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REVIEW

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Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment?

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Abstract Autopsy studies have shown that atherosclerosis begins in adolescence in otherwise healthy individuals, and imaging techniques have shown that atherosclerosis develops earlier and is more prevalent in children with diabetes than in age-matched healthy controls. Cardiovascular disease has now overtaken diabetic nephropathy as the leading cause of premature mortality in young adults with diabetes, and the emphasis on disease prevention has accordingly shifted to a younger age group. The majority of children and adolescents with diabetes have suboptimal blood glucose control, and this contributes to accelerated arterial disease in this age group. Other conventional risk factors for coronary heart disease also need to be considered and treated aggressively. Effective early prevention of cardiovascular disease will involve lifestyle modification and full implementation of existing treatment guidelines, and large-scale prospective studies will be needed to establish the risks and benefits of early pharmacological intervention in children and adolescents.

Keywords Adolescence · Atherosclerosis · Cardiovascular disease · Childhood · Type 1 diabetes

Abbreviations ADA: American Diabetes Association · CVD: cardiovascular disease · DCCT: Diabetes Control and Complications Trial · EDIC: Epidemiology of Diabetes Interventions and Complications · ISPAD: International Society for Pediatric and Adolescent Diabetes · IVUS: intravascular ultrasound

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Introduction

The mortality and morbidity of cardiovascular disease (CVD) are increased 2–4 fold in type 1 diabetes [1–6], and are comparable to the standardised mortality ratio of 3.3 observed in familial hypercholesterolaemia [7]. The increased risk is most evident in the young, and in the Diabetes UK cohort the death rate per 100,000 person-years was increased 12-fold in men aged between 20 and 29 years, and 7-fold in those between 30 and 39 years; the corresponding values in females were 14- and 48-fold, respectively (Fig. 1). The mortality and cumulative incidence of CVD increases significantly with the presence of diabetic nephropathy [8], and myocardial infarction has a worse prognosis in those with diabetes [9, 10].

Atherosclerosis starts in childhood and adolescence

Atherosclerotic changes in the vessel wall begin long before symptoms appear [11, 12]. The Pathobiological Determinants of Atherosclerosis in Youth Research Group (PDAY) reported on the prevalence and extent of atherosclerosis identified at autopsy in 2,876 adolescents and young adults who died from external causes between 1987 and 1994 [13]. The first intimal lesions (fatty streaks) appeared in all the aortas and in 50% of the right coronary arteries in the youngest age group (15–19 years), and increased in both prevalence and extent through to the oldest age group (30–34 years). VLDL cholesterol and LDL cholesterol were positively associated with both fatty streaks and raised intimal lesions, whereas HDL cholesterol was negatively associated with these changes [14, 15]. Smoking was associated with both fatty streaks and raised lesions [14]. Elevated HbA_1c values were associated with an excess of fatty streaks and raised lesions in the right coronary artery and aorta [16], and atherosclerosis was also associated with hypertension and BMI [15]. In other words, atherosclerosis not only begins in childhood, but its rate of progression is determined by the same risk factors as in adult CHD.

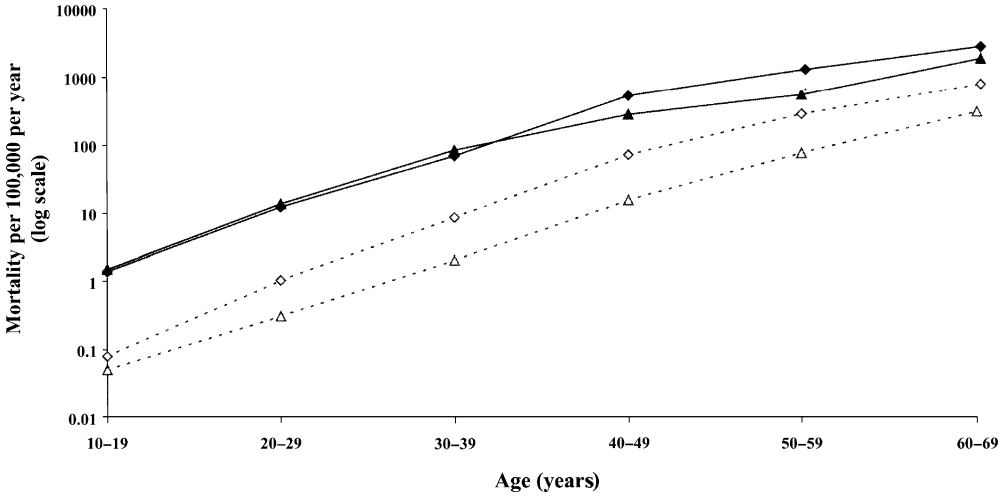

Fig. 1 Mortality from heart disease in the Diabetes UK cohort of 23,000 patients with insulin-treated diabetes and in the UK general population. The patients were diagnosed before 30 years of age between 1972 and 1993 and were followed until 2000 [6]. Of these, 34 men (*black diamonds*, *solid line*) and 34 women (*black triangles*, *solid line*) died from ischaemic heart disease before the age of 40 years. The corresponding numbers in the general population were ten men (*white diamonds*, *dotted line*) and two women (*white triangles*, *dotted line*)

The recent development of very small high-frequency ultrasound transducers has made it possible to perform direct intravascular ultrasound imaging (IVUS) of the vessel wall in living humans. In a recent IVUS study of 262 heart transplant recipients, the prevalence of coronary atherosclerosis was 17% in hearts from individuals younger than 20 years of age [17]. Prospective studies that have included a follow-up period longer than 20 years have demonstrated an association between traditional cardiovascular risk factors in healthy children and carotid vascular changes in adult life [18, 19].

Atherosclerosis is earlier and more severe in type 1 diabetes

The Oslo study demonstrated a high prevalence of silent coronary atherosclerosis in adult patients with childhood-onset type 1 diabetes. The mean age at the time of study was 43 years, the mean diabetes duration was 30 years, and none had symptoms of coronary heart disease. IVUS examination of the coronary arteries revealed that all had clinically important atherosclerosis [20]. As compared with age- and sex-matched non-diabetic controls, all indicators of coronary atherosclerosis (plaque area, plaque volume, maximal plaque thickness and luminal area) were more severe in the diabetic group [21]. Coronary angiography revealed that 34% had >50% vessel stenosis, although only 15% had a pathological exercise ECG [20]. These findings illustrate the clinical point that it is not sufficient to rely on exercise ECGs to diagnose coronary heart disease in type 1 diabetes. The relationship between IVUS and quantitative coronary angiography is a complex one (see Fig. 2 taken from Ref. [22]). High-grade stenoses (>70% obstruction) are rarely the source of acute coronary syndromes, and coronary occlusion and myocardial infarction evolve most frequently from plaques that are only mildly to moderately obstructive on angiography [23]. Carotid intima–media thickness was also increased in patients enrolled in the Oslo study [24], and resembled that observed in non-diabetic individuals who were 20–30 years older.

Even in children with a mean age of 11 years and a mean diabetes duration of only 4 years, intima–media thickness of the carotids and aorta was significantly greater than in healthy age-matched controls [25]. The thickening was more prominent in the aorta than in the carotids, and the magnitude of the increase was similar to that observed in children with hypercholesterolaemia. Endothelial dysfunction in the same patients, as measured by flow-mediated dilation (mainly a result of the endothelial release of nitric oxide), was positively correlated with intima–media thickness and LDL cholesterol [26]. This suggests that an insufficient release of nitric oxide in type 1 diabetes is an early phenomenon that is associated with increased intima–media thickness and the subsequent development of atherosclerosis. This is consistent with reports that levels of asymmetric dimethyl arginine, an endogenous inhibitor of nitric oxide, are elevated in type 1 diabetes [27].

Several studies have documented an increased prevalence of symptomatic CVD in type 1 diabetes [28]. Compared with non-diabetic individuals, these patients are more likely to have severe narrowing of the coronary arteries, and stenoses in all three major coronary arteries and in distal segments than non-diabetic individuals [29]; involvement of the distal segments makes them less suitable for bypass surgery.

Why, whom, when and how to treat?

The benefits of early, active prevention of atherosclerosis must be weighed against the risks of the intervention itself. In adults, cardiologists calculate the 10-year risk of cardiovascular events in the individual patient when deciding treatment [30, 31]. Such tools are lacking in paediatrics. Furthermore, the long-term safety of preventive drugs has not been studied extensively in children and adolescents. Lifestyle intervention is safe, but may be associated with psychological concerns. Paediatricians should therefore evaluate all known risk factors in the individual patient. In the following sections we discuss areas that may be focused

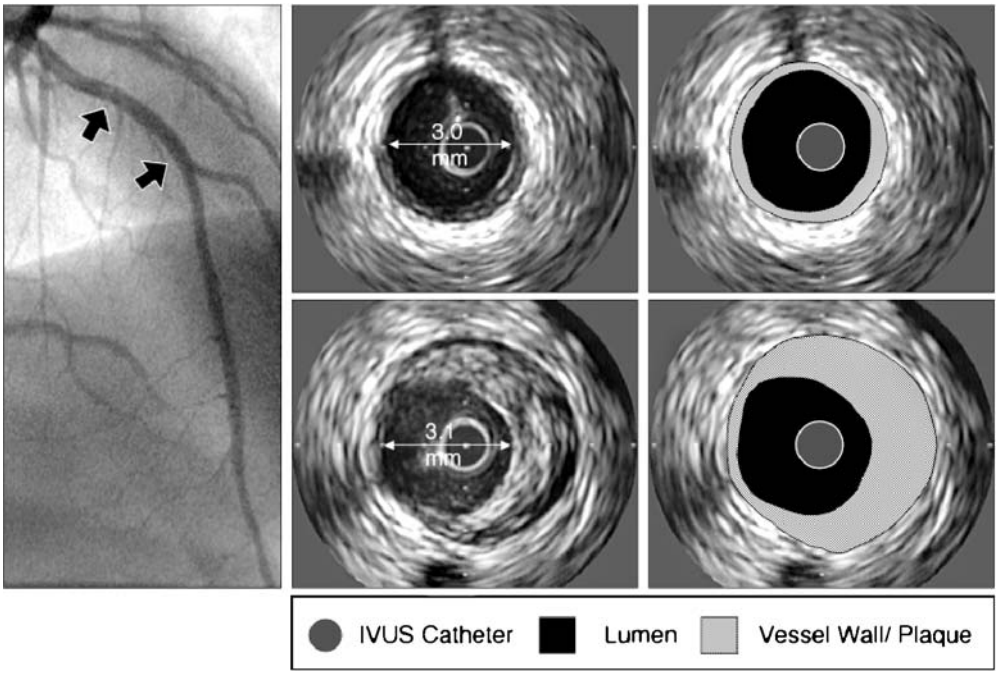

Fig. 2 An example of a coronary angiograph with corresponding IVUS images from two sites. Vessel lumen area (*centre*) and surrounding plaque areas are indicated on the IVUS images. Reproduced with permission from [22]

on, whether early screening and intervention should be carried out and, if so, when this should be initiated.

Family history A family history of early cardiovascular disease (before 55 years of age) and lipid disturbances are considered risk factors for atherosclerosis in the general population [32, 33]. In childhood-onset type 1 diabetic patients, the most important factor for CVD is a family history of type 2 diabetes [34, 35] and hypertension [35]. In Norway, 28% of children with type 1 diabetes have a first- or second-degree relative with type 2 diabetes, and insulin resistance is higher in those who have a family history of type 2 diabetes (unpublished observation). A full family history should thus be taken in every child with diabetes, and updated regularly, since parents and grandparents are at an age where cardiovascular events are more likely.

Impaired blood glucose control Although controversy exists regarding the direct influence of blood glucose control on the development of atherosclerosis in diabetes, there is increasing evidence for such an effect. In women enrolled in the Oslo study the increase in the intima–media thickness of the carotid artery correlated with mean 18-year HbA_1c [24]. In the Stockholm study, tight blood glucose control over a 10-year period had a positive effect on the development of atherosclerosis, as assessed indirectly by endothelial function and carotid artery stiffness [36]. In the Diabetes Control and Complications Trial (DCCT), the number of macrovascular events was lower in the intensively treated group than in the conventionally treated group, but the difference between the two groups was not statistically significant. The patients studied were, however, relatively young and the follow-up period lasted only 6 years [37]. In the Epidemiology of Diabetes Interventions and Complications (EDIC) Study, a 6-year non-randomised follow-up of the DCCT, increased intima–media thickness of the carotid artery was reported in diabetic patients relative to control subjects, and intima–media thickness was related to HbA_1c levels obtained during the DCCT. In patients who had received intensive insulin treatment 6 years previously, thickening had progressed to a lesser extent than in the conventionally treated patients [38]. In a recent up-date of the EDIC study cardiovascular events were reduced by 50% in the previously intensively treated group compared to the previous control group; 4% versus 7% had at least one cardiovascular event at a mean age of 43 years during mean 17 years of follow-up (Note added in proof. late braking abstract, ADA Scientific Sessions, San Diego, 12.June 2005). In a prospective study of 177 adult type 1 diabetic patients diagnosed after 30 years of age, the incidence of coronary events during the 7-year follow-up period was related to HbA_1c levels at the time of inclusion in the study [28].

The Oslo study follow-up demonstrated that long-term blood glucose control, age and total cholesterol predict coronary atherosclerosis as detected by IVUS in young childhood-onset type 1 diabetic patients with no symptoms of CVD [20]. Regression analysis suggested that a 1% increase in mean HbA_1c over 18 years implied a 6.4% rise in coronary vessel area stenosis. Given that approximately 10% of children and adolescents with type 1 diabetes have HbA_1c levels >10% and that 60% have HbA_1c levels >8% (DCCT standard), this will significantly influence the development of early atherosclerosis [39]. According to the standards of care set out by the American Diabetes Association (ADA), HbA_1c levels <7.5% should be aimed for in adolescents [40]. Because of the risk of hypoglycaemia, target levels are higher in younger patients: <8% in 6 to 12-year-olds and <8.5% in children <6 years of age

[40]. The International Society for Pediatric and Adolescent Diabetes (ISPAD) have adopted similar recommendations [41]. Optimal blood glucose control should be aimed for from the time that the initial diagnosis is made in all children with diabetes, and sufficient resources assured for this purpose.

Increased urinary albumin excretion As compared with that in the general population, the risk of CVD mortality is nearly 100-fold higher in patients with diabetic nephropathy [4], but most type 1 diabetic patients who develop cardiovascular disease do not have nephropathy. During the 18-year follow-up of the Oslo study, all patients had preclinical cardiovascular disease, but only 15% had microalbuminuria [20]. Microalbuminuria is a well-established marker of cardiovascular disease [42]; even very low levels of microalbuminuria are associated with increased risk [43]. This complication is prevented [44, 45] and is partly reversed [44] by optimal blood glucose control. If microalbuminuria develops, and even in the absence of hypertension, the progression of diabetic nephropathy is delayed by optimal blood pressure treatment [46]. The increased risk of cardiovascular disease in microalbuminuric patients warrants consideration of statin therapy. Microalbuminuria should be screened for from 10 years of age, or at 5 years after disease onset, in children and adolescents with diabetes [47], and should start 2 years after the onset of the disease in those with pubertal onset [41]. Persistent and progressive microalbuminuria is improved by the use of ACE inhibitors. Although these agents may delay progression to overt nephropathy, their place in protecting long-term renal function in children has not yet been established in long-term prospective studies. Both the ISPAD guidelines [41] and the new statement from the ADA [40] recommend that confirmed persistent microalbuminuria should be treated with ACE inhibitors even in the absence of hypertension, and regardless of the age of the patient.

Hypertension Hypertension has a greater impact on cardiovascular disease in diabetic patients than in non-diabetic individuals [48]. Hypertension in children is defined as blood pressure levels at or above the 95th percentile, confirmed by measurements taken on three different days, and blood pressure values between the 90th and 95th percentiles are defined as prehypertension according to US recommendations [40, 49]. Given the large between-hospital difference reported with respect to mean blood pressure values in diabetic children, blood pressure measurement in children may need to be standardised [39], and new consensus guidelines for blood pressure measurement in children, with reference values and percentiles by sex, age and height, are available [49]. Protocols and reference values for 24-h ambulatory blood pressure monitoring in children have also been published [50, 51].

Blood pressure should be kept below the 90th percentile for kidney protection; this level corresponds to approximately 130/80 mmHg in adults. In a large population-based study of children and adolescents with type 1 diabetes, elevated systolic blood pressure was identified in 8.5% of patients, and elevated diastolic blood pressure in 3.3%; only 1.9% received antihypertensive treatment [52]. It is important to treat hypertension, even if microalbuminuria is not present. Blood pressure control (<140/80 mmHg in adults) is effective in decreasing cardiovascular morbidity and mortality in diabetes [53–56]. The ADA recommends that a target blood pressure of <130/80 mmHg should be aimed for in adult patients if this can be safely achieved [57]. No long-term randomised trials have investigated the effect of kidney function and cardiovascular disease in children or adolescents with diabetes, and the consensus statements are based on extrapolations from adult studies. In short-term studies, ACE inhibitors have been effective and safe in non-diabetic hypertensive children [58, 59], but long-term studies are lacking.

The pulse pressure—the difference between the systolic and diastolic blood pressure—has been recognised as an important early predictor of CVD [60]. Pulse pressure increases with age as a result of arterial stiffening. As compared with age-matched, non-diabetic controls, patients with type 1 diabetes have stiffer arteries, and the process of arterial stiffening is initiated before any signs of microvascular or macrovascular disease can be detected [61]. The increase in stiffness is correlated with duration of disease, independently of age [62], and this may be of particular importance in childhood-onset diabetes. Increased radial arterial stiffness was recently reported in type 1 diabetic children compared with age- and sex-matched control subjects [63]. Increased arterial stiffness is related to increased glycation cross-links in tissue proteins [64], and increased levels of glycation endproducts have been observed in diabetic children [65, 66]. In a large cross-sectional case-control study of 3,000 type 1 diabetic patients and 5,500 randomly selected non-diabetic controls, the diabetic group had significantly higher pulse pressures and a higher prevalence of isolated systolic hypertension [67]. The early age-related increase in pulse pressure was more pronounced in patients with nephropathy, but was also evident in those with a normal albumin excretion rate. These studies indicate that arterial ageing is accelerated from an early age in type 1 diabetic subjects.

The American National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents [49] and the ADA [40] have developed the following recommendations regarding the treatment of hypertension in children and adolescents:

1. Treatment of prehypertension (90–95th percentile of blood pressure values) with dietary intervention, weight control and increased physical activity, if appropriate. Despite the lack of firm evidence for dietary intervention in children, it is generally accepted that hypertensive individuals can benefit from a dietary increase in fresh vegetables, fresh fruits, fibre and non-fat dairy products, and a reduction in sodium intake. If target blood pressure (<90th percentile) is not reached within 3–6 months, pharmacological treatment is indicated.

2. Pharmacological treatment of hypertension (blood pressure ≥95th percentile, or >130/80 if 95th percentile exceeds this value) should be initiated as soon as the diagnosis is confirmed.
3. ACE inhibitors should be considered for initial treatment. If the highest recommended dose [49] is reached, a second drug from a different class should be added, i.e. a diuretic or beta-adrenergic blocker. If ACE inhibitors are not well tolerated, angiotensin receptor blockers are recommended.

If the new recommendations of the ADA are implemented, approximately 5–10% of all diabetic children, regardless of age, should be pharmacologically treated (Tables 1 and 2).

Lipid disturbances Cholesterol plays an important role in the initiation and progression of atherosclerosis [68]. Well-controlled type 1 diabetes is not associated with gross blood lipid disturbances when lipids are examined by conventional analysis and fasting blood sampling, but conventional measurements do not provide information on the lipoprotein subclasses that may be important for cardiovascular risk. In DCCT/EDIC patients, lipoprotein particle size was measured by nuclear magnetic resonance [69]. The observed adverse changes generally included an increase in VLDL subclass levels, a decrease in VLDL particle size, increased LDL levels, a shift towards smaller atherogenic LDL particles, a decrease in levels of cardioprotective large HDL particles, and an increase in non-cardioprotective small HDL particles. Poor glycaemic control was associated with a potentially more atherogenic lipoprotein profile [69]. The increased glycation and oxidation of LDL cholesterol may increase binding to scavenger macrophage receptors in the endothelium, leading to increased foam cell formation [70]. This may be important at moderately increased HbA_1c levels. Poorly controlled type 1 diabetes is also associated with abnormalities in postprandial lipid metabolism.

The ADA recommendations for children and adolescents with type 1 or type 2 diabetes [40] are similar to established paediatric guidelines [33, 71], with modifications in response to the higher cardiovascular risk status of these patients. Target levels for the different lipid subclasses are as follows: LDL <2.6 mmol/l, HDL >1.1 mmol/l) and triglycerides <1.7 mmol/l. Medication should be considered in children with LDL levels ≥4.1 mmol/l. In the presence of a high cardiovascular risk factor, this limit is lowered to 3.4 mmol/l. Treatment should aim to lower LDL levels to <2.6 mmol/l. Resins (bile acid sequestrants) or statins (HMG-CoA reductase inhibitors) may be used, but resins are associated with low compliance.

Screening for fasting blood lipids should be performed at diagnosis in all children with type 1 diabetes aged over 12 years [40]. If normal results are obtained, this should be repeated every 5 years. If there is a family history of hypercholesterolaemia, if early CVD is present or if the family history is unknown at diagnosis, screening should start at 2 years of age. It has been suggested screening for other lipoproteins may be more suitable. The ratio of apolipoprotein B : apolipoprotein A1 may be a better predictor of CVD and, from a practical point of view, fasting values are not necessary [72].

Statins are effective in the primary prevention of major cardiovascular events in diabetes. The Heart Protection Study included 5,963 patients with diabetes, 10% of whom had type 1 diabetes [73]. In this 5-year, randomised, double-blind, controlled trial statins reduced the risk of first myocardial infarction, stroke and limb re-vascularisation by 25%. This effect was independent of glycaemic control and cholesterol levels. The risk reduction in type 1 patients was proportionally similar to that in the type 2 patients, but was statistically insignificant. Mean LDL cholesterol levels were 2.3 mmol/l in the simvastatin group and 3.3 mmol/l in the placebo group. Short-term trials have shown that simvastatin and lovastatin are effective and safe in children and adolescents [74, 75]. In a

Table 1 Target levels for different parameters to prevent CVD in children and adolescents with type 1 diabetes

Parameter	Target level	Reference
HbA_1c (DCCT standard)	≤7.5% without severe hypoglycaemia[a]	[40, 41]
LDL cholesterol	<2.6 mmol/l	[40]
HDL cholesterol	>1.1 mmol/l	[40]
Triglycerides	<1.7 mmol/1	[40]
Blood pressure	<90th percentile by age, sex and height	[40, 49]
BMI	<95th percentile (non-obese)	[40]
Smoking	None	[40]
Physical activity	>1 h of moderate physical activity daily	[40]
Sedentary activities	<2 h daily	[40]
Healthy diet	Caloric intake appropriate for normal growth; fat <30% of caloric intake, saturated fat <10% of caloric intake; fibre intake 25–35 g daily; increased intake of fresh fruit and vegetables	[40]

[a]Different targets may be appropriate in toddlers and preschool children <6 years of age (HbA_1c <8.5%) and school children 6–12 years of age (HbA_1c <8%) when at greater risk of severe hypoglycaemia [40]

Table 2 Suggested threshold values for different parameters for intervention and the primary prevention of CVD in children and adolescents with type 1 diabetes

Threshold value	Type of intervention	Reference
Blood pressure >90th percentile for age, gender and height	Lifestyle intervention	[40, 41]
Blood pressure >90th percentile despite lifestyle intervention	ACE inhibitor[a]	[40, 41]
Blood pressure >95th percentile	Lifestyle intervention and ACE inhibitor[a]	[40]
LDL cholesterol >2.6 mmol/l	Dietary intervention	[40]
LDL cholesterol >4.1 mmol/l and no other CVD risk factors	Statins	[40]
LDL cholesterol >3.4 mmol/l and one or more CVD risk factors	Statins	[40]

[a]ACE inhibitor is considered first choice, but angiotensin II receptor blockers, diuretics or beta-blockers may be indicated [49]

2-year placebo-controlled trial in children aged 8–18 years with familiar hypercholesterolaemia, carotid intima–media thickness showed a trend towards regression with pravastatin but a trend towards progression with placebo [76]. No differences were observed between the two groups in terms of growth, pubertal Tanner grading, testicular volume, menarche, endocrine function parameters, or liver or muscle enzymes. Special attention should be paid to symptoms associated with muscles and connective tissues. In a study of more than 250,000 patients treated with statins or fibrates, 24 were hospitalised for rhabdomyolysis [77]. The average incidence per 10,000 person-years of treatment was low (0.44) for treatment with atorvastatin, pravastatin or simvastatin, and was increased when statin treatment was combined with fibrates. Patients with diabetes on statin monotherapy had a 2.9-fold increased relative risk of rhabdomyolysis. Events that were considered less serious were not examined, and no information was given on the risk in children or adolescents. The efficacy and safety of statins for the primary prevention of CVD in children with type 1 diabetes still need to be determined, as does the age at which treatment should be initiated. In this review we have put forward arguments for early preventative measures.

Disturbances of platelet function, coagulation and fibrinolysis Increased coagulation and impaired fibrinolysis favour the formation and persistence of thrombi in diabetes [78, 79]. Primary prevention of cardiovascular events through aspirin use is well studied in the general population. In a meta-analysis of 55,580 randomised participants (11,466 women), aspirin treatment was associated with a statistically significant 32% reduction in the risk of a first myocardial infarction and a 15% reduction in all important vascular events, but did not have any significant effects on non-fatal stroke or vascular death [80]. A position statement by the ADA recommended aspirin therapy for primary prevention in diabetic individuals with the following risk factors: a family history of CHD, smoking, hypertension, obesity, microalbuminuria and dyslipidaemia [81]. Many children with diabetes possess these risk factors. Use of aspirin has not been studied in diabetic individuals under 30 years of age and, in the absence of further studies, aspirin should not be recommended for those under the age of 21 years because of the increased risk of Reye's syndrome [81]. In this age group the benefits of aspirin may also be outweighed by the risk of gastric bleeding.

Lifestyle The prevalence of complications and mortality in type 1 diabetes has been evaluated in a large prospective study [82]. Sedentary men were three times more likely to die than active ones. A similar relationship was seen in women, though this was not statistically significant. As with healthy individuals, patients with type 1 diabetes show a decrease in total cholesterol and an increase in HDL cholesterol during physical training [83], as well as increased insulin sensitivity. These metabolic changes, and perhaps the psychological benefits of regular exercise [84], may contribute to the improved prognosis in these patients. In children with diabetes HbA_1c is strongly correlated with physical inactivity, as indicated by hours spent watching television (unpublished observation).

Obesity and the metabolic syndrome are risk factors for cardiovascular disease. In the Bogalusa cohort of nearly 10,000 healthy children aged between 5 and 17 years, the obese children (weight >95th percentile) had significantly higher risk ratios for cardiovascular risk factors than the children of normal weight (<85th percentile) [85]. An increased prevalence of cardiovascular disease has been associated with BMI and WHR in type 1 diabetes [4, 86]. Smoking is an independent risk factor for atherosclerosis, and type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality [87, 88]. The age-adjusted prevalence of smoking is similar for people with or without diabetes [89, 90]. This is a big problem in teenagers with diabetes, and is challenging to approach [91, 92]. Even passive smoking may increase the risk of cardiovascular disease [93].

It is important to include these lifestyle factors within an integrated plan of treatment, from the onset of diabetes onwards, in all children and adolescents. Better strategies to change the attitudes and behaviour of the whole family are urgently needed. Lifestyle interventions at an early stage, together with optimal blood glucose control, may be the most promising areas to focus on for improved long-term prognosis.

Limitations of current knowledge

The natural history of atherosclerosis in children is incompletely understood, and atherosclerosis is difficult to quantify in its early stages with non-invasive methods in vivo. Prospective studies from diagnosis are needed to better assess the age at which atherosclerosis accelerates in children with type 1 diabetes relative to those without. To allow comparison with non-diabetic individuals, it is important to have excellent reference values specified for sex, age and pubertal development, and there is often a lack of well-defined reference values due to difficulties in blood and tissue sampling in large healthy control populations. Smaller, less well-defined cohorts are often used. This is the case for many biochemical blood tests. Thus, cut-off values for risk factors (e.g. fasting lipid values) are more difficult to define in this age group. The same is true for tests of inflammation, blood rheology, coagulation and platelet function. Better tests for endothelial dysfunction need to be developed and these should be combined with measurement of intima–media thickness for individual assessment of atherosclerosis development in young patients with type 1 diabetes.

Less clinical research is performed in children. There are legal and ethical concerns, and special care is needed when carrying out interventions and examinations in children. The testing of new drugs in children is often subject to a long time delay. When considering pharmaceutical interventions in chronic diseases in this age group, the importance of the long-term efficacy and safety of the agents increases. The consensus statements and recommendations are largely based on the extrapolation of arguments from studies in adults [40, 41, 49]. Although long-term trials are needed in children, these are seldom performed. Such trials are needed both for antihypertensive treatment and for statin treatment.

Conclusion

We present evidence from epidemiological, autopsy and clinical studies to show that atherosclerosis starts in childhood. Earlier implementation of measures to prevent heart disease in the general population has been advocated by several authors [94]. Atherosclerosis begins even earlier in type 1 diabetes, and the progression of cardiovascular disease is much more aggressive. Treatment targets for type 1 diabetes in childhood and adolescence are difficult to reach, and present a major challenge. Better means of improving mean blood glucose and reducing the frequency of severe hypoglycaemia are needed. Paediatric diabetologists need to focus on preventing the development of atherosclerosis in childhood. Physical activity and a healthy diet should actively be encouraged, and smoking abandoned. ACE inhibitors should be used in microalbuminuria, and statin treatment may be warranted at an early age. Hypercholesterolaemia and hypertension should be actively screened for and treated according to existing guidelines. Many studies suggest that pharmaceutical intervention should be initiated earlier, but more information is needed to determine the optimal age for this. The long-term efficacy and, in particular, the safety of drugs used for the lifelong primary prevention of CVD need to be tested carefully and systematically in randomised trials in children and adolescents with diabetes.

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