

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Microvascular and macrovascular complications in children and adolescents

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

Prevention

- Intensive education and treatment should be used in children and adolescents to prevent or delay the onset and progression of complications (A).
- Improvement in glycemic control will reduce the risk for onset and progression of diabetes vascular complications (A).

Screening

- Screening for retinopathy and microalbuminuria should start from 10 yr of age, or at onset of puberty if this is earlier, with 2–5 yr diabetes duration (C) (Table 1).

Retinopathy

- Assessment for retinopathy should be performed by an ophthalmologist or a trained experienced observer through dilated pupils (B).
- Initial eye examination should also be considered to detect cataracts or major refractive errors (E).
- The frequency of retinopathy screening in general should occur annually, but should be more frequently if there are high risk features for visual loss. For those with duration <10 yr, minimal background retinopathy on fundus photography and reasonable glycemic control, biennial assessment by fundal photography can occur (E) (Table 1).
- Because of potential worsening of retinopathy for patients with longstanding poor glycemic control when control is improved, ophthalmological monitoring is recommended before initiation of

intensive treatment and at 3-month intervals for 6–12 months thereafter, particularly if retinopathy severity is at the moderate non-proliferative stage or worse at the time of intensification (E).

- Laser treatment reduces the rate of visual loss for individuals with vision-threatening retinopathy (severe proliferative retinopathy or proliferative retinopathy) (A).

Microalbuminuria

- Annual screening for albuminuria should be undertaken by any of these methods: first morning urine samples for urinary albumin/creatinine ratio (ACR) or timed urine collections for albumin excretion rates (AER) (E) (Table 1).
- Because of biological variability, two of three consecutive collections should be used as evidence of microalbuminuria. Confounders are exercise, menstrual bleeding, infections, fever, kidney diseases, and marked hyperglycemia. Abnormal screening tests should be repeated, as microalbuminuria may disappear and not be persistent (E).
- Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) agents should be used in patients with persistent microalbuminuria to prevent progression to proteinuria (E) (in adolescents).

Blood pressure

- Blood pressure (BP) should be measured at least annually (E). Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is >95th percentile for gender, age, and height on more than three occasions (B).

- The blood pressure target for adolescents is <130/80 mmHg
- Confirmation of hypertension may be assisted by 24 h ambulatory blood pressure measurements (E).
- ACEI are recommended for use in children with diabetes and hypertension (E) Table 3. They have been effective and safe in children in short-term studies (A, B), but are not safe during pregnancy.

Lipids

- Screening for dyslipidemia should be performed soon after diagnosis (when diabetes stabilized) in all children with type 1 diabetes aged >10 yr (E). If normal results are obtained, this should be repeated every 5 yr (Table 1). If there is a family history of hypercholesterolemia, early cardiovascular disease (CVD) or if the family history is unknown, screening should commence as early as 2 yr of age (E).
- High low-density lipoprotein (LDL) cholesterol is defined as ≥ 2.6 mmol/L (100 mg/dL) (E). If this is present then interventions to improve metabolic control, dietary changes, and increased exercise should be instituted (Table 3).
- If the above interventions do not lower LDL cholesterol <4.1 mmol/L (or <3.4 mmol/L (130 mg/dL) and one or more CVD risk factors), statins should be considered in children aged >10 yr, although long-term safety is not established (E) (Table 3).

Lifestyle

- Cessation of smoking/never initiating smoking will reduce progression of microalbuminuria and CVD (B).

Table 1. Screening, risk factors and interventions for vascular complications

| | When to commence screening? | Screening methods | Risk factors | Potential interventions |
|-----------------------|---|---|--|--|
| Retinopathy | Annually from age 10 or at onset of puberty if this is earlier, after 2 to 5 years' diabetes duration | Fundal photography or mydriatic ophthalmoscopy (less sensitive) | Hyperglycemia High blood pressure Lipid abnormalities Higher BMI | Improved glycemic control Laser therapy |
| Nephropathy | Annually from age 10 or at onset of puberty if this is earlier, after 2 to 5 years' diabetes duration | Urinary albumin/creatinine ratio or first morning albumin concentration | High blood pressure Lipid abnormalities Smoking | Improved glycemic control ACEI or ARBs Blood pressure lowering |
| Neuropathy | Unclear | History and physical examination | Hyperglycemia Higher BMI | Improved glycemic control |
| Macrovascular disease | After age 10 yr | Lipid profile every 5 yr, blood pressure annually | Hyperglycemia High blood pressure Lipid abnormalities Higher BMI Smoking | Improved glycemic control BP control Statins |

ACEI, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BMI, body mass index; BP, blood pressure.

Macrovascular

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

Type 2 diabetes

- Complications screening should commence at diagnosis. Attention to risk factors should be escalated because of the increased risk of complications and mortality (B).

Introduction

The long-term vascular complications of diabetes include retinopathy, nephropathy, neuropathy, and macrovascular disease. The outcomes are:

- visual impairment and blindness due to diabetic retinopathy;
- renal failure and hypertension due to diabetic nephropathy;
- pain, paresthesia, muscle weakness, and autonomic dysfunction due to diabetic neuropathy; and
- cardiac disease, peripheral vascular disease, and stroke due to macrovascular disease.

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 the disease.

Childhood and adolescence is a period during which intensive education and treatment may prevent or delay the onset and progression of complications in later adult life (1).

There has been a declining incidence of complications in young people, including retinopathy and nephropathy, reported in many areas with specialized clinics (2–6). In adults, the incidence and prevalence of retinopathy has declined over time (7–8). These changes have occurred over a period of time during which there have been major changes in diabetes management, identification of putative risk factors, and the advent of regular screening for complications (9, 10). However, there is no evidence that this is a worldwide occurrence: in areas where health care is not optimal, a greater risk of complications will remain (11, 12).

Interventional studies of intensive glycemic control

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized controlled

clinical trial involving 1441 patients with type 1 diabetes conducted in North America from 1983 to 1993 (13). Patients were randomized to two treatment arms of intensive and conventional treatment which achieved a significantly lower hemoglobin A1c (HbA1c) in the intensive group. There were 195 pubertal adolescents (aged 13–17 yr) but no younger children (1). After completion of the DCCT (a median in the adolescent group of 7.4 yr) and hence the end of randomization, the Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow patients. After 4 yr there was no significant difference in HbA1c between the former intensive and conventional treatment groups.

The DCCT provided unequivocal evidence that intensive diabetes treatment and improved glycemic control conferred a significant risk reduction for microvascular complications compared with conventional treatment (13).

The EDIC study demonstrated that this positive effect continued after randomization, i.e., that there was a memory effect of improved glycemic control. In addition it showed a positive effect of intensive therapy for reduction in macrovascular disease (14).

In the adolescent cohort, intensive treatment compared with conventional treatment, reduced the risk and progression of non-proliferative retinopathy by 53%, clinical neuropathy by 60%, and microalbuminuria by 54%. The difference in HbA1c was 8.1 vs. 9.8%. The benefits of intensive therapy persisted in the former adolescent cohort during the first four years of the EDIC study: the previously intensively managed group had 74% less retinopathy, 48% less microalbuminuria, and 85% less albuminuria (15).

Compared with conventional treatment, intensive treatment in the total age group reduced the risk of clinical neuropathy by 60%. Cardiovascular events were reduced by 50% in the previously intensively treated group compared with the control group during a mean 17 yr follow-up (14).

The DCCT confirmed that improved glycemic control may initially worsen diabetic retinopathy. However, within 1.5–3 yr, the advantage of intensive treatment is evident (16). In the DCCT, the long-term benefits of intensive insulin treatment outweighed the risk of early retinal deterioration, while in the EDIC study, the benefit of intensive treatment for retinopathy progression was sustained in adults for 10 years, but not in adolescents (17). This supports the need for long-term maintenance of glycemic targets.

Other risk factors for the development of complications

Longer duration of diabetes, older age, and puberty are risk factors for complications (18). The prepubertal

years of diabetes duration have a significantly lesser impact especially further from the onset of gonadarche (19); however, the risk of vascular complications is greater for those living with diabetes during puberty, compared with young people who develop diabetes after puberty (20). For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated AER (6, 19–21). Longitudinal studies have also reported that younger age of type 1 diabetes onset, particularly before puberty, is associated with a longer time free of complications such as nephropathy and retinopathy (19). However, in the long-term this initial advantage disappears (22, 23).

High rates of cardiovascular risk factors have been found in children and adolescents with type 1 diabetes from Norway and in SEARCH for Diabetes in Youth (www.searchfordiabetes.org) SEARCH, a population based study from the USA (24, 25).

Smoking is associated with an increased risk of developing persistent microalbuminuria or macroalbuminuria (4, 26). The evidence for the effect of smoking on retinopathy is less clear (27), although changes in retinal microvasculature that are early markers of retinopathy (eg vessel diameter) have been associated with smoking (28). Type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality (29).

High BP and alterations in the circadian BP rhythm have been associated with the risk of developing nephropathy and retinopathy in youth with type 1 diabetes (30–32). Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (33). BP control (<130/80 mmHg in adults) is effective in decreasing cardiovascular morbidity and mortality in diabetes (34).

Dyslipoproteinemia is associated with microalbuminuria and retinopathy development in the DCCT/EDIC (35, 36). This included higher total and LDL cholesterol and higher triglyceride levels for microalbuminuria, as well as larger LDL particle size and apolipoprotein B (apoB) in men.

Family history of complications increases the risk for nephropathy (37) and retinopathy (38). Higher body mass index (BMI) is a risk factor for retinopathy (39), neuropathy (40), microalbuminuria (41), and CVD (42, 43).

Life style issues also contribute to complications risk; sedentary men with diabetes have higher mortality than active individuals (44).

Diabetic retinopathy

Adolescents have a higher risk of progression to vision-threatening retinopathy (severe non-proliferative retinopathy or proliferative retinopathy) compared

with adults with diabetes (23, 45, 46). The progression may be rapid, especially in those with poor glycemic control (47). Hence, adolescence is the time when efforts should be directed to screening for early signs of diabetic retinopathy and modifiable risk factors. Regression of retinopathy can also occur (45, 46, 48, 49). After 20-yr diabetes duration the later onset group of type 1 patients aged <30 yr at diagnosis had less proliferative retinopathy (PDR) than the earlier onset group: 18 vs. 43%; examined 2007–2011, earlier group examined 1980–1996.

Progression of retinopathy

Non-proliferative (background) retinopathy is characterized by microaneurysms, retinal haemorrhages (blot, dot and flame-shaped), hard exudates (protein and lipid leakage), cotton wool spots (microinfarction), intraretinal microvascular abnormalities and beading, dilatation, constriction and tortuosity of vessels. Non-proliferative retinopathy can be classified as mild (microaneurysms only), moderate (more than microaneurysms) and severe (≥ 20 or more retinal hemorrhages in each of 4 quadrants, definite venous beading in 2 quadrants and intraretinal microvascular abnormalities in 1 quadrant).

Severe non-proliferative retinopathy is characterized by increasing vascular obstruction, progressive intraretinal microvascular abnormalities, and progressive ischemia with infarctions of the retinal nerve fibers causing cotton wool spots.

Mild and moderate non-proliferative retinopathy are not vision-threatening and do not invariably progress to proliferative retinopathy.

PDR is characterized by neovascularisation in the retina and/or vitreous posterior surface. The vessels may rupture or bleed into the vitreoretinal space which is vision-threatening. Advanced PDR can result in fibrosis and adhesions, which can cause hemorrhage and retinal detachment. High-risk characteristics for visual loss are the location and extent of neovascularisation and signs of vitreous or preretinal hemorrhage (50).

Diabetic macular edema (DME or maculopathy) is classified separately from stage of retinopathy, and is characterized by decreased vascular competence and microaneurysm formation which produce increased exudation and swelling in the central retina. DME is vision-threatening but is very uncommon in children and adolescents with type 1 diabetes.

Assessment of retinopathy

The most sensitive detection methods for retinopathy screening are bimicroscopic fundus slit examination through dilated pupils by an ophthalmologist or

optometrist and mydriatic seven-field stereoscopic retinal photography (51–54). The latter is optimal for research but not often available in the clinical setting. Other methods are mydriatic and non-mydriatic two-field fundal photography, direct ophthalmoscopy, indirect ophthalmoscopy, fundus fluorescein angiography, and optical coherence tomography (OCT). Fundal photography provides a validated result 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 (55). Fluorescein angiography reveals functional abnormalities (vascular permeability) as well as structural abnormalities in the blood vessels whereas OCT reveals only structural abnormalities, specifically macular oedema.

The landmark study of retinopathy carried out in Wisconsin starting in 1980–1982, examined prevalence of retinopathy using seven-field stereoscopic retinal photography in people diagnosed with diabetes <30 yr of age and on insulin within 1 yr of diagnosis (48). With longer diabetes duration there was an increase in retinopathy, so that after 15 yr 98% had background retinopathy and after 35 yr duration 62% had PDR. This study helped establish the existence of screening for diabetic retinopathy and the search and treatment of risk factors. Subsequent changes in diabetes management have been associated with a reduction in PDR demonstrated by comparison with a later diagnosed study group. After 20 yr diabetes duration the later onset group of type 1 patients examined in 2007–2011, had less PDR than the earlier onset group examined 1980–1996: 18 vs. 43% (49).

When an incident cohort of children was examined for retinopathy after 6 yr duration, the relative effects of age and puberty could be compared. Seven-field stereoscopic fundal photography was performed with early retinopathy defined as one microaneurysm or hemorrhage, which was present in 24%. Comparing children before and after 11 yr, retinopathy was present in 8 vs. 25%; and comparing children before and after puberty, it was present in 12 vs. 29%. The incident cohort was diagnosed in 1990–1992 and examined in 1996–1998 when their median HbA1c was 8.7% (21).

More recent data using the same methods in mid-adolescence (median age 16.4 yr) with median diabetes duration of 8.6 yr demonstrated that retinopathy declined from 53% (in 1990–1994) to 23% (2000–2004) and then to 12% (2005–2009) (5). In a younger group aged 11–17 yr (median age 14.5 yr, duration 2–5 yr), the prevalence of mild background retinopathy declined from 16% in 1990–1994 to 7% in 2003–2006 (6). Furthermore, those with shorter duration had

considerably less retinopathy, and retinopathy was present in only 6% of the youngest group (aged 11–13 yr) over the whole time of observation.

Laser treatment for retinopathy

Once vision-threatening retinopathy (severe non-proliferative retinopathy or PDR) has been detected, the treatment options are limited. Panretinal photocoagulation, 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 patients with PDR (50, 56). There are benefits of early panretinal photocoagulation at the severe nonproliferative retinopathy stage and other factors, such as poor compliance with follow up, impending cataract extraction or pregnancy, and status of fellow eye will help in determining the timing of the panretinal photocoagulation. However, photocoagulation is not indicated for eyes with mild or moderate non-PDR (57). Side effects of treatment are decreased night and peripheral vision and subtle changes in color perception. Complications of laser therapy are vitreal and choroidal hemorrhages or visual sequelae of misplaced burns.

For DME without foveal center involvement when no vision loss has occurred, focal laser photocoagulation to leaking microaneurysms is indicated. For DME with center involvement and vision loss, consideration should be given for intraocular anti-vascular endothelial growth factor (VEGF) therapy (13, 62).

Diabetic nephropathy

Diabetic nephropathy is defined as persistent proteinuria >500 mg/24 h or albuminuria >300 mg/24 h and is usually associated with hypertension, and a diminishing glomerular filtration rate (GFR) (58). End-stage renal failure may occur many years later and requires dialysis or kidney transplantation. Diabetic nephropathy is a major cause of morbidity and mortality among young adults with type 1 diabetes (59). Recent data have suggested that in the absence of diabetic nephropathy mortality, mortality in patients with type 1 diabetes is similar to that in the general population, whereas it is significantly higher in subjects with abnormal urinary AER (60, 61).

Early detection of diabetic nephropathy and timely treatment of blood pressure have a pivotal role in the prevention of end-stage renal failure in young people and adults with diabetes (62) E.

Assessment of incipient nephropathy

The first clinical sign is elevation of albumin excretion. This is generally defined as any of those below (63):

- AER between 20 and 200 $\mu\text{g}/\text{min}$
- AER between 30 and 300 $\text{mg}/24\text{ h}$ in 24 h or timed urine collections
- Albumin concentration 30–300 mg/L (early morning urine sample)
- ACR 2.5–25 mg/mmol or 30–300 mg/g in males and 3.5–25 mg/mmol in females (because of lower creatinine excretion)

Timed overnight or 24 h collections are more burdensome and add little to prediction or accuracy (64).

In the recent American Diabetes Association Clinical practice recommendations, the terms ‘microalbuminuria’ and ‘macroalbuminuria’ have been replaced by two levels of persistent albuminuria (30–299 $\text{mg}/24\text{ h}$ and $>300\text{ mg}/24\text{ h}$), to emphasize the continuous nature of albumin excretion as a risk factor for nephropathy and macrovascular disease.

Other definitions have also been used, in longitudinal studies. The relationship between timed overnight urine collections with first morning urine ACR has now been determined in children and adolescents by linear regression: AER 20–200 mg/min corresponds to ACR of 3.5–35 mg/mmol in males and 4.0–35 mg/mmol for females (33, 59). This also corresponds to 2.4 and 2.2 standard deviations above the mean of the general population.

Microalbuminuria is confirmed by finding two or all of three samples abnormal over a 3- to 6-month period. Persistent microalbuminuria has been shown to predict the progression to end stage renal failure (2, 48, 50, 65–67) and is associated with an increased risk of macrovascular disease (68, 69).

An increase of AER within the microalbuminuric range identifies patients at risk of progression to renal damage (41, 70, 71). Loss of nocturnal dipping on 24 h blood pressure monitoring is an early marker of diabetic renal disease, preceding microalbuminuria (72). Microalbuminuria can also regress (73), especially in adolescents (41, 74). Progression to microalbuminuria is preceded by renal hypertrophy (75).

Confounders exercise increases the AER in the non-diabetic individual and more markedly in diabetes. Even moderate exercise may interfere with the interpretation of data (58). For interpretation of persistently elevated AER values, especially in children with short diabetes duration it is essential to exclude other causes of albuminuria such as immunoglobulin A (IgA) or other types of nephritis common in childhood.

In an incident cohort, after 6-yr duration, early elevation of AER ($>7.5\mu\text{g}/\text{min}$) was examined as an even earlier marker of renal dysfunction. Comparing children before and after 11 yr, elevated AER was present in 5% compared with 25%; and comparing children before and after puberty, it was present in 5% compared with 26% (21). There has been no secular reduction in AER or microalbuminuria in the same cohort that has shown a reduction in retinopathy: 24–22% in the short duration cohort (2- to $<5\text{-yr}$ duration) (6); 45–30% in the cohorts with median duration 8.6 yr (5).

Antihypertensive treatment for prevention of nephropathy

Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease (76). A recent prospective study has shown improved prognosis of renal function from 5 to 7 yr from onset of nephropathy to a median of 21.7 yr (77), predominantly due to aggressive antihypertensive treatment, with smaller contributions from improved glycemic control and smoking cessation (78).

BP values between the 90th and 95th percentiles are defined as prehypertension (79–81). Protocols and reference values for 24 h ambulatory blood pressure monitoring in children have also been published (38, 72). ACEI are recommended for use in children and adolescents with hypertension (79). They have been effective and safe in children in short-term studies (46, 82). The clinical beneficial effect of angiotensin II receptor antagonists in hypertension is similar to that observed with ACEI, but have not been used extensively in children.

In adults, ACEI and ARBs reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria (83, 84). A recent systematic review and meta-analysis has shown that in subjects with diabetes, only ACEI can prevent the doubling of serum creatinine compared with placebo (85). In addition, in placebo controlled studies, only ACEI (at the maximum tolerable dose) were found to significantly reduce the risk of all-cause mortality (86).

Despite the above evidence mainly in adults, there are still some concerns regarding the use of ACEI in protecting long-term renal function in young people without hypertension. In meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria (87). Young people with microalbuminuria would potentially be taking ACEI for decades. Side effects include cough, hyperkalemia, headache, and impotence (83, 88). A key safety issue related to the use of ACEI, as well as to ARBs, is the potential risk of congenital

malformation when used during pregnancy. A recent systematic review has highlighted that fetal exposure to ACEI or ARBs has serious neonatal and long-term complications and recommend to improve the awareness of these potential deleterious effects (89). Therefore, when starting treatment with these drugs in adolescent girls, they need to be aware of this risk and birth control measure need to be recommended.

Diabetic neuropathy

Diabetes can affect the somatic and autonomic nervous system. The somatic neuropathies associated with diabetes fall into two broad categories: focal/multifocal and generalized (90).

Focal neuropathies include mononeuropathies such as carpal tunnel syndrome, palsy of the peroneal nerve, palsy of the third cranial nerve, and proximal nerve conditions (e.g., diabetic amyotrophy).

Diabetic sensorimotor polyneuropathy is the most common generalized neuropathy and, for this reason, the simplified term '*diabetic neuropathy*' is commonly used. It is a polyneuropathy because of the diffuse damage to all peripheral nerve fibers, motor, sensory, and autonomic. Such damage occurs insidiously and progressively and is characterized at first by sensory loss and later by loss of motor function, in a stocking and glove distribution. Small fiber dysfunction precedes large-fiber damage in diabetic sensorimotor polyneuropathy (91).

Autonomic neuropathy can cause postural hypotension, vomiting, diarrhea, bladder paresis, impotence, sweating abnormalities, impaired light reflex, impotence, and retrograde ejaculation. Abnormal heart rate responses and prolonged QT intervals have been associated with increased risk of sudden death (92). While overt autonomic neuropathy is rare in childhood and adolescence, subclinical signs of autonomic dysfunction are common, and can be found soon after diabetes diagnosis. Risk factors for autonomic neuropathy in young people include longer diabetes duration, poor glycemic control, and presence of aldose reductase gene (AKR1B1) polymorphisms, specifically the Z-2/Z-2 genotype. Autonomic dysfunction is accelerated by puberty (93).

Assessment of neuropathy

Clinical assessment involves history taking, especially of numbness, persistent pain, or paresthesia; and physical examination of ankle reflexes, vibration, and light touch sensation (by conventional neurological examination or by graduated monofilaments).

Autonomic nerve tests include: heart rate response to deep breathing, standing from a lying position, Valsalva Manoeuvre, heart rate variation at rest,

QT interval, postural changes in blood pressure, and pupillary responses to light and dark adaptation (93). Peripheral nerve tests include: quantitative vibration and thermal discrimination thresholds and nerve conduction. These are mostly used in research settings. Age and gender specific normal ranges need to be applied where relevant when interpreting results. In youth, prevalence rates of peripheral neuropathy vary from <10% to as high as 27% (5, 94, 95), although some of this variability may relate to different methods of screening in addition to recognized risk factors.

Clinical symptoms of autonomic neuropathy are uncommon in the pediatric population. However, subclinical findings have been reported including significant cardiac autonomic neuropathy detected with heart rate variability studies in youth with type 1 diabetes (96).

Macrovascular disease

The mortality and morbidity of CVD are markedly increased in diabetic individuals compared with the non-diabetic population (97).

Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (33). BP control (<140/80 mmHg in adults) reduces cardiovascular morbidity and mortality in diabetes (34, 64).

A family history of early CVD (before 55 yr of age), lipid disturbances, type 2 diabetes, hypertension (98), and smoking place the individual with diabetes at higher risk.

Atherosclerosis starts in childhood and adolescence as shown by intima-media thickness of the carotids and aorta (92, 99) and silent coronary atherosclerosis measured by intravascular ultrasound in young adults with childhood onset diabetes (100). Silent coronary atherosclerosis (100) and cardiovascular events (15) are strongly associated with poor glycemic control.

Cholesterol plays an important role in the initiation and progression of atherosclerosis (80). Well controlled type 1 diabetes is not associated with gross blood lipid disturbances, but more advanced lipoprotein subclass examinations reveal atherogenic profiles (35). Poor glycemic control was associated with a potentially more atherogenic lipoprotein profile (101).

Changes in lipids associated with increased cardiovascular risk are also associated with central obesity in type 1 diabetes (as well as type 2 diabetes) (102). Individuals with type 1 diabetes are at risk for hypercholesterolemia; the prevalence approached 50% of young adults in one study (103). The prevalence of elevated non-high-density lipoprotein (non-HDL) cholesterol was 25% in a study of individuals <21 yr of age with type 1 diabetes (104).

Adolescents with type 1 diabetes have higher levels of apoB compared with similar age non-diabetics (105). Studies in adults and adolescents with type 1 diabetes suggest a possible complimentary role for measurement of apoB in addition to screening Low-density lipoprotein cholesterol (106). However, data are insufficient at this time to warrant the addition of apoB screening to current lipid screening guidelines for youth with diabetes.

Management of dyslipidemia

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 (107, 108). The Heart Protection Study was a 5-yr interventional study of 5963 patients with diabetes, 10% of whom had type 1 diabetes. This effect was independent of glycemic control and cholesterol levels.

Short-term trials have shown that simvastatin, lovastatin, and pravastatin are effective and safe in children and adolescents (109–111). No significant side effects were observed in terms of growth, pubertal Tanner grading, testicular volume, menarche, endocrine function parameters, or liver or muscle enzymes (112). The efficacy and safety of statins in children with type 1 diabetes still need to be determined in randomized trials, as does the age at which treatment should be initiated. Special attention should be paid to symptoms associated with muscles and connective tissues, as there is an increased risk of rhabdomyolysis (113).

High \geq cholesterol is defined as ≥ 2.6 mmol/L (100 mg/dL). If this is present then interventions to improve metabolic control, dietary changes, and increased exercise should be instituted. If the above interventions do not lower LDL cholesterol to < 4.1 mmol/L (or < 3.4 mmol/L/130 mg/dL and one or more CVD risk factors), statins should be considered in children aged > 10 yr, although long-term safety is not established. Lipid target levels are shown in Table 2 and management in Table 3.

Functional changes in cardiac and peripheral vascular function

Diabetes is also associated with changes in cardiac and peripheral vascular function. In adults diabetes is associated with increased cardiovascular risk and altered cardiovascular function independent of hypertension or other coronary artery disease (114). Diastolic dysfunction is characterized by reduced early diastolic relaxation, changes in ventricular filling patterns (115, 116), increases in left ventricular filling pressure during exercise (117), and decreases in resting and exercising end-diastolic volume (EDV) (118). At

Table 2. Target levels for different parameters to reduce the risk of microvascular and CVD in children and adolescents with type 1 diabetes

| Parameter | Target level |
|-----------------------|---|
| HbA1c (DCCT standard) | $< 7.5\%$ (< 58 mmol/mol) without severe hypoglycemia |
| LDL cholesterol | < 2.6 mmol/L (100 mg/dL) |
| HDL cholesterol | > 1.1 mmol/L (40 mg/dL) |
| Triglycerides | < 1.7 mmol/L (150 mg/dL) |
| Blood pressure | < 90 th percentile by age, sex, and height |
| ACR | $< 130/80$ for adolescents |
| BMI | < 2.5 – 25 mg/mmol in males |
| Smoking | < 3.5 – 25 -mg/mmol in females |
| Physical activity | < 95 th percentile (non-obese) |
| Sedentary activities | > 1 h of moderate physical activity daily |
| Healthy diet | < 2 h daily |
| | Caloric intake appropriate for age and normal growth. |
| | Fat $< 30\%$ of caloric intake, saturated fat $< 10\%$ of caloric intake. |
| | Fiber intake 25–35 g daily. |
| | Increased intake of fresh fruit and vegetables. |

ACR, albumin/creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. Recommended threshold values for different parameters primary prevention and intervention

| Threshold value | Type of intervention |
|--|--|
| Blood pressure > 90 th percentile for age, gender, and height | Lifestyle intervention |
| Blood pressure > 90 th percentile despite lifestyle intervention | ACE inhibitor |
| Blood pressure > 95 th percentile for age, gender, and height | Lifestyle intervention and ACE inhibitor |
| LDL cholesterol ≥ 2.6 mmol/L (100 mg/dL) | Dietary and lifestyle intervention |
| LDL cholesterol ≥ 3.4 mmol/L (130 mg/dL) and one or more CVD risk factors | Statins |

ACE, angiotensin converting enzyme inhibitor; CVD, cardiovascular disease; LDL, low-density lipoprotein.

a more advanced stage, these changes are collectively defined as diabetic cardiomyopathy, which may be a precursor to diastolic heart failure (1). Abnormalities in diastolic filling will affect stroke volume and thus cardiac output. Previous studies in diabetic adults have shown that aerobic capacity and left ventricular stroke volume during exercise are associated with diastolic dysfunction in adults (118, 119). Adults with asymptomatic type 1 diabetes have reduced exercise capacity and lower stroke volume at peak exercise compared with non-diabetic peers, limitations that are strongly associated with diastolic dysfunction (119,

120) and reduced EDV during exercise (118, 119). Current evidence suggests that healthy adolescents with diabetes may also have lower aerobic capacity (121, 122) and lower exercise stroke volume (121). In a recent study, 52 type 1 diabetic adolescents (mean duration of diabetes was 6 yr) were assessed at rest and during submaximal exercise (at a fixed heart rate) by cardiac magnetic resonance imaging (123). These data confirmed that not only was there reduced diastolic filling at rest but this was exacerbated with exercise reducing stroke volume further. Moreover peak heart rate (the only other mechanism to increase cardiac output) was lower in adolescents with diabetes suggesting they will have impaired cardiac output which may limit their aerobic capacity. Diastolic filling was associated with HbA1c but not diabetes duration suggesting this could be reversed with improved control. Indeed there are data from adult elite athletes with diabetes; those with better control have better cardiovascular performance compared with those with poorer control.

Similar to adults, peripheral vascular function is also impaired in children and adolescents with type 1 diabetes. Endothelial dysfunction is an early event in the development of atherosclerosis and it occurs early in type 1 diabetes (124–127). It appears to be intimately involved in the pathogenesis of microvascular and macrovascular complications of diabetes (125, 128, 129). Studies looking at flow mediated vasodilatation and glyceryl trinitrate have elegantly demonstrated impaired vasodilatation in children and adolescents (130–133). Associations with both hyperglycemia and hypoglycemia and reduced endothelial function have been made as well as an improvement of endothelial function with folate (131, 134, 135). However, folate supplementation was only successful when folate was deficient, with no effect of folate in vascular function in folate replete children (136). Increased physical activity may also be beneficial although this data remains conflicting. Impaired vasodilation of muscle capillary beds also results in increased SBP and DBP during exercise. This has been demonstrated in maximal and submaximal exercise paradigms (123).

Prevention of the later vascular complications of diabetes would be assisted by the identification of early abnormalities such as those observed in the heart and peripheral vasculature. While better glycaemic control has been associated with better cardiac and peripheral vascular function, other strategies improving these early changes will potentially reduce the risk of later microvascular and macrovascular complications.

Type 2 diabetes and complications

Type 2 diabetes in youth is associated with greater risk for microalbuminuria and hypertension (95, 137) than

type 1 diabetes. Neuropathy may also be increased (95, 138). Mortality data of those diagnosed 15–30 yr suggest that mortality is higher in type 2 diabetes than type 1 diabetes, for same level of glycaemic control (138). Hence complications screening and attention to risk factors should be more aggressive for youth with type 2 diabetes. In comparison to older people diagnosed with type 2 diabetes youth with type 2 diabetes have greater risk of PDR for the same glycaemic control (139).

Conclusions

Complications become less common when diabetes management is optimized. Other modifying factors are blood pressure, weight, smoking, and lipids, which are more significant/important in type 2 diabetes and insulin resistance. Screening for complications is important during adolescence and also to prepare for lifelong screening.

Conflicts of interest

The authors have declared no conflicts of interest.

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