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Microvascular and macrovascular complications

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

- Visual impairment and blindness due to diabetic retinopathy.
- Renal failure and hypertension due to diabetic nephropathy.
- Pain, paresthesiae, muscle weakness, and autonomic dysfunction due to diabetic neuropathy.
- Cardiac disease, peripheral vascular disease, and stroke due to macrovascular disease.

Clinically evident diabetes-related vascular complications should be rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease.

There has been a declining incidence of complications reported in many areas with specialized clinics (1–3). This has 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. 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.

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 (4). At recruitment, 195 were pubertal adolescents (aged 13–17 yr); there were no children (5). After completion of the DCCT (a median of 7.4 yr in the adolescent group) and hence the end of randomization to the two treatment groups (intensive and conventional treatments), the Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow patients (6). After 4 yr, there was no significant difference in hemoglobin A1c (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 (5) (A).

The EDIC study has shown that this positive effect continued after randomization, i.e., there was a memory effect of the improved glycemic control. In addition, it showed a positive effect of intensive therapy for reduction in macrovascular disease (7) (A).

Table 1. Screening, risk factors, and interventions for vascular complications: the levels of evidence for risk factors and interventions pertaining to adult studies, except for improved glycemic control. For clarity, references for these evidence levels are included in the text

	When to commence screening?	Screening methods	Risk factors	Potential intervention
Retinopathy	Annually from age 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration (E)	Fundal photography or mydriatic ophthalmoscopy (less sensitive) (E)	Hyperglycemia (A), high blood pressure (B), lipid abnormalities (B), and higher BMI (C)	Improved glycemic control (A) and laser therapy (A)
Nephropathy	Annually from age 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration (E)	Urinary albumin/creatinine ratio or first morning albumin concentration (E)	High blood pressure (B), lipid abnormalities (B), and smoking (B)	Improved glycemic control (A), ACEI and AIIRA (A), and blood pressure lowering (B)
Neuropathy	Unclear	History and physical examination	Hyperglycemia (A) and higher BMI (C)	Improved glycemic control (A)
Macrovascular disease	After the age of 12 yr (E)	Lipid profile every 5 yr and blood pressure annually (E)	Hyperglycemia (A), high blood pressure (A), lipid abnormalities (B), higher BMI (B), and smoking (B)	Improved glycemic control (A), blood pressure control (B), and statins (A)

ACEI, angiotensin-converting enzyme inhibitors; AIIRA, angiotensin II receptor antagonists; BMI, body mass index.

In the adolescent cohort, intensive treatment compared with conventional treatment reduced the risk and progression of background 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 EDIC study: the previously intensively managed group had 74% less retinopathy, 48% less microalbuminuria, and 85% less albuminuria (6).

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 that of the control group during a mean 17 yr follow-up (7).

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 (8–10). In the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risk of early retinal deterioration. Ophthalmological monitoring is recommended before initiation of intensive treatment and at 3-month intervals for 6–12 months thereafter for patients with long-standing poor glycemic control, particularly if

Table 2. Target levels for different parameters to reduce the risk of microvascular and cardiovascular diseases in children and adolescents with type 1 diabetes; the levels of evidence pertain to adult studies

Parameter	Target level	Evidence grade
Hemoglobin A1c (Diabetes Control and Complications Trial standard)	≤7.5% without severe hypoglycemia	A
Low-density lipoprotein cholesterol	<2.6 mmol/L	A
High-density lipoprotein cholesterol	>1.1 mmol/L	C
Triglycerides	<1.7 mmol/L	C
Blood pressure	<90th percentile by age, sex, and height	C/B
Body mass index	<95th percentile (non-obese)	E
Smoking	None	A
Physical activity	>1 h of moderate physical activity daily	B
Sedentary activities	<2 h daily	B
Healthy diet	Caloric intake appropriate for age and normal growth Fat <30% of caloric intake and saturated fat <10% of caloric intake Fiber intake 25–35 g daily Increased intake of fresh fruit and vegetables	E

Table 3. Recommended threshold values for different parameters for intervention and the primary prevention; the levels of evidence pertain to adult studies

Threshold value	Type of intervention	Evidence grade
Blood pressure >90th percentile for age, gender, and height	Lifestyle intervention	B
Blood pressure >90th percentile despite lifestyle intervention	ACEI	E
Blood pressure >95th percentile	Lifestyle intervention and ACEI	A
LDL cholesterol >2.6 mmol/L	Dietary intervention	A/C
LDL cholesterol >3.4 mmol/L and one or more cardiovascular disease risk factors	Statins	A/C

ACEI, angiotensin-converting enzyme inhibitors; LDL, low-density lipoprotein.

retinopathy severity is at or past the moderate non-proliferative stage at the time of intensification (E).

Other risk factors for the development of complications

Longer duration of diabetes, older age, and puberty are risk factors for complications (11). The pre-pubertal years of diabetes duration have a significantly lesser impact especially further from the onset of gonadarche (12) (B). For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated albumin excretion rate (AER) (13) (B).

Smoking is associated with an increased risk of developing persistent microalbuminuria or macroalbuminuria (4, 14). The evidence for the effect of smoking on retinopathy is less clear. Type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality (15) (B).

Hypertension has a greater impact on cardiovascular disease (CVD) in diabetic patients than in non-diabetic individuals (16). Blood pressure control (<140/80 mmHg in adults) is effective in decreasing cardiovascular morbidity and mortality in diabetes (17) (A).

Dyslipoproteinemia is associated with microalbuminuria and retinopathy developments in the DCCT/EDIC (18, 19). This included higher total and low-density lipoprotein (LDL) cholesterol and higher triglyceride levels for microalbuminuria, as well as larger LDL particle size and apoprotein B in men (B).

Family history of complications increases the risk for nephropathy (20) and retinopathy (21) (B).

Higher body mass index (BMI) is a risk factor for retinopathy (22), neuropathy (23), microalbuminuria (24), and CVD (25) (B).

Lifestyle issues – sedentary men with diabetes have higher mortality than active individuals (26) (B).

Diabetic retinopathy

Adolescents have a higher risk of progression to vision-threatening retinopathy compared with adult

patients with diabetes (27, 28). The progression may be rapid, especially in those with poor glycemic control (29). 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 (27, 28, 30).

Progression of retinopathy

Background retinopathy is characterized by microaneurysms specific to diabetic retinopathy; hemorrhages both pre-retinal and intraretinal; soft and hard exudates involving microinfarction and protein and lipid leakages, respectively; intraretinal microvascular abnormalities and dilatation; and constriction and tortuosity of vessels. Background retinopathy is not vision threatening and does not invariably progress to proliferative retinopathy.

Preproliferative retinopathy is characterized by vascular obstruction, progressive intraretinal microvascular abnormalities, and infarctions of the retinal nerve fibers causing cotton wool spots.

Proliferative retinopathy is characterized by neovascularization in the retina and/or vitreous posterior surface. The vessels may rupture or bleed into the vitreoretinal space which is vision threatening. Encasement in connective tissue results in adhesions, which can cause hemorrhage and retinal detachment. High-risk characteristics for visual loss are the location and extent of neovascularization and signs of vitreous or pre-retinal hemorrhage (31).

Maculopathy is characterized by decreased vascular competence and microaneurysm formation, which produce exudation and swelling in the central retina.

Assessment of retinopathy

The most sensitive detection methods for retinopathy are stereoscopic fundal photography and fluorescein angiography. Seven-field stereoscopic fundus photography provides greater sensitivity for detecting both background and proliferative retinopathies compared

with direct ophthalmoscopy (28, 32, 33) (A). Fluorescein angiography reveals functional abnormalities (vascular permeability) as well as structural abnormalities in the blood vessels, whereas fundal photography reveals only structural abnormalities.

Other techniques used in the detection of diabetic retinopathy include indirect ophthalmoscopy and monochromatic single-field photography. In adults with diabetes, mydriasis reduced the technical failure rate over non-mydriatic fundal photography but did not improve sensitivity and specificity for detection of diabetic retinopathy or reduce the need for referral compared with undilated fundal photography of a single field (34).

In an incident cohort, after 6 yr of duration with HbA1c of 8.7%, 7-field stereoscopic fundal photography detected early retinopathy (one microaneurysm or hemorrhage) in 8% of children less than 11 yr and 12% of prepubertal children. This compares with retinopathy detection in 25% of adolescents older than 11 yr and 29% of pubertal adolescents (13) (B). Screening from age 11 yr with 2 yr of diabetes duration or from 9 yr with 5 yr of duration will capture most retinopathy developing in children and adolescents (E).

Laser treatment for retinopathy

Once sight-threatening retinopathy 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 areas but sparing the central macula. It has been proven to reduce the progression of visual loss by more than 50% in patients with proliferative retinopathy (31, 35) (A). However, photocoagulation is not indicated for eyes with mild or moderate non-proliferative retinopathy (36). Side effects of treatment are decreased night and peripheral visions and subtle changes in color perception. Complications of laser therapy are vitreal and choroidal hemorrhages or visual sequelae of misplaced burns.

Diabetic nephropathy

Diabetic nephropathy is defined as persistent proteinuria greater than 500 mg/24 h or albuminuria greater than 300 mg/24 h and is usually associated with hypertension and a diminishing glomerular filtration rate (37). 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 (38, 39).

Assessment of incipient nephropathy

The first clinical sign is microalbuminuria. This is defined (37) as any of those below:

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

Other definitions have also been used in longitudinal studies.

Microalbuminuria is confirmed by finding two or all three samples abnormal over a period of 3–6 months.

Persistent microalbuminuria has been shown to predict the progression to end-stage renal failure (2, 30, 31, 40–42) and is associated with an increased risk of macrovascular disease (43, 44) (B).

An increase of AER within the microalbuminuric range identifies patients at risk of progression to renal damage (24, 45, 46) (B). Loss of nocturnal dipping on 24-h blood pressure monitoring is an early marker of diabetic renal disease preceding microalbuminuria (47). Microalbuminuria can also regress (48), especially in adolescents (24, 49). Progression to microalbuminuria is preceded by renal hypertrophy (50) (B).

Confounders – exercise increases the AER in non-diabetic individual and increases it more markedly during diabetes. Even moderate exercise may interfere with the interpretation of data (37). 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 or other types of nephritis common in childhood.

In an incident cohort, after 6 yr of duration, early elevation of AER (greater than 7.5 $\mu\text{g}/\text{min}$) was detected in 5% of children younger than 11 yr and 5% of prepubertal children: no microalbuminuria was detected. This compared with early elevation of AER in 25% adolescents older than 11 yr and 26% of pubertal adolescents. (13). Screening from age 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration will capture most evolving microalbuminuria in children and adolescents (E).

Antihypertensive treatment for prevention of nephropathy

Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease (51) (B). 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 (52), predominantly due to aggressive antihypertensive treatment, with smaller contributions from improved glycemic control and smoking cessation (B).

Blood pressure values between the 90th and 95th percentiles are defined as prehypertension (53, 54). Protocols and reference values for 24-h ambulatory blood pressure monitoring in children have also been published (21, 47). Angiotensin-converting enzyme inhibitors (ACEI) are recommended for use in children and adolescents with hypertension (55). They have been effective and safe in children in short-term studies (28, 56). The clinical beneficial effect of angiotensin II receptor antagonists (AIIRA) in hypertension is similar to that observed with ACEI but have not been used extensively in children.

ACEI and AIIRA reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria (57) (A). For those with microalbuminuria, ACEI and AIIRA reduce the doubling of serum creatinine. While ACEI reduces all-cause mortality, AIIRA use was associated with higher all-cause mortality compared with placebo (A).

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 individuals without hypertension. In meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria (58) (A). Young people with microalbuminuria would potentially be taking ACEI for decades. Side effects include cough, hyperkalemia, headache, and impotence (57). Furthermore, an increase in major congenital malformations has recently been reported after first-trimester exposure to ACEI but not with other antihypertensive agents in non-diabetic women (59).

Diabetic neuropathy

Diabetes can affect the somatic and autonomic nervous systems. The somatic neuropathies associated with diabetes fall into the following two broad categories:

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.

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 (60).

Assessment of neuropathy

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

Autonomic nerve tests include heart rate response to deep breathing, standing from a lying position, Valsalva maneuver, heart rate variation at rest, QT interval, postural changes in blood pressure, and pupillary responses to light and dark adaptation. Peripheral nerve tests include quantitating 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.

Nerve function test abnormalities have not decreased in an adolescent population in which retinopathy and microalbuminuria have decreased over the same time: peripheral nerve abnormalities actually increased (3). This is probably due to the increasing BMI which has occurred over the same time (B).

Macrovascular disease

The mortality and morbidity of CVD are markedly increased in diabetic individuals compared with that in non-diabetic population (61) (B).

Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (16). Blood pressure control (<140/80 mmHg in adults) reduces cardiovascular morbidity and mortality in diabetes (17) (A).

A family history of early CVD (before 55 yr of age), lipid disturbances, type 2 diabetes, hypertension (10), and smoking place the individual with diabetes at higher risk (B).

Atherosclerosis starts in childhood and adolescence as shown by intima-media thickness of the carotids and aorta (62) and silent coronary atherosclerosis measured by intravascular ultrasound in young adults with childhood-onset diabetes (9) (B). Silent coronary atherosclerosis (9) and cardiovascular events (7) are strongly associated with poor glycemic control (A).

Cholesterol plays an important role in the initiation and progression of atherosclerosis (53). Well-controlled type 1 diabetes is not associated with gross blood lipid disturbances, but more advanced lipoprotein subclass examinations reveal atherogenic profiles (18). Poor glycemic control was associated with a potentially more atherogenic lipoprotein profile (63).

Changes in lipids associated with increased cardiovascular risk are also associated with central obesity in type 1 diabetes (as well as type 2 diabetes) (64). Individuals with type 1 diabetes are as much at risk for hypercholesterolemia as the non-diabetic population. The prevalence approached 50% of young adults in one study (65). The prevalence of elevated non-high-density lipoprotein cholesterol was 25% in a study of individuals younger than 21 yr of age with type 1 diabetes (66).

In adults, statins are effective in the primary and secondary preventions of major cardiovascular events, stroke, and limb revascularization in patients with diabetes (67) (A). The Heart Protection Study was a 5-yr interventional study of 5963 patients with diabetes, in which 10% 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 (68–70). No significant side effects were observed in terms of growth, pubertal Tanner grading, testicular volume, menarche, endocrine function parameters, or liver or muscle enzymes. 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 (71).

Screening for and prevention of complications

Screening for diabetes complications aims to detect subclinical complications, which may be treated to delay progression to clinical disease.

- Improvement in glycemic control will reduce the risk for onset and progression of diabetes vascular complications (A).
- Initial eye examination should occur shortly after diagnosis to detect cataracts or major refractive errors that require treatment for binocular vision (E).
- Screening for retinopathy and microalbuminuria should start from 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration and after 2 yr of diabetes duration in an adolescent (13) (E).
- Minimum assessment for retinopathy should be by ophthalmoscopy through dilated pupils by an experienced observer (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 less than 10 yr, minimal background retinopathy on fundal photography and reasonable glycemic control, biennial assessment by fundal photography, can occur (27) (E).

- Laser treatment reduces the rate of visual loss for vision-threatening retinopathy (A).
- Annual screening for microalbuminuria should be undertaken by any of the methods below (13):
- First morning urine samples (AC).
- Spot urine: ACR.
- Timed urine collections (AER). Timed overnight urine collections are generally easier for adolescents and are less subject to the effects of exercise and posture.
- Because of biological variability, two of three consecutive collections should be used as evidence of microalbuminuria. Confounders are exercise and menstrual bleeding.
- Abnormal screening tests should be repeated, as microalbuminuria may disappear and not be persistent.
- When persistent microalbuminuria is confirmed, screening for retinopathy, neuropathy, and lipid abnormalities is also recommended (E).
- ACEI are recommended for use in children with hypertension (55) (E). They have been effective and safe in children in short-term studies (28, 56) but are not safe during pregnancy.
- ACEI or AIIIRA agents should be used in patients with persistent microalbuminuria to prevent progression to proteinuria (E) in adolescents.
- Blood pressure should be measured at least annually. (E) Confirmation of hypertension may be assisted by 24-h ambulatory blood pressure measurements (E).
- Blood pressure values should be compared with age-appropriate centile charts (55). Blood pressure should be maintained at less than the 95th centile for age as in all children with hypertension (55) (E).
- Screening for fasting blood lipids should be performed soon after diagnosis (when diabetes stabilized) in all children with type 1 diabetes older than 12 yr (E). If normal results are obtained, this should be repeated every 5 yr. If there is a family history of hypercholesterolemia, early CVD, or if the family history is unknown, screening should start at 2 yr of age (8) (E).
- Target level for LDL cholesterol should be lower than 2.6 mmol/L. If interventions to improve metabolic control and dietary changes cannot help reach the target level, statins should be considered, although long-term safety is not established (55) (E).
- Cessation of smoking/never initiating smoking will reduce progression of microalbuminuria and CVD (52) (B).

References

1. BOJESTIG M, ARNOVIST HJ, HERMANSSON G, KARLBERG BE, LUDVIGSSON J. Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 1994; 330: 15–18.

2. MOHSIN F, CRAIG ME, CUSUMANO J et al. Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002. *Diabetes Care* 2005; 28: 1974–1980.
3. ROSSING P, HOUGAARD P, PARVING HH. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients: a 10-year prospective observational study. *Diabetes Care* 2002; 25: 859–864.
4. DCCT 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.
5. DCCT RESEARCH GROUP. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994; 125: 177–188.
6. DCCT/EDIC WRITING GROUP. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003; 290: 2159–2167.
7. NATHAN DM, CLEARY PA, BACKLUND JY et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353: 2643–2653.
8. AMERICAN DIABETES ASSOCIATION. Management of dyslipidemia in children and adolescents with diabetes. *Diabetes Care* 2003; 26: 2194–2197.
9. LARSEN J, BREKKE M, SANDVIK L, ARNESEN H, HANSEN KF, DAHL-JØRGENSEN K. Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glyemic control. *Diabetes* 2002; 51: 2637–2641.
10. MAKIMATTILA S, YLITALO K, SCHLENZKA A et al. Family histories of Type II diabetes and hypertension predict intima-media thickness in patients with Type I diabetes. *Diabetologia* 2002; 45: 711–718.
11. KROLEWSKI AS, WARRAM JH, CHRISTLIEB AR, BUSICK EJ, KAHN CR. The changing natural history of nephropathy in type I diabetes. *Am J Med* 1985; 78: 785–794.
12. DONAGHUE KC, FAIRCHILD JM, CRAIG ME et al. Do all prepubertal years of diabetes duration contribute equally to diabetes complications? *Diabetes Care* 2003; 26: 1224–1229.
13. DONAGHUE KC, CRAIG ME, CHAN AK et al. Prevalence of diabetes complications 6 years after diagnosis in an incident cohort of childhood diabetes. *Diabet Med* 2005; 22: 711–718.
14. COUPER JJ, STAPLES AJ, COCCIOLONE R, NAIRN J, BADCOCK N, HENNING P. Relationship of smoking and albuminuria in children with insulin-dependent diabetes. *Diabet Med* 1994; 11: 666–669.
15. GAY EC, CAI Y, GALE SM et al. Smokers with IDDM experience excess morbidity. The Colorado IDDM Registry. *Diabetes Care* 1992; 15: 947–952.
16. STAMLER J, VACCARO O, NEATON JD, WENTWORTH D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16: 434–444.
17. HANSSON L, ZANCHETTI A, CARRUTHERS SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351: 1755–1762.
18. JENKINS AJ, LYONS TJ, ZHENG D et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. *Kidney Int* 2003; 64: 817–828.
19. LYONS TJ, JENKINS AJ, ZHENG D et al. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. *Invest Ophthalmol Vis Sci* 2004; 45: 910–918.
20. SEAQUIST ER, GOETZ FC, RICH S, BARBOSA J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 1989; 320: 1161–1165.
21. SOERGEL M, KIRSCHSTEIN M, BUSCH C et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects *J Pediatr* 1997; 130: 178–184.
22. DORCHY H, CLAES C, VEROUSTRATE C. Risk factors of developing proliferative retinopathy in type 1 diabetic patients: role of BMI. *Diabetes Care* 2002; 25: 798–799.
23. DE BLOCK CE, DE LEEUW IH, VAN GAAL LF. Impact of overweight on chronic microvascular complications in type 1 diabetic patients. *Diabetes Care* 2005; 28: 1649–1655.
24. STONE ML, CRAIG ME, CHAN AK, LEE JW, VERGE CF, DONAGHUE KC. Natural history and risk factors for microalbuminuria in adolescents with type 1 diabetes: a longitudinal study. *Diabetes Care* 2006; 29: 2072–2077.
25. KOIVISTO VA, STEVENS LK, MATTOCK M et al. Cardiovascular disease and its risk factors in IDDM in Europe. EURODIAB IDDM Complications Study Group. *Diabetes Care* 1996; 19: 689–697.
26. MOY CS, SONGER TJ, LAPORTE RE et al. Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol* 1993; 137: 74–81.
27. MAGUIRE A, CHAN A, CUSUMANO J et al. The case for biennial retinopathy screening in children and adolescents. *Diabetes Care* 2005; 28: 509–513.
28. SOFFER B, ZHANG Z, MILLER K, VOGT BA, SHAHINFAR S. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens* 2003; 16: 795–800.
29. MAGUIRE A, CUSUMANO JM, CRAIG ME, DONAGHUE KC. The case for biennial retinopathy screening in children and adolescents: response to Stefánsson. *Diabetes Care* 2006; 29: 178–179.
30. KLEIN R, KLEIN BE, MOSS SE, DAVIS MD, DEMETS DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984; 102: 520–526.
31. DIABETIC RETINOPATHY STUDY RESEARCH GROUP. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. *Ophthalmology* 1978; 85: 82–106.
32. HUTCHINSON A, MCINTOSH A, PETERS J et al. Effectiveness of screening and monitoring tests for diabetic retinopathy – a systematic review. *Diabet Med* 2000; 17: 495–506.
33. MOSS SE, KLEIN R, KESSLER SD, RICHIE KA. Comparison between ophthalmoscopy and fundus photography in determining severity of diabetic retinopathy. *Ophthalmology* 1985; 92: 62–67.
34. MURGATROYD H, ELLINGFORD A, COX A et al. Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. *Br J Ophthalmol* 2004; 88: 920–924.
35. BAILEY CC, SPARROW JM, GREY RH, CHENG H. The National Diabetic Retinopathy Laser Treatment Audit. III. Clinical outcomes. *Eye* 1999; 13(Pt 2): 151–159.

36. FERRIS F. Early photocoagulation in patients with either type I or type II diabetes. *Trans Am Ophthalmol Soc* 1996; 94: 505–537.
37. MOGENSEN CE, KEANE WF, BENNETT PH et al. Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; 346: 1080–1084.
38. ROSSING P. The changing epidemiology of diabetic microangiopathy in type I diabetes. *Diabetologia* 2005; 48: 1439–1444.
39. RUGGENENTI P, REMUZZI G. Kidney failure stabilizes after a two-decade increase: impact on global (renal and cardiovascular) health. *Clin J Am Soc Nephrol* 2007; 2: 146–150.
40. MATHIESEN ER, OXENBOLL B, JOHANSEN K, SVENDSEN PA, DECKERT T. Incipient nephropathy in type I (insulin-dependent) diabetes. *Diabetologia* 1984; 26: 406–410.
41. MOGENSEN CE, CHRISTENSEN CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 1984; 311: 89–93.
42. VIBERTI GC, HILL RD, JARRETT RJ, ARGYROPOULOS A, MAHMUD U, KEEN H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982; 1: 1430–1432.
43. BORCH-JOHNSEN K, ANDERSEN PK, DECKERT T. The effect of proteinuria on relative mortality in type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1985; 28: 590–596.
44. VALDORF-HANSEN F, JENSEN T, BORCH-JOHNSEN K, DECKERT T. Cardiovascular risk factors in type I (insulin-dependent) diabetic patients with and without proteinuria. *Acta Med Scand* 1987; 222: 439–444.
45. AMIN R, TURNER C, VAN AKEN S et al. The relationship between microalbuminuria and glomerular filtration rate in young type I diabetic subjects: The Oxford Regional Prospective Study. *Kidney Int* 2005; 68: 1740–1749.
46. COUPER JJ, CLARKE CF, BYRNE GC et al. Progression of borderline increases in albuminuria in adolescents with insulin-dependent diabetes mellitus. *Diabet Med* 1997; 14: 766–771.
47. LURBE E, SOROF JM, DANIELS SR. Clinical and research aspects of ambulatory blood pressure monitoring in children. *J Pediatr* 2004; 144: 7–16.
48. PERKINS BA, FICOCIELLO LH, SILVA KH, FINKELSTEIN DM, WARRAM JH, KROLEWSKI AS. Regression of microalbuminuria in type I diabetes. *N Engl J Med* 2003; 348: 2285–2293.
49. RUDBERG S, DAHLQUIST G. Determinants of progression of microalbuminuria in adolescents with IDDM. *Diabetes Care* 1996; 19: 369–371.
50. ZERBINI G, BONFANTI R, MESCHI F et al. Persistent renal hypertrophy and faster decline of glomerular filtration rate precede the development of microalbuminuria in type I diabetes. *Diabetes* 2006; 55: 2620–2625.
51. PARVING HH. Impact of blood pressure and antihypertensive treatment on incipient and overt nephropathy, retinopathy, and endothelial permeability in diabetes mellitus. *Diabetes Care* 1991; 14: 260–269.
52. ASTRUP AS, TARNOW L, ROSSING P, PIETRASZEK L, RIIS HP, PARVING HH. Improved prognosis in type I diabetic patients with nephropathy: a prospective follow-up study. *Kidney Int* 2005; 68: 1250–1257.
53. STEINBERG D. Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. *Nat Med* 2002; 8: 1211–1217.
54. YOSHINO G, KAZUMI T, IWAI M et al. Recommendation for strict control of plasma triglyceride in diabetic subjects. *Diabetes Care* 1988; 11: 794–795.
55. NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM WORKING GROUP ON HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; 114(Suppl. 2): 555–576.
56. WELLS T, FRAME V, SOFFER B et al. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. *J Clin Pharmacol* 2002; 42: 870–880.
57. STRIPPOLI GF, CRAIG M, DEEKS JJ, SCHENA FP, CRAIG JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004; 329: 828.
58. ACE INHIBITORS IN DIABETIC NEPHROPATHY TRIALIST GROUP. Should all patients with type I diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001; 134: 370–379.
59. COOPER WO, HERNANDEZ-DIAZ S, ARBOGAST PG et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354: 2443–2451.
60. MASER RE, MITCHELL BD, VINIK AI, FREEMAN R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; 26: 1895–1901.
61. LAING SP, SWERDLOW AJ, SLATER SD et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 2003; 46: 760–765.
62. JARVISALO MJ, RAITAKARI M, TOIKKA JO et al. Endothelial dysfunction and increased arterial intima-media thickness in children with type I diabetes. *Circulation* 2004; 109: 1750–1755.
63. JENKINS AJ, LYONS TJ, ZHENG D et al. Serum lipoproteins in the diabetes control and complications trial/epidemiology of diabetes intervention and complications cohort: associations with gender and glycemia. *Diabetes Care* 2003; 26: 810–818.
64. IDZIOR-WALUS B, MATTOCK MB, SOLNICA B, STEVENS L, FULLER JH. Factors associated with plasma lipids and lipoproteins in type I diabetes mellitus: the EURO-DIAB IDDM Complications Study. *Diabet Med* 2001; 18: 786–796.
65. WADWA RP, KINNEY GL, MAAHS DM et al. Awareness and treatment of dyslipidemia in young adults with type I diabetes. *Diabetes Care* 2005; 28: 1051–1056.
66. MAAHS DM, MANIATIS AK, NADEAU K, WADWA RP, MCFANN K, KLINGENSMITH GJ. Total cholesterol and high-density lipoprotein levels in pediatric subjects with type I diabetes mellitus. *J Pediatr* 2005; 147: 544–546.
67. COLLINS R, ARMITAGE J, PARISH S, SLEIGH P, PETO R, HEART PROTECTION STUDY COLLABORATIVE GROUP. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial [see comment]. *Lancet* 2003; 361: 2005–2016.
68. DE JONGH S, OSE L, SZAMOSI T et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation* 2002; 106: 2231–2237.
69. STEIN EA, ILLINGWORTH DR, KWITEROVICH PO Jr et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; 281: 137–144.
70. WIEGMAN A, HUTTEN BA, DE GROOT E et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; 292: 331–337.
71. GRAHAM DJ, STAFFA JA, SHATIN D et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004; 292: 2585–2590.