrhea, bladder paresis, and impotence, due to autonomic neuropathy.
- Cardiac disease, peripheral vascular disease, and stroke due to macrovascular disease.

These guidelines include evidence-based recommendations for prevention, screening, and treatment of these complications. Complementary information and guidance will also be provided in the ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes in the Youth and Chapter 25 on Managing Diabetes in Limited-Resource Setting.

Clinically evident diabetes-related vascular complications are rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of T1D, and already at onset in T2D. Please note that detailed management of advanced disease will not be covered in this chapter.

Childhood and adolescence are periods during which intensive education and treatment may prevent or delay the onset and progression of complications.[1] There has been a declining incidence of vascular complications in T1D reported in many areas with specialized clinics.[2,3] This has occurred over a period of time during which there have been major changes in and intensification of diabetes management, better identification of risk factors, and the advent of regular screening for complications. There is no evidence that this is a worldwide occurrence: in areas where health care is suboptimal, a greater risk of complications remains.[4] Overall, vascular complications continue to be a key contributor to premature mortality in young people with onset of diabetes during childhood.[5,6]

Although youth-onset T2D remains an uncommon disease in many countries, the incidence of this condition is projected to increase by 600% from 2017 to 2060.[7,8] Compounding this increase, youth-onset T2D exhibits a more extreme metabolic phenotype compared to adult-onset T2D, including greater insulin resistance and more rapid deterioration of pancreatic β-cell function.[9,10] These factors contribute to increased risk for vascular complications,[10–14] as highlighted in a recent systematic review,[15] and data from the 2021 Treatment Options for T2D in Adolescents and Youth (TODAY) 2 outcome study.[16] The burden of micro- and macrovascular complications is greater in youth-onset T2D compared to youth-onset T1D.[11]

3.1 | Interventional studies of intensive glycemic management

The diabetes control and complications trial (DCCT) was a multicenter, randomized controlled trial (RCT) involving 1441 people with diabetes with T1D conducted in North America from 1983 to 1993.[17] Study participants included 195 adolescents (aged 13–17 years), who were randomized to either intensive or conventional treatment. The DCCT provided unequivocal evidence that intensive diabetes treatment and improved glycemia conferred a significant risk reduction for microvascular complications compared with conventional treatment.[17] After completion of the DCCT (a median duration of participation of 6.5 years in the whole group), the epidemiology of diabetes interventions and complications (EDIC) study continued to follow the cohort. The EDIC study demonstrated that the positive effect of earlier intensive treatment continued after the end of the intervention: that is, that there was a "metabolic memory" effect of improved glycemia, now referred to as a "legacy effect."[18–20] During the EDIC study, a positive effect of the intensive therapy on macrovascular disease was also identified with a 50% reduction in cardiovascular events over 17 years[21,22] Benefits have persisted after 30 years of follow-up, resulting in substantial benefits in the incidence of retinopathy (5% vs. 45%), kidney failure (0% vs. 5%), clinical neuropathy (15% vs. 50%), myocardial infarction (3% vs.5%), stroke (3% vs. 5%) and death (6% vs. 20%). In addition, there was a gain of 1.62 quality of life years and reduced healthcare costs.[15,23]

Contemporary long-term follow-up studies continue to support the importance of achieving glycemic targets as the most important determinant of vascular complications in youth with T1D.[24] Similarly in the TODAY2 study, HbA1c was among the strongest risk factors for the onset of micro- and macrovascular complications over 15 years in youth with T2D.[16]

3.2 | Other risk factors for the development of complications

Longer duration of diabetes, older age and puberty are well-known risk factors for complications. In addition, a higher prevalence of microvascular complications has been reported for adolescent girls compared with boys.[25,26] The pre-pubertal years of diabetes duration have a significantly lesser impact on complication.[27] However the risk of vascular complications is greater for those living with diabetes during puberty, compared to young people who develop diabetes after puberty.[28] For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated albumin excretion rate.[29] Longitudinal studies have also reported that younger age of T1D onset, particularly before puberty, is associated with a longer time free of complications such as nephropathy and retinopathy,[27] but in the long-term this initial advantage disappears.[25] A recent study has developed a prediction model for kidney failure in adults with T1D, which includes age, sex, diabetes duration, estimated glomerular filtration rate (eGFR), albuminuria, systolic BP, HbA1c, smoking, and previous cardiovascular disease (CVD).[30] Incorporation of such models in clinical practice may have the potential to individualize care according to individual risk.

High rates of cardiovascular risk factors have been reported in children and adolescents with T1D.[5,31–33] The SEARCH study reported that 26% youth with T1D were overweight, 14% had obesity, 13% hypertension, and 29% dyslipidemia.[5] Of note, a clustering of these risk factors was associated with high rates of multiple vascular complications.[23] The prevalence of cardiometabolic risk factors increases with long T1D duration; however, they can be present even shortly after diagnosis.[33,34]

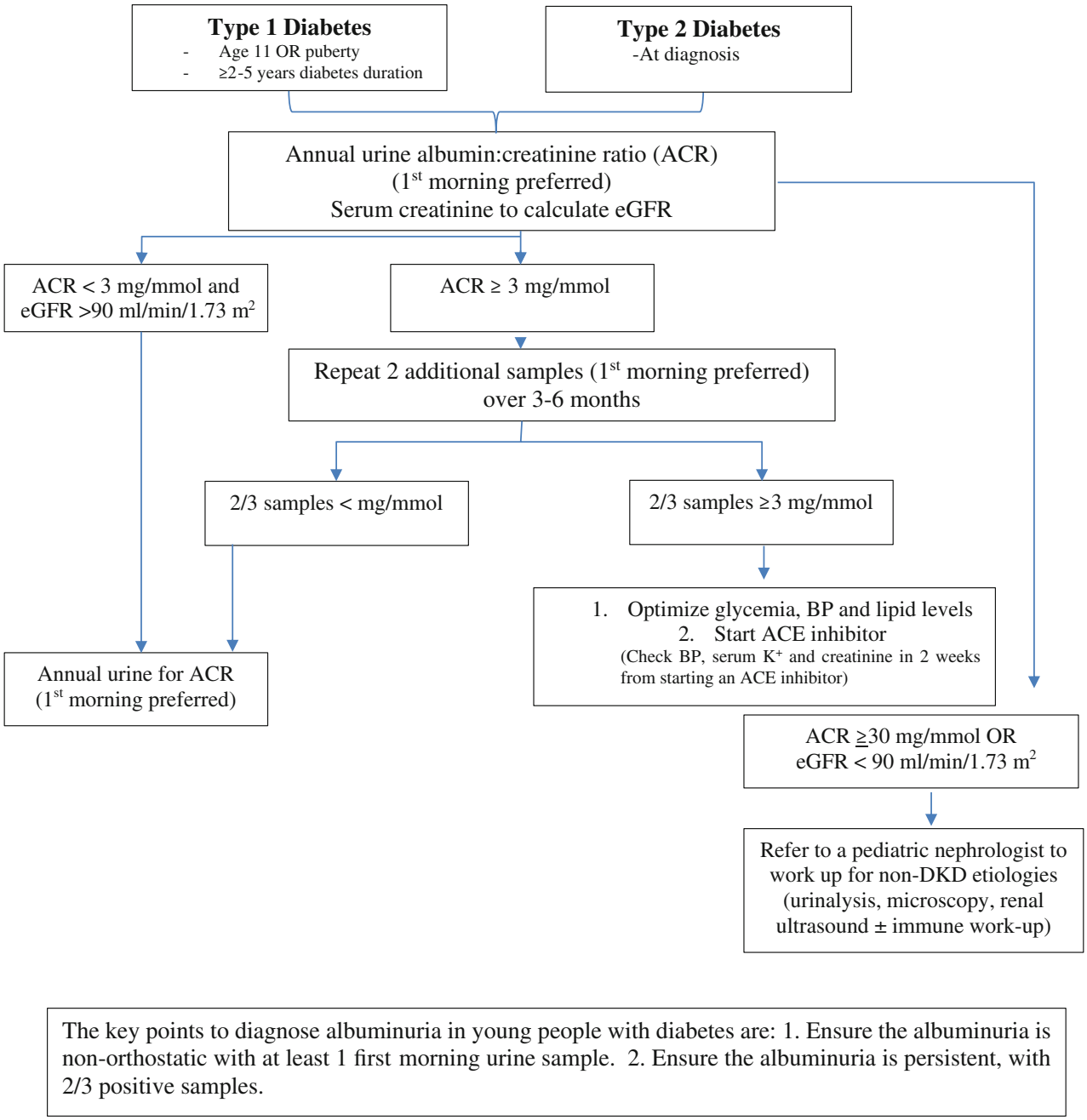

FIGURE 1 Diabetes kidney disease (DKD) screening algorithm in young persons with type 1 and 2 diabetes

Smoking is associated with an increased risk of developing persistent albuminuria.[35] The evidence for the effect of smoking on retinopathy is less clear. T1D and smoking interact to produce excess cardiovascular morbidity and mortality.[36]

High BP and alterations in the circadian BP rhythm have been associated with the risk of developing nephropathy, retinopathy and neuropathy in youth with T1D[37–39] Hypertension has a greater impact on CVD in individuals with than without diabetes,[40] and BP management is effective in decreasing cardiovascular morbidity and mortality in diabetes.[41]

Dyslipidemia was associated with DKD, retinopathy, neuropathy, and CVD in the DCCT/EDIC and other studies.[42–44] This included higher total LDL cholesterol and non-HDL cholesterol levels, as well as larger LDL particle size and higher apolipoprotein B.

Family history of CVD or the presence of risk factors for CVD increases the risk for DKD.[45–47] Higher BMI is a risk factor for nephropathy,[48,49] retinopathy,[50] neuropathy,[51] and CVD.[52] Indeed, a recent study found that higher BMI portends a more abnormal cardiovascular profile among adolescents with T1D, which is similar to, or less favorable than, youth with T2D on numerous metrics.[53]

Lifestyle issues also contribute to risk of complications; sedentary men with diabetes have higher mortality than active individuals.[54] Celiac disease is also an independent risk factor for retinopathy and early elevation of albuminuria in young people with T1D.[55,56]

In the TODAY2 study the major risk factors for microvascular complications in youth-onset T2D included BMI, insulin resistance, hypertension, and dyslipidemia.[16]

4 | DIABETIC KIDNEY DISEASE

Kidney complications are a major cause of morbidity and mortality among young adults with T1D. In their absence, mortality is similar to that in the general population, whereas it is significantly higher with elevated albuminuria.[57–59] The changes occurring in the kidney in individuals with T1D are generally classified into five stages, reflecting specific and progressive alterations in renal morphology and function. The earliest stage is characterized by glomerular hypertrophy, hyperfiltration and hyperperfusion. This is followed by a stage of subclinical morphological changes and increases in albumin excretion rates (AER) within the normal range.[60] Further increases in albumin excretion, with an AER between 30 and 300 mg/24 h or 20–200 μg/min in a 24-h or timed urine collection or an ACR between 3 and 30 mg/mmol (30–300 mg/g), indicate the development of moderately increased albuminuria (formerly referred to as microalbuminuria) (stage 3), which may further progress to severely increased albuminuria (formerly termed macroalbuminuria) (AER >200 μg/min or >300 mg/24 h; ACR >30 mg/mmol [>300 mg/g]) (stage 4) and, without any treatment, to kidney failure (stage 5) (Figure 1).[60,61]

CKD is defined as abnormalities of kidney structure or function, present for >3 months. CKD is now classified on Cause, GFR (G1-5) and Albuminuria category (A1-3) (KDIGO guidelines).[62] CKD, which is attributed to diabetes, is now called DKD. The prevalence of kidney failure is fortunately relatively rare in T1D.[63] In a Finnish cohort, the cumulative risk of kidney failure was 2.2% after 20 years and 7.0% after 30 years diabetes duration. The relative risk of kidney failure is as low as 0.13 (95% CI 0.08–0.22) in people diagnosed during more recent decades (2005–2011) compared to those diagnosed in 1965–1979.[64] A recent study with 50-year follow-up, however, identified kidney failure in more than 25% of the T1D population with 40 years of follow-up.[65]

Although advanced stages of DKD, such as overt proteinuria or kidney failure, are rare in children and adolescents with T1D, early structural and functional renal alterations develop soon after diagnosis of diabetes, and often progress during puberty. Rates of increased albuminuria in youth with T1D have decreased over time, likely reflecting improvements in glycemia. Data from historical cohorts,[25] such as the ORPS study, indicated a prevalence of microalbuminuria up to 26% after 10 years diabetes duration; whereas more recent studies report a prevalence between 4% and 9% after 4–8 years of diabetes duration.[11,66,67] Biopsy studies have shown that renal lesions, such as basement membrane thickening and mesangial expansion, can be detected in young normoalbuminuric individuals with T1D and these changes are predictive of subsequent albuminuria.[68]

In contrast, children and adolescents with T2D can have significant increased albuminuria at the time of diagnosis or early after diagnosis. The prevalence of increased albuminuria in a recent systematic review was 22.2% (95% CI 17.3%–27.4%).[69] Risk factors that increase the risk of non-DKD are more prevalent in adolescents with T2D, and especially in Indigenous populations,[70,71] impacted by the intergenerational effects of European colonization.[72,73] Important risk factors include exposure to diabetes in utero, the higher prevalence of obesity and immune-mediated kidney disease, such as IgA nephropathy, in Indigenous and Asian populations.[74,75] As such, many adolescents with T2D demonstrate histological findings not characteristic of DKD. In Canadian First Nation children, histologic changes include large glomeruli, focal, mild arteriolosclerosis, and focal and mild glomerular basement membrane thickening.[76]

Albuminuria has classically been considered the earliest clinical manifestation of DKD and a key risk factor for progression to proteinuria. However, 40%–50% of cases of increased albuminuria in youth with T1D can be transient or intermittent and thus not necessarily progress to more advanced stages of nephropathy.[25,77] However, as highlighted by recent studies, even if albuminuria regresses into the normal range, young people with diabetes with intermittent microalbuminuria have an increased cardio-renal risk.[25,78]

Extensive evidence indicates that increases in albumin excretion, even within the normal range, predict CVD risk in adults with T1D as well as in populations without diabetes.[79] In young people with T1D, early increases in AER can occur during the first years after diagnosis and can predict future risk of albuminuria and proteinuria.[80] In an incident cohort of childhood-onset T1D, after 6 years duration, early elevation of AER (>7.5 μg/min) was detected in 5% of children younger than 11 years and 25% of those older than 11 years. Comparing children before and after puberty, it was present in 5% compared to 26%.[81] There has been no secular reduction in AER or albuminuria in the same cohort that has shown a reduction in retinopathy: 24%–22% in the short duration cohort (2– < 5 years duration)[81]; and 45%–30% in the cohorts with median duration of 8.6 years.[3] Similar results have been reported in a study from Bangladesh.[82] The Adolescent T1D cardio-renal Intervention Trial (AdDIT) study showed that adolescents aged 10–16 years with increased urinary albumin excretion levels (upper tertile of the normal range) were at higher risk of developing not only elevated albuminuria but also had increased CVD risk, as indicated by higher carotid-intima media thickness, systolic BP, and high-sensitivity C-reactive protein levels, and higher risk of retinopathy progression.[83–85]

4.1 | Screening for albuminuria and abnormal eGFR

Albuminuria is one of the first markers of DKD.[61] Previously, ISPAD used sex-based criteria to define increased albuminuria. However, to align with international expert guideline recommendations,[62] a uniform definition of values ≥30 mg/g or 3 mg/mmol is now recommended.

Assessing ACR in a spot urine sample is the easiest method to carry out in an office setting and it generally provides accurate

information. First-voided urine in the morning is preferable because of the known diurnal variation in albumin excretion and postural effects. A random sample can be used but one should be aware that this is associated with an increased risk of false positive results. An abnormal screening value should be confirmed with at least one first morning urine collections. Timed overnight or 24-h collections are more burdensome and add little to prediction or accuracy.[86]

Confounding factors to be considered when screening for albuminuria include strenuous exercise, heat stress, urinary infections, kidney disease (i.e., IgA nephropathy or other types of nephritis, marked hyperglycemia, fever, and menstrual bleeding). All these factors can lead to elevated albuminuria.

Increased albuminuria is confirmed by finding 2 or all of 3 samples abnormal over a 3–6 month period. Persistently increased albuminuria predicts progression to kidney failure[87,88] and is associated with an increased risk of macrovascular disease and mortality.[79]

Regular follow-up is important to identify rapid or slow progression to albuminuria, as well as cases of regression to normoalbuminuria. Regular longitudinal follow-up of albuminuria is also important to identify young people with diabetes with progressive small increases of albuminuria within the normal range, which might be a prelude to the development of elevated albuminuria (previously "microalbuminuria").

It is also important to note that DKD can occur in the absence of increased albuminuria. Epidemiological studies suggest wide heterogeneity of DKD in T1D. For example, early progressive renal decline, defined as annual eGFR loss ≥3.3%, may precede the onset of microalbuminuria and its progression to macroalbuminuria.[89] Additionally, CKD in the absence of albuminuria is prevalent in people with T1D, supporting distinct pathways of DKD in T1D, including albuminuric CKD and normoalbuminuric CKD.[90] In fact, up to one-third of all cases of microalbuminuria (moderately elevated albuminuria) are known to regress to normoalbuminuria.[91] Therefore, the absence of albuminuria in a patient does not preclude DKD.

As albuminuria is not the only indicator of DKD, evaluation of kidney function is also important. Regular monitoring of eGFR is important to detect both declining kidney function and hyperfiltration, a potentially important risk factor early in the disease course. There are unfortunately limited studies that have evaluated the validity of eGFR equations in children with diabetes. Existing creatinine-based formulas have been shown to have poor agreement with urine creatinine clearance.[92] One study recently showed that the new sex-dependent CKiD equation[93] performed best in 53 children with T1D with respect to bias, precision and accuracy, compared with measured iohexol-based GFR.[94] The iCARE eGFR equation was developed and validated in Canadian First Nation children[95] with T2D, but warrants validation in additional cohorts, as well in those with T1D.

4.2 | Antihypertensive treatment for prevention of nephropathy

Effective antihypertensive therapy in young people with diabetes and nephropathy prolongs the time to ESKD.[96,97] A recent prospective study has shown further improvement in prognosis with preservation of renal function in those diagnosed with nephropathy after 2000, associated with better control of BP, greater use of renin-angiotensin aldosterone system (RAAS) inhibition, better control of lipids and glycemia and less smoking.[98]

In adults, ACE Inhibitors and ARBs reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria.[99,100] A systematic review and meta-analysis showed that in individuals with diabetes, only ACE inhibitors can prevent the doubling of serum creatinine compared to placebo.[101] In addition, in placebo-controlled studies, only ACE inhibitors (at the maximum tolerable dose) significantly reduced the risk of all-cause mortality.[102] Inhibitors of the RAAS slow progression of established advanced DKD, but the Renin Angiotensin System Study (RASS) demonstrated that RAAS blockade does not prevent the histologic or clinical features of DKD in early T1D.[103] A meta-analysis including trials comparing RAS blockers versus other antihypertensive agents in people with diabetes (and largely without albuminuria or proteinuria) did not show any superior effect of RAS blocker for the prevention of renal and cardiovascular outcomes, and suggest that that any class of antihypertensive agents can be used in people with diabetes especially in those without renal impairment.[104]

Despite the above evidence mainly from adult studies, there are still some concerns regarding the use of ACE Inhibitors in protecting long-term kidney function in young people without hypertension. In a meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria.[105] Young people with albuminuria would potentially be taking ACE inhibitors for decades. Side effects include cough, hyperkalemia, headache and impotence.[106,107] A key safety issue related to the use of ACE Inhibitors, as well as to ARBs, is the potential risk of congenital malformation when used during pregnancy. A 2012 systematic review has highlighted that fetal exposure to ACE inhibitors or ARBs has serious neonatal and long-term complications and recommended to improve awareness of these potential deleterious effects.[108] Therefore, when starting treatment with these drugs in adolescent girls, they must be made aware of this risk and contraception counseling must be provided.

Recent data from AdDIT, where 443 adolescents were randomized to treatment with an ACE inhibitor (Quinapril, 5 mg), a statin (Atorvastatin, 10 mg), a combination of both or placebo using a 2-by-2 factorial design, indicated that treatment with ACE inhibitors over 2–4 years in adolescents with T1D deemed to be at risk of complication based on their ACR in the upper tertile of the normal range is safe, with only few reported side effects, mainly hypotension (requiring dose reduction). Treatment with ACE inhibitors in this group did not have any significant effect on the primary outcome measure (change in area under the curve of $\log_{10}$ACR), but was associated with a 43% decrease in the secondary outcome, cumulative incidence of microalbuminuria during the 2–4 year treatment period, although this did not reach statistical significance.[109]

Sodium glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RA) are highly effective next

generation therapies that are already changing management of T2D.[110–113] These drugs have shown significant protective benefits with respect to progression of CKD[111] in at least 3 large RCTs. International guidelines for the management of adults with DKD now recommend SGLT2 inhibitors as first line therapies.[62] At this point they have not been approved for use in children; however, several trials are currently underway and their guidance will be available at the time of the next guideline.

5 | DIABETIC RETINOPATHY

DR is a progressive, potentially sight threatening disease of the retinal neuro-vasculature. Duration of diabetes, suboptimal glycemia, high BP and albuminuria are known risk factors contributing to the development of DR.[3,85,114,115] DR was defined and classified according to the International Clinical Diabetic Retinopathy Disease Severity Scale by Wilkinson et al.[116]

NPDR is characterized by microaneurysms, retinal hemorrhages (both pre- and intra-retinal), cotton wool spots related to ischemia and microinfarction, hard exudates due to protein and lipid leakage, intraretinal microvascular abnormalities (IRMAs) and venular dilatation and tortuosity. Mild (microaneurysms only) and moderate stages of NPDR are not vision-threatening and do not invariably progress to more severe stages of retinopathy.[117,118]

Severe NPDR (previously known as pre-proliferative) is characterized by vascular obstruction, increase in number of retinal hemorrhages and microaneurysms, IRMAs, marked venous abnormalities, and ischemia and infarctions of the retinal nerve fibers causing cotton wool spots.

Proliferative diabetic retinopathy (PDR) is characterized by neovascularisation in the retina and/or vitreous posterior surface. This can result in vision threatening events such as vessels rupturing with bleeding into the vitreoretinal space; and/or fibrosis and contraction resulting in traction retinal detachment, which can cause irreversible blindness.

DME/maculopathy is characterized by decreased vascular competence (increased vascular permeability) and microaneurysm formation, which produce exudation and swelling in the central retina.

The prevalence of any form of DR is variable in several studies and NPDR is common in children and adolescents with T1D.[119–121] Recent data from 156,090 individuals with T1D aged 10–21 years old (median T1D duration 5.2 years) from 11 countries showed an unadjusted prevalence of any DR of 5.8%. The variation across countries was 0%–16.2% with <1% youth having severe retinopathy. Four national registries reported rates >10%.[122]

Although the progression may be rapid, especially in those with suboptimal glycemia,[3,117,120,121,123] regression of DR can also occur with improved HbA1c levels.[124,125] Adolescents have a higher risk of progression to vision threatening stages of DR (severe NPDR or worse and/or DME) compared to adults with diabetes.[126] Hence, adolescence is the time when efforts should be directed to screening for early signs of DR and identification of modifiable risk factors. Regular screening for DR has reduced the proportion of blindness due to diabetes.[127]

In the UK a national screening program was introduced from 2002 with the initial age of screening starting at 12 years, because there were no reports of vision-threatening DR before this age.[128] Data from 2125 adolescents screened at age 12–13 years showed referral DR rates of less than 20%, but of these, three individuals with short duration (<5 years) required fast track referral for moderate to severe DR. At subsequent five-year follow-up, progression to vision-threatening DR had occurred in 9% of adolescents diagnosed before age 5 years and in 3% diagnosed at age 5–7 years.[128] A recent study in 662 young people with T1D in Bangladesh showed that 6.6% had DR.[119]

Several reports have found low rates of referral for DR screening in pediatric diabetes clinics.[123,124] In the T1D Exchange Registry in the US, less than 1% of 12,235 young people with diabetes reported treatment for DR at a mean age of 12 years and duration of 5 years, although this is likely to under-report the actual prevalence since the data were based on self-reported DR and only cases requiring treatment.[125]

Conversely insurance claims data show markedly higher rates reported by optometrists or ophthalmologists in a large US managed-care network: 20% of 2240 youth had developed DR at a median duration of 3.2 years with an incident rate of 52.3 per 1000 person-years; estimated to be 25% at 5 years duration. Severe DR or DME were present in 2% and the youngest patient with PDR was 6 years old. Lower rates of screening uptake were found in those with lower family income and this group had higher rates of DR, suggesting that the actual rate may be even higher.[127]

Initial worsening of DR can occur with improvement in HbA1c as occurred in the DCCT, but such worsening did not result in clinically significant visual loss when detected and managed appropriately and, over time, intensive insulin therapy continued to be superior to standard therapy.[129] This initial worsening of DR associated with improved glycemia also occurred in young people with diabetes with growth failure due to severe under-insulinization.[130] However within 1.5–3 years, the advantage of intensive treatment is evident.[129]

Pregnancy is a recognized risk factor for acceleration and progression of DR[131,132]; hence screening should be undertaken preconception, every trimester, and 1 year postpartum.

5.1 | Assessment of retinopathy

The most sensitive detection methods for DR screening are a clinical bio-microscopic fundus slit-lamp examination through dilated pupils by an ophthalmologist or optometrist and mydriatic 7-field stereoscopic retinal photography. The latter is optimal for research but not often available in the clinical setting where, instead, mydriatic and nonmydriatic 2-field fundal photography is often used for screening. Other methods are direct ophthalmoscopy, indirect ophthalmoscopy, fundus fluorescein angiography, ultrawide-field imaging and optical coherence tomography (OCT). Fundal photography provides a

validated tool that can be useful for monitoring clinical quality and in research, but photographs may not be gradable in which case ophthalmoscopy needs to be performed; mydriasis can reduce the technical failure rate.[133] Ultrawide-field imaging may improve the detection of retinopathy and predict progression to proliferative retinopathy.[134] Fluorescein angiography reveals functional vascular abnormalities (vascular permeability) as well as structural abnormalities in the blood vessels, whereas OCT reveals only structural abnormalities, specifically DME and other anomalies including loss of the various layers of the neural retina. The newer technique of optical coherence tomography angiography (OCTA) is promising due to the possibility to detect disturbances in retinal vessel density, foveal thickness and foveal avascular zone, which are predictive for future DR occurrence and severity. Alterations in retinal vessel density occur early before the onset of clinically detectable other diabetes-related complications, which may contribute greatly to the early detection of DR.[135,136]

When an incident cohort of children diagnosed in 1990–1992, with a median HbA1c of 8.7%, was examined for DR after 6 years diabetes duration, the relative effects of age and puberty could be compared. Early DR, defined as one microaneurysm or hemorrhage, was present in 24% of the study population. DR was present in 8% of children younger than 11 years of age and 25% of those 11 years old or older; and when comparing prepubertal versus pubertal children, it was present in 12% versus 29%.[29]

More recent data using the same methods in mid-adolescence (median age 16.4 years) with minimum duration of 5 years demonstrated that DR declined from 53% (in 1990–1994) to 23% (in 2000–2004) and then to 12% (in 2005–2009).[3] This reduction has not been sustained at the same referral clinic in Australia, with the rate being 21% in the decade 2000–2009 and 20% in 2010–2019.[137] In a younger population with T1D (median age 14.5 years, duration 2–5 years), the prevalence of mild background retinopathy declined from 16% in 1990–1994 to 7% in 2003–2006.[81] Furthermore, those with shorter duration had considerably less DR, and retinopathy was present in only 6% of the youngest group (aged 11–13 years). Moderately severe DR was only found in those with diabetes duration greater than 10 years[137]; and nine cases of sight-threatening retinopathy were found in the last decade.[138] The prevalence of DME in youth with T1D was 0.9% in the last decade.[137]

The DCCT/EDIC study group has reviewed optimal frequency for rescreening for DR, and recommends repeat screening at intervals, which varies, based on the baseline DR status and HbA1c in adults with T1D.[139] Whilst the participants in that study consented to randomization to intensive therapy or standard therapy for the DCCT, a free-living observational cohort of adolescents in Australia, also demonstrated that screening could be extended to 3 years if no DR was present with less than 1% chance of progression to moderately severeDR.[140]

For adolescents with T2D, the TODAY follow-up study shows a worrying increase in DR over 7 years. At the second assessment in 2017–2018, 51% of participants had retinopathy compared to 13% in 2010–11. Their mean age was 24 years and duration 11 years: 9% had moderate to severe DR and 3.5% had DME.[16]

5.2 | Specific treatment for DR

Once sight-threatening DR is detected, treatment options include laser photocoagulation and/or anti-VEGF therapy.[117,141] Panretinal laser photocoagulation (PRP), commonly known as "laser therapy," consists of multiple discrete outer retinal burns throughout the mid and far peripheral area but sparing the central macula. It has been proven to reduce the progression of visual loss by more than 50% in young people with PDR.[142,143] However, photocoagulation is not indicated for mild or moderate NPDR.[144] Side effects of treatment are decreased night and peripheral vision and subtle changes in color perception. Complications of laser therapy include vitreous hemorrhage, choroidal neovascularisation or detachments and visual sequelae of misplaced burns.

For PDR, intravitreal injection of antiVEGF (ranibizumab, aflibercept, and bevacizumab) is now increasingly used and show better 12-month results for visual acuity than PRP.[145] This treatment is not destructive but does require repeated visits and injections for efficacy, (e.g., monthly injections for the first 5 months with up to nine injections in the first year); and carries the rare risk of ocular infection.[145] In the DRCR network Protocol S study at 5 years, visual acuity was similar for both the PRP and intravitreal ranibizumab groups, although eyes treated with antiVEGF had better visual fields and lower incidence of DME.[146,147]

For DME with vision loss, anti-VEGF (ranibizumab, aflibercept, and bevacizumab) is now considered standard of care and has shown superior outcomes over 5 years compared to laser treatment.[148,149] Intravitreal use of longer acting steroids (dexamethasone and fluocinolone) is an alternative to antiVEGF for DME, with a possible reduced burden of injections.[150] However, because of the inferior visual acuity results and the potential adverse effects of cataract and glaucoma development, intravitreal steroid is rarely used as first-line therapy for DME.

Surgical treatment such as vitrectomy may be indicated for persistent vitreous hemorrhage, tractional retinal detachment or extensive fibrosis.[141]

6 | DIABETIC CATARACTS

Cataracts have been reported in people with T1D close to or even preceding the diagnosis, with a prevalence between 0.7% and 3.4%.[151] Hence comprehensive initial eye examination to detect cataracts should also be considered at the time of retinopathy screening, or earlier, if there is any visual disturbance.

7 | DIABETIC NEUROPATHY IN YOUTH

The somatic and autonomic components of the peripheral nervous system (PNS) are commonly affected by both T1D and T2D in youth and adults.[152] The unique anatomy of the somatic branch of the PNS, with the cell body lying adjacent to or in the spinal cord with select nerve fibers projecting long distances to the most distal extremities, renders the PNS susceptible to shifts in energy sources, as is often present in diabetes.[153,154] Small unmyelinated nerve fibers that carry

pain and temperature perception are frequently affected first in diabetes, followed by injury to myelinated nerve fibers, which convey vibratory and position sense.[155] Weakness is a late sign and rarely present in youth.[156] The most frequent type of injury occurs in a symmetric distal to proximal gradient, known as a stocking and glove pattern, and is commonly termed diabetic neuropathy.

The reported prevalence of diabetic neuropathy in children and youth varies due to the use of different diagnostic tests,[157] and the frequent presence of subclinical neuropathy,[158] which is challenging to detect. The Pittsburgh Epidemiology of Diabetes Complications study reported a 3% prevalence of diabetic neuropathy in youth with T1D ($n = 400$) less than 18 years of age.[159] A larger EURODIAB study of individuals with T1D ($n = 3250$) found a 19% prevalence in the 15–29 year-old bracket.[160] An Australian study reported that 14% of T1D youth ($n = 819$) as young as 11–17 years-old developed diabetic neuropathy after only 2–5 years of disease duration.[81] The SEARCH for Diabetes in Youth study found diabetic neuropathy in 7% of T1D youth ($n = 1734$).[161] This variability in prevalence estimates could be attributable to the diagnostic test employed; a small study of individuals with T1D ($n = 73$) concluded that prevalence was 4% by neuropathy symptoms, 36% by abnormal neurological exam, 57% by nerve conduction abnormalities, 51% by vibration perception threshold, and 26% by tactile perception threshold.[157]

In T2D, the overall trend is for an increasing prevalence of diabetic neuropathy in recent years in parallel with the rising pediatric T2D prevalence.[162–164] The SEARCH study reported diabetic neuropathy in 22% of T2D youth ($n = 258$),[11,161] while the TODAY study reported a cumulative incidence of diabetic neuropathy of 38.5% in males and 27.2% in females.[165]

The most frequently studied autonomic neuropathy is cardiac autonomic neuropathy,[166] an independent risk factor for cardiovascular mortality.[167] The SEARCH study found early signs of cardiovascular autonomic dysfunction[168] at a similar prevalence in youth with T1D (12%) and T2D (17%).[169] A systematic review of published studies of young people with T1D (aged less than 24 years) estimated cardiac autonomic neuropathy prevalence from 16% to 75%, based on the diagnostic method.[170]

7.1 | Assessment of diabetic peripheral neuropathy in youth

Young people with diabetes initially experience burning, prickling and/or paresthesiae of their feet caused by small fiber dysfunction. Over time, large fiber involvement occurs and young people with diabetes experience numbness and, in extreme cases, poor balance due to proprioceptive loss.[152,155] While there are multiple symptom scores for adults,[155] none exist for youth.[171]

7.1.1 | Clinical examination

Physical examination should include a bedside evaluation of small fiber function, assessing temperature or pinprick sensation in the feet.[172,173] Large fiber function is assessed at the great toe with a 128 Hz tuning fork (high specificity but low sensitivity) for vibratory perception[174] and a 10 g monofilament for touch/pressure sensation.[174] Evaluation of ankle reflexes complete the assessment of large fiber function.[172,173] There are several simple clinical tools that can be used to assess diabetic neuropathy in youth.[156] The DCCT,[175] SEARCH,[161] and the TODAY[165] studies all used the Michigan Neuropathy Screening Instrument.[176]

7.1.2 | Quantitative testing

Quantitative testing is rarely required and is primarily used for research purposes. Quantitative sensory testing normative values exist for youth.[177] Other available tests include thermal discrimination testing[178] for small fiber function, and assessment of vibration for large fiber function using a biothesiometer,[157] pocket-sized Vibratip™.[179] Again, these are mostly used in research settings and age- and sex-specific normal ranges need to be applied when interpreting results.

7.1.3 | Nerve conduction studies

Nerve conduction studies are clinically useful if the presentation of diabetic neuropathy is atypical, with more evident motor than sensory symptoms and signs and/or a strong asymmetrical clinical presentation.[180–182] Normative values for nerve conduction velocities for youth are published.[183]

7.2 | Assessment of diabetic autonomic neuropathy in youth

Autonomic neuropathy can manifest in the cardiovascular, gastrointestinal, and sudomotor systems as resting state tachycardia, exercise intolerance, gastroparesis, and dysfunctional sweating responses.[152,184] Cardiovascular autonomic neuropathy may be detected by impaired HRV or BP changes in response to certain maneuvers, for example, deep breathing, standing, and Valsalva maneuver; however, cardiovascular reflex tests are the gold standard. Importantly, normative values for HRV must be consulted.[185] Autonomic neuropathy in the gastrointestinal system can be detected by gastric emptying scintigraphy, whereas in the sudomotor system, thermoregulatory sweat test and Sudoscan may be used.[186,187] These diagnostic tests are rarely used in pediatric practice.

8 | MACROVASCULAR DISEASE

CVD remains the major cause of mortality in people with T1D.[188] Individuals with T1D experience an earlier onset of cardiovascular events and a higher CVD mortality compared to their peers without

diabetes.[189] Recent data from the Swedish Diabetes Registry showed that young people diagnosed with T1D before the age of 10 years had 10-times higher risk of future acute myocardial infarction compared to those diagnosed between the ages of 26–30 years, and over 30-times higher CVD risk than the general population.[190]

In youth with T1D, overt manifestations of CVD such as angina or myocardial infarction are rare, but early subclinical signs can be detected by surrogate measures, such carotid and aortic intima-media thickness (cIMT and aIMT), pulse wave velocity, and flow mediated dilation.[191] Atherosclerosis starts in childhood and adolescence as shown by thickening of cIMT and aIMT[192–194] and silent coronary atherosclerosis measured by intravascular ultrasound in young adults with childhood onset diabetes.[195]

Suboptimal glycemia is one of the main modifiable risk factors related to early vascular abnormalities and increased risk of later CVD events.[5] However, other traditional cardiometabolic risk factors such as obesity, hypertension and dyslipidemia, renal function along with non-modifiable risk factors, such as sex and diabetes duration, and lifestyle factors, contribute to CVD risk.[5] Hypertension has a greater impact on CVD in young people with diabetes than in individuals without this condition.[40] BP control reduces cardiovascular morbidity and mortality in diabetes.[41] Cholesterol plays an important role in the initiation and progression of atherosclerosis. Well-controlled T1D is not associated with gross blood lipid disturbances, but changes in lipoprotein subclasses can be detected.[44] In contrast, youth with suboptimal HbA1c concentrations have a more atherogenic lipid profile than youth without diabetes, with a positive association between HbA1c and increased levels of total cholesterol, LDL-cholesterol, non-HDL cholesterol and triglycerides.[42,196–198] Adolescents with T1D also show higher levels of apolipoprotein B (apoB) compared to their peers without diabetes, regardless of HbA1c levels.[197] Studies in adults and adolescents with T1D suggest a possible complementary role for measurement of apoB in addition to screening LDL-cholesterol. However, current data are insufficient to warrant the addition of apoB screening to current lipid screening guidelines for youth with diabetes. Changes in lipids associated with increased cardiovascular risk are also associated with central obesity in T1D as well as T2D.[199]

A high BMI is associated with increased rates of CVD events and mortality in adults with T1D.[200] Overweight and obesity are common among youth with T1D, with rates of 9%–20%, and are associated with higher LDL-cholesterol and triglycerides, and lower HDL-cholesterol concentrations.[201,202]

Insulin resistance is another well-known CVD risk factor, which is common among adolescents with T1D.[203] In adults with T1D, risk of CVD and related mortality increases with the presence and severity of DKD.[204] Recent data from cohorts of adolescents with T1D have confirmed the value of AER as an early marker of vascular complications.[84,205] In the AdDIT study, an albumin-creatinine ratio (ACR) in the top tertile of the population distribution was associated with greater cIMT, and flow-mediated dilation and BP.[84]

Lifestyle factors can also contribute to CVD. These include smoking, alcohol, sedentary lifestyle, and stress.[189] In a recent study, 10% of youth with T1D reported alcohol consumption, 10% cigarette smoking and 6% both alcohol and cigarette use.[206] Compared to non-drinker and non-smoker youth, smokers showed significantly higher percentages of CVD risk factors. In a cohort of adolescents with T1D, those achieving 4–6 of the goals of Screening Guidelines had better surrogate markers of macrovascular disease than those achieving less and have comparable results to nondiabetic controls.[207]

8.1 | Management of hypertension

Hypertension in children and adolescents (<13 years) is defined as BP equal to or above the 95th percentile for age, sex and height, whereas in older adolescents (age ≥13 years) it is defined as SBP ≥130 and/or DBP ≥80 mmHg. Elevated BP (previously known as "prehypertension") is defined as BP ≥90th percentile for age, sex, and height, or from the age of 13 years as BP between 120 and 129/80 mmHg.[208] Similarly to overt hypertension, elevated BP is associated with adult hypertension.[209,210]

Children and adolescents with elevated BP or hypertension should have elevated BP confirmed on three separate days. Confirmation of hypertension is recommended by 24-h ambulatory BP measurements (ABPM). Normative ABPM values are available and should be used to interpret the results.[211]

In children and adolescents with elevated BP, initial treatment includes lifestyle interventions, including DASH diet and moderate to vigorous physical activity at least 3–5 days per week (30–60 min per session).[209,212,213] If target BP is not reached within 6 months of initiating lifestyle intervention and pharmacologic treatment should be started.

When hypertension is confirmed in children and adolescents with T1D, in addition to lifestyle modification, pharmacologic treatment should be considered.[208] Pharmacologic treatment of hypertension in children and adolescents should be initiated with an angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), long-acting calcium channel blocker, or a thiazide diuretic. ACE inhibitors are recommended for use in children and adolescents with hypertension and/or albuminuria, but an ARB can be used if the ACE inhibitor is not tolerated (e.g., due to cough).[208] They have been effective and safe in children in short-term studies.[109,214,215] Reproductive counseling and implementation of effective birth control is required when treatment is initiated due to the potential teratogenic effects of both drug classes. The goal of treatment is BP consistently <90th percentile for age, sex, and height.

8.2 | Management of dyslipidemia

Screening for dyslipidemia should commence from 11 years of age in youth with T1D. If there is a family history of either hypercholesterolemia or early cardiovascular death, screening should be commenced earlier from age 2 years. It is appropriate to screen with a non-fasting blood lipid profile; if this is abnormal (i.e., triglycerides or LDL levels are elevated), then a fasting profile should be performed.[216,217] Data

from the NHANES III study suggest that non-fasting lipids screening has good prognostic value[216] but data in young people with diabetes are lacking.[217] Fasting lipids are also indicated for young people with diabetes receiving treatment for dyslipidemia.

High LDL-cholesterol is defined as values >2.6 mmol/L (100 mg/dL).[218] If this is present then interventions to improve glycemia, dietary changes and increased exercise should be the first approach to management. Dietary changes restrict saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day.[219]

Previous studies have reported that a 6-month dietician-led program prioritizing a Mediterranean-style diet improved levels of LDL-C and non-HDL-C. Another 6-month trial evaluating the effect of a supervised exercise program showed improvements in dyslipidemia.[220,221] Improved glucose control has been associated with a more favorable lipid profile but may be insufficient to completely restore normal lipid levels.[196]

If the implementation of lifestyle interventions for 6 months does not lower LDL-cholesterol to <3.4 mmol/L (130 mg/dL), statins should be considered in children aged >10 years, with an ideal target of LDL cholesterol <2.6 mmol/L (100 mg/dL). In adults with diabetes, statins are effective in the primary and secondary prevention of major cardiovascular events, including vascular mortality, stroke and limb and coronary revascularization.[222,223] Short-term trials, mainly in the context of familial hypercholesterolemia, have shown that simvastatin, lovastatin and pravastatin are effective and safe in children and adolescents.[224–226] No significant side effects were observed in terms of growth, pubertal progression, endocrine function parameters, or liver or muscle enzymes.[224–226] The AdDIT trial confirmed the efficacy and safety of statin therapy (atorvastatin) in adolescents with T1D treated for a 2–4 year period.[109] In the AdDIT trial, atorvastatin use was associated with a decreased in total, LDL and non-HDL cholesterol levels as well as in an improved ratio of the apolipoprotein B/apolipoprotein A ratio; however, statin treatment did not lead to any improvement in cIMT or FMD.[109,227]

CONFLICT OF INTEREST

PB has acted as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Sanofi, Novo Nordisk and Horizon Pharma. PB serves on the advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk and XORTX. RPW has research support from Dexcom, Eli Lilly & Co and Tandem Diabetes Care. RPW has served on an advisory board for Dompe.

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