Early Diabetes-Related Complications in Adolescents

Risk Factors and Screening

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Key Words

Type 1 diabetes · Type 2 diabetes · Diabetes-related complications · Microvascular · Macrovascular · Retinopathy · Nephropathy · Microalbuminuria · Neuropathy · Cardiovascular disease

Abstract

Micro- and macrovascular complications account for the major part of the morbidity and mortality associated with diabetes developing in childhood. Although advanced complications are exceptionally rare in the adolescent age group, it is during this phase that the progression of risk may accelerate. A number of potentially important factors have been identified which might contribute to risk of complication development: some provide insights into the genetics of these complications, while others are potentially modifiable, such as metabolic control, hypertension, smoking, obesity and hyperlipidemia. Recently, both consensus and evidence-based guidelines have been developed to guide those involved in the care of adolescents with diabetes in the prevention, screening and management of early diabetes-related complications in this vulnerable population. This article reviews the literature that underpins the available guidelines and stresses the pivotal role of excellent metabolic control in complication prevention.

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Introduction

A recent analysis from the US Centers for Disease Control and Prevention estimated that among children diagnosed with diabetes at age 10 years, boys would lose, on average, 18.7 life-years and 31.0 quality-adjusted life-years (QALYs), and girls 19.0 life-years and 32.8 QALYs [1]. For this analysis the investigators weighted each year with diabetes as 0.75 of a year without diabetes. This compares to 7.3 life-years lost and 11.1 QALYs lost for a man developing diabetes at age 60. They estimated that only 3% of all cases of diabetes in the US developed before age 20 years, the majority being type 1 diabetes. This may change as the prevalence of type 2 diabetes increases in youth [2]. Thus, while childhood diabetes represents only a small fraction of the total diabetes burden in Western society, those who develop their diabetes at the youngest ages will have disproportionately greater morbidity and mortality over the long term.

This morbidity and mortality is overwhelmingly associated with the long-term micro- and macrovascular complications of diabetes, since early mortality (due to ketoacidosis or hypoglycemia) is very low [3]. The microvascular complications, namely retinopathy, nephropathy and neuropathy, although seldom seen in their florid forms during the childhood years, almost certainly begin soon after diagnosis and accelerate during adolescence [4, 5]. There are good studies available of the natural history

Fig. 1. Estimated probability of MA at final evaluation based on HbA1c level at initial assessment with upper and lower 95% CIs. Broken line represents those initially microalbuminuric ($n = 28$); solid line represents normoalbuminuric group ($n = 47$). Two lines are parallel and linear, with significantly higher probability of MA at final evaluation in those initially microalbuminuric ($p < 0.001$). From Gorman et al. [6].

Table 1. Risk factors for the development of microvascular complications

1	Younger age at onset
2	Longer duration of diabetes
3	Poor glycemic control
4	Higher blood pressure
5	Hyperlipidemia
6	Smoking
7	Family history of diabetes complications, including genetic factors

of and risk factors for diabetic retinopathy and nephropathy, much less in neuropathy [6–10]. Much less is known about the earliest features of macrovascular disease in youth with diabetes [11, 12].

This review focuses on: (1) risk factors for the development of diabetes-related complications; (2) a description of diabetic retinopathy, nephropathy and neuropathy with emphasis on screening recommendations, and (3) macrovascular disease. Given the rarity of advanced complications in youth, health care professionals ought to understand more about the risk factors for these complications and methods for early screening, rather than the details of interventions available for advanced com-

plications. Specific attention will be paid to the evidence-based Clinical Practice Guidelines of the Canadian Diabetes Association (CDA) published in 2003 [13] and the Consensus Guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) of 2000 [14]. The psychological impact of complication awareness and screening has not been well studied and is beyond the scope of this review.

Risk Factors for Microvascular Complications

Numerous factors have been identified that influence the onset and progression of diabetes-related complications (table 1): some, such as specific genes, age of onset or disease duration, are not modifiable; others, such as glycemic control, hypertension, hyperlipidemia and smoking, provide targets for complication prevention and/or intervention.

Glycemic Control

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) established beyond doubt the pivotal role of glycemic control in the onset and progression of microvascular complications in types 1 and 2 diabetes respectively [15, 16]. The DCCT included an adolescent cohort. The approximately 50% (range ~30–70%) lower risk of onset or progression of all three microvascular complications was evident in the adolescents as well as in the adults. This occurred despite the fact that, on average, adolescents achieved HbA1c levels ~1% higher in both treatment groups than in the adults (Intensive treatment group: adults 7.2%, adolescents 8.1%; Conventional treatment group: adults 8.9%, adolescents 9.8%).

The DCCT and UKPDS are supported by cross-sectional and epidemiologic studies assessing the relationship between control and early complications, specifically nephropathy and retinopathy, in adolescents with diabetes [6–10]. For example, our group reported a linear and parallel relationship between initial HbA1c and risk of microalbuminuria an average of 6 years later in teens who were both microalbuminuric and normoalbuminuric at the start of the observation period (fig. 1) [6]. Similarly, Holl and Danne and their colleagues reported a relationship between HbA1c levels and presence and severity of diabetic retinopathy [10, 17]. Furthermore, Schultz et al. [18] in the Oxford Regional Prospective Study demonstrated that children who developed diabetes at the youngest age were at highest risk for nephropathy.

Table 2. Type 1 diabetes: glycemic targets for children and adolescents according to the Canadian Diabetes Association Clinical Practice Guidelines 2003 [19]

Age years	HbA1c %	Preprandial PG mmol/l	Considerations
<5	≤9.0	6.0–12.0	extreme caution is required to avoid severe hypoglycemia because of the risk of cognitive impairment in this age group
5–12	≤8.0	4.0–10.0	targets should be graduated to the child's age
13–18	≤7.0 ≤6.0	4.0–7.0 4.0–6.0	appropriate for most patients consider for patients in whom these targets can be achieved safely

HbA1c = Glycosylated hemoglobin; PG = plasma glucose.

While many have paid less attention to metabolic control before the onset of puberty and while there are data to suggest that the pubertal period may accelerate complication development, most investigators now agree that the prepubertal period does in fact contribute to complication risk (see later) [4, 5, 9, 10, 18]. This provides a challenge in the youngest children to balance the advantages of excellent control against the risk of severe hypoglycemia and its potential neurocognitive consequences [19].

Furthermore, the follow-up of the DCCT (the Epidemiology of Diabetes Interventions and Complications or EDIC Study) provides evidence of what can be termed 'hyperglycemia memory'. Although the institution of improved glycemic control will lower future risk of complication development, the preceding period of poor control continues to contribute significantly to ongoing risk. For example, in the EDIC study both previously intensive and conventional treatment groups now achieved similar HbA1c levels in the years following completion of the DCCT; nonetheless, new microalbuminuria and new proteinuria developed in 4.2 and 0.6%, respectively, of those initially treated intensively compared to 12.7 and 5.4%, respectively, of those who had received conventional treatment [20]. Thus, the benefits of 6.5 years of intensive treatment extend well beyond the period of its most intensive implementation. This has led to the recommendation that intensive treatment be started as soon as is safely possible after the onset of type 1 diabetes and maintained thereafter, aiming for target HbA1c levels of 7.0% or less [21]. These advantages of prior intensive management over conventional treatment were also evident in the adolescent cohort [22].

These data provide the major impetus for development of treatment strategies that can achieve outstanding

Table 3. Barriers to achieving glycemic targets in children and teens with type 1 diabetes

A Biologic factors, e.g.
1 Impaired insulin action ('insulin resistance') during puberty
2 'Exuberant' counterregulatory hormone responses
B Associated illnesses: e.g.
1 Hypo- or hyperthyroidism
2 Celiac disease
C Psychologic or psychosocial factors: e.g.
1 Inadequate knowledge about diabetes and its management – 'knowledge deficit'
2 Lack of appropriate parental supervision, including premature transfer of self-care from parent to child
3 Family dysfunction
4 Adolescent noncompliance, including risk-taking behaviors
5 Psychiatric disturbance, including depression, eating disorders
D Lack of treatment tools capable of achieving physiological outcomes

glycemic control. The Canadian Diabetes Association Clinical Practice Guidelines provide age-specific glycemic and HbA1c targets based on this information [13] (table 2). Unfortunately, there are numerous barriers, some biologic, some associated with other medical conditions, and others psychologic or psychosocial, to achieving these goals in children and teens (table 3). The HbA1c goals in the children aged <5 and 5–12 years are higher than the general recommendations of the DCCT. These recommendations are based on avoidance of hypoglycemia and its consequences in the youngest children, and on the realistic outcomes achieved in the school-aged child. The management of the child or teen with type 1

diabetes with persistently poor glycemic control represents an enormous challenge to health care professionals.

What has not been resolved is whether those teens with the highest HbA1c levels should be targeted for earlier and/or more aggressive screening. Although these are the individuals at highest risk of complication development, the results of the DCCT failed to demonstrate a threshold level of HbA1c below which complications were prevented [15]. As a result no recommendation can be made on the basis of HbA1c levels alone.

Hypertension

Although a clear association has been demonstrated between systemic hypertension and the progression of both microalbuminuria and frank proteinuria, there are very few adolescents whose BP measurements are >97th centile for age and gender [23]. Nonetheless, clinic BP readings are statistically greater in adolescents with microalbuminuria than those with normoalbuminuria, and 24-hour ambulatory BP measurements reveal not only higher mean BPs, but also both the absence of nocturnal dipping and higher pressure burden (defined by percent of readings >97th centile) in the microalbuminuric adolescents [24, 25]. Similarly, hypertension has been implicated in the pathophysiology of diabetic retinopathy and its control may prevent visual loss [26].

Hyperlipidemia

Although a relationship has been established between abnormal lipid metabolism in diabetes and the macrovascular complications [27], less attention has been paid to the relationship between lipid levels and microvascular complications. The Berlin Retinopathy Study found a correlation between the presence of retinopathy and low HDL-cholesterol and raised triglyceride levels [27]. A similar relationship has also been reported between lipid abnormalities and diabetic nephropathy both in experimental animals and humans [28].

Smoking

Smoking is reported in 7–48% of adolescents with diabetes [29, 30]. While studies of the effects of smoking on diabetes-related complications have been performed in adults, there is evidence that smoking is a strong risk factor for the onset of both diabetic nephropathy and retinopathy, and that, in individuals with essential hypertension, smoking can accelerate the progression of renal disease [31, 32].

Family History of Diabetes Complications, Including Genetic Factors

There is evidence of a genetic or familial susceptibility to the development of diabetes-related microvascular complications, particularly diabetic nephropathy: first, familial clustering of complications has been described, and, second, a number of candidate genes have been linked to the evolution of complications.

Quinn et al. [33] examined concordance for diabetic nephropathy in families with multiple siblings with type 1 diabetes: the cumulative risk in siblings after 25 years of type 1 diabetes post-puberty was 71.5% if the proband had persistent proteinuria, but only 25.4% if the proband did not. Similarly, Fioretto et al. [34] evaluated the glomerular structure in sib-pairs with type 1 diabetes: there was very strong concordance in both the severity and patterns of the glomerular lesions, despite a lack of concordance in glycemic control. These two examples of studies support an important role for genetic factors in diabetic nephropathy. The predisposition to essential hypertension may be the key inherited risk factor for the development of both nephropathy and hypertension in type 1 diabetes [35].

No single gene or cluster of genes can explain a major portion of the risk of microvascular complications. Candidate genes include those related to the putative mechanism(s) for development of complications, e.g. those involved in the renin-angiotensin system in nephropathy (e.g. angiotensin-converting enzyme gene or angiotensin II receptor genes); genes related to derangements in growth factors and cytokines (e.g. vascular endothelial growth factor or VEGF), the polyol pathway (e.g. aldose reductase), protein kinase C activation, vascular or platelet function or the nitric oxide pathway [36–39]. The interactions reported between gene polymorphisms and diabetes-related complications have been relatively weak and, in some instances, controversial.

Disease Duration and Impact of Puberty

Although duration of diabetes is recognized as a major contributor to diabetes-related complications, the extreme rarity of complications in prepubertal children and their appearance during puberty, has led some to postulate that the prepubertal years do not contribute substantially to the risk [4]. This view is challenged by the finding of the very earliest stages of microalbuminuria and/or retinopathy even in prepubertal children [4, 9, 10, 40]. However, it is likely that factors during puberty accelerate the development of early complications [4, 9]. Murphy et al. [41] reported that the relative risk of the puber-

tal years was 4.6-fold greater than that for the prepubertal years. Although the factors that mediate this acceleration are not well understood, changes in the GH-IGF-I axis, TGF- β and other hormones, perhaps androgens, likely play important roles [42].

Microvascular Complications

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of new blindness in the developed world. Screening for and management of sight-threatening retinopathy ought to reduce the morbidity associated with this complication, although inadequate or inappropriate use of facilities by health professionals may lessen the effectiveness of such programs.

Diabetic retinopathy proceeds through a series of recognizable stages:

(1) Background retinopathy: develops in almost all people with type 1 diabetes of 20 years' duration. It is not sight-threatening, and may or may not progress. This is the most advanced stage likely to be present in teens [10].

(2) Proliferative retinopathy is highly predictive of progression to more severe stages and, on occasion, may threaten sight.

(3) Proliferative retinopathy is a high risk stage for sight impairment through either retinal detachment or retinal and/or vitreous hemorrhage.

(4) Macular edema, often, but not necessarily present in association with proliferative changes, can also impair vision.

The recommendations for screening for diabetic retinopathy in people with type 1 and type 2 diabetes derive from the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) conducted in the 1980s and 1990s [43]. The WESDR data have been confirmed by smaller clinic-based studies [10]. The findings can be summarized as follows: Diabetic retinopathy rarely develops before 10 years of age in individuals with type 1 diabetes, regardless of disease duration [10, 43]. The prevalence rate increases dramatically after 5 years duration of diabetes in postpubertal individuals with type 1 diabetes [43]. In the WESDR, among those under 15 years of age, 2% were found to have nonproliferative diabetic retinopathy, with none having more severe levels of retinopathy such as macular edema or proliferative changes. In a 4-year follow-up of these subjects, there was no individual under 17 years of age who progressed to

sight-threatening proliferative retinopathy or macular edema [43].

Conversely, the WESDR suggests that in people with type 2 diabetes, retinopathy is already present in 21–39% soon after diagnosis, with sight-threatening retinopathy in 3% [44]. Screening should begin soon after diagnosis in those with type 2 diabetes, although the data are derived from individuals presenting with diabetes over 30 years of age.

Modifiable risk factors, namely glycemic control, hypertension and hyperlipidemia, may be identifiable before the onset of obvious diabetic retinopathy and provide targets for prevention or early intervention [20–22, 27, 45, 46]. Thus, to prevent the onset and delay the progression of diabetic retinopathy, people with diabetes should be treated to achieve optimal control of blood glucose, BP and lipids.

The recommendations of the CDA Clinical Practice Guidelines are appropriate at the present time and make good use of often scarce ophthalmological resources (table 4) [13]:

(1) In people with type 1 diabetes, screening and evaluation for retinopathy by an experienced professional should be performed annually 5 years after the onset of diabetes in individuals ≥ 15 years of age.

(2) In people with type 2 diabetes, screening and evaluation for retinopathy by an experienced professional should be performed at the time of diagnosis [61]. The interval for follow-up assessments should be tailored to the severity of the retinopathy. In those with no or minimal retinopathy, the recommended interval is 1–2 years.

The ISPAD Consensus Guidelines advise screening for retinopathy depending on the presence or absence of puberty at diabetes onset, i.e. in those with prepubertal onset: screening should start 5 years after onset or at age 11 years, or at puberty (whichever is earlier), and annually thereafter; and in those with pubertal onset: 2 years after onset, and annually thereafter [14]. The earlier starting age recommended by the ISPAD guidelines is not supported by the evidence and would lead to demand for ophthalmological services in individuals with exceptionally low likelihood of having retinopathy requiring intervention.

What is certain is that the screening for retinopathy should be performed by experienced professionals, usually ophthalmologists, either in person or through their interpretation of fundus photographs [47]. Although used in a number of studies, fluorescein angiography is no longer an appropriate screening method, while digital, auto-

Fig. 2. Patterns of albumin excretion rates (AERs) in children with type 1 diabetes: (a) persistent normoalbuminuria; (b) intermittent microalbuminuria during adolescence with reversion to normal; (c) intermittent followed by persistent progression of microalbuminuria to frank proteinuria, and (d) rapidly progressive diabetic nephropathy.

mated and nonmydriatic methods appear sufficiently sensitive and specific for large-scale screening [48, 49]. Given the paucity of sight-threatening retinopathy in this age group, rational decisions need to be made about the most cost-effective way in which to screen these teens; in most centers this is likely to be through referral to an ophthalmologist.

Diabetic Nephropathy

Not all individuals appear equally susceptible to developing diabetic nephropathy. This suggests that there are individual susceptibility factors which either increase or decrease risk of nephropathy. Five stages of nephropathy have long been recognized:

(1) Increased kidney size and glomerular filtration rate are often present at disease diagnosis and are considered reversible.

(2) The next stage develops in all individuals over the 2–5 years after diagnosis and consists of mesangial matrix expansion and glomerular basement membrane thickening.

(3) The third stage, usually late in the first decade of the diabetes, is the appearance of microalbuminuria, defined by an albumin excretion rate (AER) in timed overnight or 24-hour urine collections $>15\text{--}20 < 200 \mu\text{g}/\text{min}$. This definition of microalbuminuria is arbitrary given that AER in nondiabetic individuals rarely exceeds $7.2 \mu\text{g}/\text{min}$ [50]. The albumin:creatinine ratio (ACR) is an acceptable alternative screening method: levels above

$2.0 \text{ mg}/\text{mmol}$ in males and $2.8 \text{ mg}/\text{mmol}$ in females warrant further investigation [13].

(4) Overt proteinuria heralds the onset of the fourth stage and is often found in association with hypertension and decreasing GFR. Proteinuria is an ominous finding since studies report a forty-fold increase in mortality in this group.

(5) The final stage occurs with the progression to end-stage renal failure (ESRD), usually 5–10 years after the appearance of overt proteinuria.

As with retinopathy, children and teens with type 1 diabetes rarely progress to the more advanced stages of nephropathy. However, biopsy data reveal the classical changes of diabetic nephropathy as described above and 8–13% of teens with long duration diabetes may develop microalbuminuria. Furthermore, interventions such as glycemic, BP and lipid control may all prevent the onset or delay progression of nephropathy.

In adults with type 1 diabetes, the presence of microalbuminuria is predictive of progression to later stages of nephropathy over the next 5–10 years: earlier reports suggest rates of progression as high as 75–100%, more recently this has been lowered to 50–66% [51–53]. In teens, the predictive value of microalbuminuria has been far less impressive: of 145 teens with microalbuminuria reported in 5 studies, 53% showed regression and 47% persistence or progression of microalbuminuria over the next 3–10 years [6, 7, 18, 54]. Figure 2 demonstrates different patterns of albumin excretion rates over time in teens with

Table 4. Screening for complications in children and adolescents with type 1 diabetes according to the Canadian Diabetes Association Clinical Practice Guidelines 2003 [19]

Complication	Indications and intervals for screening	Screening test
Nephropathy	Yearly screening commencing at puberty in those with duration of type 1 diabetes ≥ 5 years Postpubertal adolescents should be screened yearly after 5 years' duration of type 1 diabetes	First morning ACR If compliance prohibits a first morning urine sample, a random ACR should be obtained Abnormal screening tests require confirmation with a first morning ACR or timed overnight or 24-hour split urine collection for determination of the albumin excretion rate; at least 1 month should elapse between sampling, and repeated sampling should be conducted every 3–4 months over a 12-month period to demonstrate persistence and/or progression
Retinopathy	Yearly screening should commence 5 years after diagnosis of diabetes in individuals >15 years of age Follow-up screening should occur annually or be tailored to severity of retinopathy, if present	7-standard field, stereoscopic-color fundus photography with interpretation by a trained reader (gold standard) Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil Digital fundus photography
Neuropathy	Postpubertal adolescents should be screened yearly after 5 years' duration of type 1 diabetes	None, other than routine clinical assessment
Dyslipidemia	Screening necessary only in those with BMI >95 th percentile, family history of hyperlipidemia or premature CAD, or poor metabolic control	Lipid profile
Hypertension	Routine	Use appropriate cuff size

type 1 diabetes. Higher initial albumin excretion rate, higher HbA1c and earlier age of onset were the best predictors of progression.

The CDA Clinical Practice Guidelines recommend that in children with duration of type 1 diabetes of ≥ 5 years, screening for microalbuminuria should commence at onset of puberty and be performed yearly thereafter. Postpubertal adolescents should be screened yearly after 5 years' duration of type 1 diabetes. Prepubertal children need not be screened (table 4) [13]. This differs only slightly from the ISPAD Consensus Guidelines which recommend that the age of starting screening depend on the onset of the diabetes: prepubertal onset: 5 years after onset or at age 11 years, or at puberty (whichever is earlier), and annually thereafter; pubertal onset of diabetes: 2 years after onset, and annually thereafter [14].

The method of screening is somewhat controversial although the CDA recommends it be conducted using a first morning urine test for determination of the albumin: creatinine ratio (ACR) (table 4) [13, 55]. Our group has used timed overnight urine collections for measurement of AER as the initial screening test. If compliance with either of the aforementioned is poor, random urine ACR should be obtained. Abnormal results require confirma-

tion [56] either with a first morning ACR, a timed overnight or 24-hour split urine collection for determination of AER. At least 1 month should elapse between the abnormal screening and confirmatory tests.

Given the high likelihood of regression of microalbuminuria in teens with type 1 diabetes, it is important that persistence and/or progression of the microalbuminuria be demonstrated by repeat testing every 3–4 months over a 12-month period, prior to any specific renoprotective intervention other than control of glycemia. Optimal glycemic control and, specifically, intensive diabetes management should be the aim of therapy in all people with type 1 or type 2 diabetes for the prevention of onset and delay in progression of early nephropathy [16, 57].

In those with evidence of persistent or progressive microalbuminuria, renoprotection with either angiotensin-converting enzyme inhibition or angiotensin receptor blockade is indicated. There are, however, very few studies of the long-term outcome of such therapy starting in the teen years [58–60]. There is a definite need for a prospective long-term study of these agents in adolescents at risk of nephropathy progression.

Diabetic Neuropathy

Much less attention has been paid to early diabetic neuropathy in children and teens. Nonetheless, numerous studies provide evidence of abnormalities in both peripheral and autonomic nerve function in children and teens with type 1 diabetes [61–65]. Once again, older age, longer duration of diabetes and poorer metabolic control appear to be contributing factors to nerve dysfunction [61, 62].

Riihimaa et al. [61] reported increasing subclinical motor nerve impairment during late puberty and after puberty, and reduced sensory nerve conduction velocity and sensory nerve action potentials in adolescents with type 1 diabetes. Similarly, Abad et al. [62] found that symptomatic abnormal cutaneous thermal perception is a common finding in young patients with type 1 diabetes. Turgut et al. [63] also reported slower dorsal sural nerve sensory action potentials in diabetic compared to healthy children.

With respect to autonomic neuropathy, some, but not all, groups have reported abnormal findings in asymptomatic children and teens [64, 65]. For example, Karavanaki and Baum [64] reported reduced papillary adaptation in darkness in 13.8% of children with diabetes versus 5.8% of controls. Suys et al. [65] found evidence of cardiac dysfunction in a significant proportion of children and adolescents with diabetes: diabetic children had significantly longer QTc intervals and a significantly larger QTc dispersion than controls. On the other hand, Vazeou et al. [66] failed to find a correlation between autonomic function and gastrointestinal symptoms in children and teens with diabetes, nor an effect of mild-to-moderate hyperglycemia on gastrointestinal motility.

Neither the CDA Clinical Practice Guidelines nor the ISPAD Consensus Guidelines [13, 14] suggest specific screening procedures, other than routine clinical assessment, for diabetic neuropathy in the childhood and adolescent population (table 4). Again, the achievement of glycemic targets will prevent the onset or delay progression of neuropathic changes [15, 16].

Notes of Caution: Accelerated Microvascular Complications

There are a few case reports of complications developing in the first few months or years after diagnosis of diabetes even in the face of near normoglycemia [67]. In 6 cases reported in the literature, neuropathy (4/6) and retinopathy (6/6) were distinctly more common than nephropathy (1/6) [67]. These cases highlight the need for clinical vigilance even early in the course of type 1 diabetes

irrespective of metabolic control and particularly perhaps in those with a long prodrome of hyperglycemic symptoms.

Similarly, there are reports of accelerated complications, most frequently retinopathy, in individuals with type 1 diabetes who have been in poor glycemic control for a long time and whose control is rapidly improved [15, 68]. The mechanism for either of these circumstances is not well understood.

Macrovascular Disease

Diabetes is a strong risk factor for all of the manifestations of atherosclerotic vascular disease, including coronary artery, cerebrovascular and peripheral vascular disease. Cardiovascular complications are the most common cause of morbidity and mortality in individuals with diabetes [69]. These clinical outcomes are preceded by changes in the structure and function of the arteries as measured by arterial compliance, distensibility and intima-media thickness (IMT) [70, 71]. Studies of both carotid artery and cardiac structure and function in adolescents with type 1 diabetes vary from normal findings to minor changes in carotid distensibility and compliance to significant differences in IMT [12, 72, 73]. Only Jarvisalo et al. [73] reported significantly greater IMT in peripubertal children with type 1 diabetes compared to controls. Our group found no differences in carotid artery IMT between late adolescents with type 1 diabetes compared to controls over a 3-year follow-up [11].

Similarly, some studies have observed left ventricular dysfunction, higher blood pressure and reduced left ventricular end systolic wall stress, while others have found no difference in these same parameters when comparing a diabetic group with control subjects [11]. Previous studies have shown that children and adolescents with type 1 diabetes did not show any significant change in left ventricular contractility compared to controls [74] and, in those under age 30 there was no difference in chamber size, wall thickness and left ventricular systolic function compared to controls [75]. Other studies found that, when there was a change in the cardiovascular status of young patients with type 1 diabetes, it related to dyslipidemia [73] or impaired renal function [76].

The CDA Clinical Practice Guidelines and the ISPAD Consensus Guidelines stress the need for accurate assessment of BP in teens with diabetes, and the suggested indications for lipid screening. For example, the CDA [13] recommends that only those children and adolescents with type 1 diabetes and other risk factors, such as severe obesity (body mass index >95th percentile), and/or a fam-

ily history of hyperlipidemia or premature coronary artery disease, or those with poor metabolic control should be screened for dyslipidemia [77]. The ISPAD Guidelines state that 'the evolution of macrovascular disease may be reduced by: improved metabolic control of diabetes, BP control; treatment of dyslipidemia (e.g. familial hypercholesterolemia), not smoking, and participation in healthy exercise [14].

With respect to lipid screening, our own approach has been to perform a lipid profile (total, HDL-, LDL-cholesterol and triglyceride concentrations) about 6 months after diagnosis of type 1 diabetes. If these levels are normal, they are repeated again during puberty. If abnormal, appropriate interventions are introduced to improve metabolic control and lower lipid concentrations (diet, exercise and medications).

Management of Diabetes-Related Complications

Intervention strategies can be divided into two categories: those that prevent the onset of complications, or primary prevention; and those that arrest or slow the course of early complications, or secondary intervention. The DCCT and other studies [15, 22] provide the incontrovertible evidence of the impact of intensive diabetes management with the achievement of excellent glycemic and HbA1c goals on both primary prevention and secondary intervention. It is beyond the scope of this review to define specific strategies to achieve age-appropriate glycemic targets (table 2), suffice it to say that the importance of glycemic control as the most important modifiable risk factor cannot be overemphasized.

Once significant complications develop, more specific approaches are required: for retinopathy, referral to a retinal specialist for more frequent follow-up and application of panretinal photocoagulation (laser) therapy, when indicated; for nephropathy, once microalbuminuria becomes persistent and/or progressive, institution of either ACE inhibitor or angiotensin receptor blocker therapy is indicated; for neuropathy, referral to a neurologist to determine specific approaches to treatment. Fortunately, these interventions are only rarely required in teens with long-standing diabetes, usually those with persistently poor glycemic control. As a result, management of these complications is beyond the expertise of most pediatric diabetes teams and expertise of those with experience in these circumstances should be sought.

Part of complication management demands that 'awareness in families, children and adolescents of potential long-term complications is a fundamental part of diabetes education. Such information should be provided

to children at a rate appropriate to their level of understanding and maturity' [14]. Furthermore, since complication development becomes more evident with older age and longer duration of diabetes, it is essential that the transition from pediatric to adult diabetes care occur with as little disruption as possible. The change of physician or diabetes team can have a major impact on disease management and glycemic control in people with diabetes. Between 25 and 65% of young adults are lost to follow-up during the transition from pediatric to adult diabetes care services [78]. Those with no follow-up are more likely to experience hospitalization for DKA during this period and may have a high risk of vascular complications in the long run.

Conclusion

Although the threat of hypoglycemia and diabetic ketoacidosis faces children and teens with diabetes and their families on an everyday basis, the future threat of micro- and macrovascular complications is far less tangible. Thus, education about complications and their prevention (and management) should start at the time of diagnosis of type 1 diabetes and form the basis of the rationale of current therapy, namely maintenance of excellent glycemic control. Regular measurement of HbA1c is the best surrogate marker of long-term complication risk, although it must be noted that there is no HbA1c threshold below which complications do not occur. Identification of other risk factors (smoking, hypertension, hyperlipidemia) and their management is also important. The onset and type of screening for microvascular complications remain debatable, although the CDA Clinical Practice Guidelines 2003 do provide highly appropriate evidence-based recommendations. Newer approaches to complication screening, prevention and management are likely to appear in the near future with techniques such as nonmydriatic fundus photography, and the introduction of targeted therapies such as protein kinase C inhibitors.

References

- Narayan KMV, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF: Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003;290:1884–1890.
- Fagot-Campagna A, Pettit DJ, Engelau MM, et al: Type 2 diabetes among North American children and adolescents: An epidemiological review and public health perspective. *J Pediatr* 2000;136:664–672.
- Matsushima M, LaPorte RE, Maruyama M, Shimizu K, Nishimura R, Tajima N: Geographic variation in the mortality among individuals with youth-onset diabetes mellitus across the world. *DERI Mortality Study Group. Diabetologia* 1997;40:212–216.
- Lawson ML, Sochett EB, Chait PG, Balfe JW, Daneman D: Effect of puberty on markers of glomerular hypertrophy and hypertension in IDDM. *Diabetes* 1996;45:51–55.
- Kostraba JN, Dorman JS, Orchard TJ, Decker DJ, Ohki Y, Ellis D, Doft BH, Lobes LA, LaPorte RE, Drash AL: Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care* 1989;12:686–693.
- Gorman D, Sochett E, Daneman D: The natural history of microalbuminuria in adolescents with type 1 diabetes. *J Pediatr* 1999;134:333–337.
- Shield JP, Hunt LP, Karachaliou F, Karavanaki K, Baum JD: Is microalbuminuria progressive? *Arch Dis Child* 1995;73:512–514.
- Rudberg S, Dahlquist G: Determinants of progression of microalbuminuria in adolescents with diabetes. *Diabetes Care* 1996;19:369–371.
- Schultz CJ, Neil HA, Dalton RN, Dunger DB, Oxford Regional Prospective Study Group: Risk of nephropathy can be detected before the onset of microalbuminuria during the early years after diagnosis of type 1 diabetes. *Diabetes Care* 2000;23:1811–1815.
- Holl RW, Lang GE, Grabert M, Heinze E, Lang GK, Debatin KM: Diabetic retinopathy in pediatric patients with type 1 diabetes: Effect of diabetes duration, prepubertal and pubertal onset of diabetes, and metabolic control. *J Pediatr* 1998;132:790–794.
- Berger E, Sochett EB, Peirone A, Parikh A, Daneman D: Cardiac and vascular function in adolescents and young adults with type 1 diabetes. *Diabetes Technol Ther* 2004;6:129–135.
- Gunczler P, Lanes R, Lopez E, Esaa S, Villarroel O, Revel-Chion R: Cardiac mass and function, carotid artery intima-media thickness and lipoprotein(a) levels in children and adolescents with type 1 diabetes mellitus of short duration. *J Pediatr Endocrinol Metab* 2002;15:181–186.
- Canadian Diabetes Association 2003: Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diab* 2003;27(suppl).
- Consensus Guidelines 2000: International Society for Pediatric and Adolescent Diabetes.
- The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.
- UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853.
- Danne T, Koudonouri O, Hovener G, et al: Monitoring for retinopathy in children and adolescents with type 1 diabetes. *Acta Paediatr* 1998;(suppl)425:35–41.
- Schultz CJ, Konopelska-Bahu T, Dalton RN, Carroll TA, Stratton I, Gale EA, Neil A, Dunger DB: Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. *Oxford Regional Prospective Study group. Diabetes Care* 1999;22:495–502.
- Ryan C, Vega A, Drash A: Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 1985;75:921–927.
- Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 2000;342:381–389.
- Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002;287:2563–2569.
- White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV: Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group: Beneficial effects of intensive therapy of diabetes during adolescence: Outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001;139:804–812.
- Cook J, Daneman D: Microalbuminuria in adolescents with insulin-dependent diabetes mellitus. *Am J Dis Child* 1990;144:234–237.
- Norgaard K, Feldt-Rasmussen B, Borch-Johnsen K, et al: Prevalence of hypertension in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1992;33:407–410.
- Sochett EB, Poon I, Balfe JW, Daneman D: Ambulatory blood pressure monitoring in IDDM adolescents with and without microalbuminuria. *J Diabetes and its Complications* 1998;12:18–23.
- Sjolie AK, Moller F: Medical management of diabetic retinopathy. *Diabet Med* 2004;21:666–672.
- Koudonouri O, Danne TH, Hopfenmuller W, et al: Lipid profiles and blood pressure: Are they risk factors for the development of early background retinopathy and incipient nephropathy in children with insulin-dependent diabetes mellitus? *Acta Paediatr* 1996;85:43–48.
- Danne T, Koudonouri O, Hovener G, et al: Diabetic angiopathy in children. *Diabet Med* 1997;14:1012–1025.
- Hargrave DR MC, O'Hare MM, Carson DJ: Tobacco smoke exposure in children and adolescents with diabetes mellitus. *Diab Med* 1999;16:31–34.
- Holl RW, Grabert M, Heinze E, Debatin KM: Objective assessment of smoking habits by urinary cotinine measurement in adolescents and young adults with type 1 diabetes: Reliability of cigarette consumption and relationship to urinary albumin excretion. *Diabetes Care* 1998;21:787–791.
- Chaturvedi N, Stephenson JM, Fuller JH: The relationship between smoking and microvascular complications in the EURODIAB IDDM Complications Study. *Diabetes Care* 1995;18:785–792.
- Ritz E, Ogata H, Orth SR: Smoking: A factor promoting onset and progression of diabetic nephropathy. *Diabetes Metab* 2000;26(suppl 4):54–63.
- Quinn M, Angelico MC, Warram JH, Krolewski AS: Familial factors determine the development of diabetic nephropathy in patients with IDDM. *Diabetologia* 1996;39:940–1045.
- Fioretto P, Steffes MW, Barbosa J, Rich SS, Miller ME, Mauer M: Is diabetic nephropathy inherited? Studies of glomerular structure in type 1 diabetic sibling pairs. *Diabetes* 1999;48:865–869.
- Barzilay J, Warram JH, Laffel LM, Canessa M, Krolewski AS: Predisposition to hypertension: Risk factor for nephropathy and hypertension in IDDM. *Kidney Int* 1992;41:732–730.
- Orsio S: Gene polymorphism of the renin-angiotensin system and progression of diabetic nephropathy. *J Nephrol* 1999;12:9–17.
- Ray D, Mishra M, Ralph S, Read I, Davies R, Brenchley P: Association of the VEGF gene with proliferative diabetic retinopathy but not proteinuria in diabetes. *Diabetes* 2004;53:861–864.
- Petrovic MG, Hawlina M, Peterlin B, Petrovic D: BgIII gene polymorphism of the alpha2beta1 integrin gene is a risk factor for diabetic retinopathy in Caucasians with type 2 diabetes. *J Hum Genet* 2003;48:457–460.
- Neugebauer S, Baba T, Watanabe T: Association of nitric oxide gene polymorphism with an increased risk for progression of diabetic nephropathy in type 2 diabetes. *Diabetes* 2000;49:500–503.

- 40 Donaghue KC, Fung AT, Hing S, Fairchild J, King J, Chan A, Howard NJ, Silink M: The effect of prepubertal diabetes duration on diabetes. Microvascular complications in early and late adolescence. *Diabetes Care* 1997;20:77–80.
- 41 Murphy RP, Randa M, Plotnik L, et al: The relationship of puberty to diabetic retinopathy. *Arch Ophthalmol* 1990;108:215–218.
- 42 Cummings EA, Sochett EB, Dekker M, Lawson M, Daneman D: Contribution of growth hormone and IGF-1 to early diabetic nephropathy in type 1 diabetes. *Diabetes* 1998;47:1341–1346.
- 43 Klein R, Klein BEK, Moss SE, et al: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1989;107:237–243.
- 44 Klein R, Klein BEK, Moss SE, et al: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Ophthalmol* 1989;107:244–249.
- 45 UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–713.
- 46 Chew EY, Klein ML, Ferris FL III, et al: Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. *Arch Ophthalmol* 1996;114:1079–1084.
- 47 Buxton MJ, Sculpher MJ, Ferguson BA, et al: Screening for treatable diabetic retinopathy: A comparison of different methods. *Diabet Med* 1991;8:371–377.
- 48 Larsen N, Godt J, Grunkin M, Lund-Ansersen H, Larsen M: Automated detection of diabetic retinopathy in a fundus photographic screening population. *Invest Ophthalmol Vis Sci* 2003;44:767–771.
- 49 Perrier M, Bouchier MC, Angioi K, Gresset JA, Olivier S: Comparison of two, three and four 45 degrees image fields obtained with the Topcon CRW6 nonmydriatic camera for screening for diabetic retinopathy. *Can J Ophthalmol* 2003;38:569–574.
- 50 Couper JJ, Clarke CF, Byrne GC, Jones TW, Donaghue KC, Nairn J, Boyce D, Russell M, Stephens M, Raymond J, Bates DJ, McCaul K: Progression of borderline increases in albuminuria in adolescents with insulin-dependent diabetes mellitus. *Diabet Med* 1997;14:766–71.
- 51 Mogensen CE, Chistensen CK: Predicting diabetic nephropathy in insulin-dependent patients. *New Engl J Med* 1984;311:89–93.
- 52 Viberti GC, Hill RD, Jarrett RJ, et al: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;i:1430–1432.
- 53 Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS: Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 2003;348:2285–2293.
- 54 Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J: Glycemic control and prognosis in type 1 diabetic patients with microalbuminuria. *Diabetes Care* 1996;19:313–317.
- 55 Shield JPH, Hunt LP, Baum JD, et al: Screening for diabetic microalbuminuria in routine clinical care: Which method? *Arch Dis Child* 1995;72:524–525.
- 56 Houlihan CA, Tsalamandris C, Akdeniz A, et al: Albumin to creatinine ratio: A screening test with limitations. *Am J Kidney Dis* 2002;39:1183–1189.
- 57 The Diabetes Control and Complications (DCCT) Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995;47:1703–1720.
- 58 Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF: Effect of antihypertensive therapy on kidney in patients with diabetes: A meta-regression analysis. *Ann Intern Med* 1993;118:129–138.
- 59 Cook J, Daneman D, Spino M, Sochett E, Perlman K, Balfe JW: Angiotensin converting enzyme inhibitor therapy decreases microalbuminuria in normotensive children with insulin-dependent diabetes mellitus. *J Pediatr* 1990;117:39–45.
- 60 Rudberg S, Osterby R, Bangstad HJ, Dahlquist G, Persson B: Effect of angiotensin converting enzyme inhibitor or beta blocker on glomerular structural changes in young microalbuminuric patients with type 1 diabetes. *Diabetologia* 1999;42:589–595.
- 61 Riihimaa PH, Suominen K, Tolonen U, Jantti V, Knip M, Tapanainen P: Peripheral nerve function is increasingly impaired during puberty in adolescents with type 1 diabetes. *Diabetes Care* 2001;24:1087–1092.
- 62 Abad F, Diaz-Gomez NM, Rodriguez I, Perez R, Delgado JA: Subclinical pain and thermal sensory dysfunction in children and adolescents with type 1 diabetes. *Diabet Med* 2002;19:827–831.
- 63 Turgut N, Karasalioglu S, Kucukugurluoglu Y, Balci K, Ekuklu G, Tutunculer F: Clinical utility of dorsal sural nerve conduction studies in healthy and diabetic children. *Clin Neurophysiol* 2004;115:1452–1456.
- 64 Karavanaki K, Baum JD: Coexistence of impaired indices of autonomic neuropathy and diabetic nephropathy in a cohort of children with type 1 diabetes. *J Pediatr Endocrinol Metab* 2003;16:79–90.
- 65 Suys BE, Huybrechts SJ, De Wolf D, et al: QTc prolongation and QTc dispersion in children and adolescents with type 1 diabetes. *J Pediatr* 2002;141:59–63.
- 66 Vazeou A, Papadopoulou A, Papadimitriou A, et al: Autonomic neuropathy and gastrointestinal motility disorders in children and adolescents with type 1 diabetes. *J Pediatr Gastroenterol Nutr* 2004;38:61–65.
- 67 Hamilton J, Brown M, Silver R, Daneman D: Early onset of severe diabetes mellitus-related microvascular complications. *J Pediatr* 2004;144:281–283.
- 68 Daneman D, Drash AL, Lobes LA, Becker DJ, Baker LM, Travis LB: Progressive retinopathy with improved control in diabetic dwarfism (Mauriac's syndrome). *Diabetes Care* 1981;4:360–365.
- 69 Calles-Escandon J, Cipolla M: Diabetes and endothelial dysfunction: A clinical perspective. *Endocr Rev* 2001;22:36–52.
- 70 Frost D, Friedl A, Beischer W: Determinants of early carotid atherosclerosis progression in young patients with type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2002;110:92–94.
- 71 Giannattasio C, Failla M, Grappiolo A, Gamba PL, Paleari F, Mancia G: Progression of large artery structural and functional alteration in type 1 diabetes. *Diabetologia* 2001;44:203–208.
- 72 Yavuz T, Akcay A, Omeroglu RE, Bundak R, Sukur M: Ultrasonic evaluation of early atherosclerosis in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002;15:1131–1136.
- 73 Jarvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Ronnemaa T, Raitakari OT: Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes* 2002;51:493–498.
- 74 Schwindshandl J, Ward C, Silink M, Sholler G: Echocardiographic load-independent indices of contractility in children and adolescents with type 1 Diabetes: Effect of metabolic control and insulin on left ventricular performance. *Pediatr Cardiol* 1995;16:1–5.
- 75 Kimball T, Daniels S, Khoury P, Magnotti R, Turner A, Dolan L: Cardiovascular status in young patients with insulin-dependent diabetes mellitus. *Circulation* 1994;90:357–361.
- 76 Chen MR, Lee YJ, Hsu CH, Kao HA, Huang FY: Cardiovascular function in young patients with type 1 diabetes mellitus. *Acta Paediatr Taiwan* 1999;40:250–254.
- 77 Abraha A, Schultz C, Konopelska-Bahu T, et al: Glycaemic control and familial factors determine hyperlipidaemia in early childhood diabetes. *Diabet Med* 1999;16:598–604.
- 78 Frank M: Factors associated with non-compliance with a medical follow-up regimen after discharge from a pediatric diabetes clinic. *Can J Diabetes Care* 1996;20:13–20.