

Preventative Medicine in Childhood and Adolescence – Looking for Atherosclerosis

a report by

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Atherosclerosis and atherosclerosis-related complications such as coronary, cerebrovascular and peripheral arterial disease show their clinical manifestation in adulthood. However, changes at the endothelial level do not occur suddenly in the elderly, but are the result of a long, on-going, slowly evolving process. We know from autopsy studies that atherosclerotic processes begin in childhood and progress rapidly in the presence of risk factors.¹ As the prevalence of obesity in children is growing, so the typical atherosclerosis promoting factors such as hypertension, dyslipidaemia and type 2 diabetes mellitus challenge the physician more and more in paediatric healthcare. Thus, a diagnostic method that not only reflects indirect atherogenic factors, but visualises directly the impact of environmental factors, should be helpful for the clinical management of children and adolescents with increased risk of atherosclerosis.

Common carotid artery intima-media thickness (IMT), as measurable by high-resolution B-mode ultrasonography, is a non-invasive marker of

subclinical atherosclerosis.^{2,3} An increased IMT has been correlated with an increased relative risk for stroke and myocardial infarction (MI) in adults.² In children, a significant thickening of the endothelial wall has been demonstrated in obesity, in patients with familial hypercholesterolaemia and after Kawasaki Disease,^{2,4-7} whereas studies in paediatric diabetics gave contradictory results.⁸⁻¹⁰ Recently, normative values for IMT in children and adolescents have been published.¹¹

Method

The ultrasonographic study is performed with the patient supine in a quiet room. For data acquisition, a high-end ultrasound machine equipped with a linear high-resolution transducer (up to 13 MHz) is applied. All studies are performed according to a standardised scanning protocol separately for the right and left common carotid arteries.¹² The common carotid artery bulb is identified and the segments of the common carotid arteries 1–2 cm proximal to the bulb region are scanned. The image

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is focused on the posterior – the far – wall, which is demonstrated as a longitudinal structure. For determination of the IMT, two hyperechogenic, horizontal lines at the posterior wall of the carotid artery are considered. The distance is measured from the first bright line (the luminal side of the intima) to the beginning of the adventitia, the second echogenic layer. Two angles are used at each side for scanning the common carotid artery IMT: lateral and anterior-oblique. Usually, the images are stored digitally for subsequent offline analysis. For calculation of the IMT, numerous still frames may be taken into account. There are several analysis methods: some study groups have used manual tracing of the distance, whereas the majority use computed software with automatic edge detection. As the distances measured are very small, automatic edge detection systems may provide better results with fewer errors than manual tracing. At the authors' institution an automatic analysing system is applied with manual over-reading of accurate border detection. One of the most recent developments in this field is QLab (Philips, Germany), which analyses the IMT distance automatically on a pixel basis within a sample of 10 mm length. Thus, on a display screen with high resolution, a maximum of up to 64 measurement points within the sample volume of 10 mm can be achieved. The value given is the arithmetic mean IMT calculated from all measurement points. At the authors' institution, two scans (anterior-oblique and lateral) of each common carotid artery are analysed. By this, four scans with a total of 256 measurement points are considered for the calculation of the mean IMT. One further scientific algorithm focuses on the quantification of minimal irregularities within the intima-media surface. This 'intima-media roughness' has been shown to exclude the age-dependent increase of the IMT appropriately. Irregularities seem to precede macroscopic atherosclerotic wall changes and have been demonstrated to be significantly related to the presence of coronary artery disease in adults.¹³

IMT in Hypercholesterolaemia

Children with familial hypercholesterolaemia were found to have higher IMT than age-matched healthy children.¹⁴ The IMT was associated directly with

elevated total and low-density lipoprotein (LDL)-cholesterol and triglyceride levels and inversely correlated with high-density lipoprotein (HDL)-cholesterol levels in the affected children. The authors conclude that the IMT is an adequate, non-invasive diagnostic tool for the determination of the impact of dyslipidaemia on the vascular layer.

In a two-year randomised, placebo-controlled trial on the IMT in children with familial hypercholesterolaemia, patients with the null alleles genotype showed a significantly higher IMT and therefore increased cardiovascular risk than children with receptor-defective mutation.⁵ Though the response of the total and LDL-cholesterol to lipid-lowering therapy (Pravastatin) was slightly less pronounced, but not significantly different, in the null alleles genetic subgroup, the IMT continued to be significantly higher in the null alleles genotype during the observation period of two years. The conclusion drawn by the researchers includes that patients with the null alleles genotype are at the highest cardiovascular risk compared with children with receptor-defective mutations.

IMT in Obesity

Vascular thickening may be related to overweight and obesity. Obesity has been shown to be associated with IMT increase.¹⁵ A comparison of overweight but non-obese children with age-matched controls of normal weight demonstrated significant carotid thickening. Matching was performed also for age, gender, blood pressure, cholesterol and glucose levels.

IMT increase has been shown to be reversible. A clinical trial enrolled overweight children and assigned them to three groups. Patients of the first group performed a modification of nutritional habits for one year. In group 2 an additional six-week period of exercise was performed. In group 3 the intervention included both dietary changes and exercise performance for one year. Dietary modification included a hypocaloric diet that provided 900–1,200 kcal/day. The menu was low in fat, high in complex carbohydrate and sufficient in protein to support growth. Exercise training

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included a 75-minute session weekly with aerobic circuit training. Though in all three groups the body mass index (BMI) remained stable throughout the observation period of one year, the cardiovascular risk parameters improved significantly in group 1 and group 3. Group 1 showed a significant reduction of total and LDL-cholesterol levels together with a reduction of IMT. In group 3 a reduction of LDL- and an increase of HDL-cholesterol levels were observed. The IMT decreased significantly in these patients. Thus, dietary modification alone or combined with aerobic exercise is able to induce protective metabolic changes in overweight children within one year. Early signs of atherosclerosis may be reversible indicating a reduced cardiovascular risk even if a reduction of the BMI is not achieved.

IMT in Hypertension

An increased IMT has been observed in essential hypertension.⁶ In a group of 72 untreated hypertensive children, 38.8% showed an IMT above two standard deviations scores (SDS) at the time of diagnosis compared with normal values and with 103 age-matched controls. The IMT-SDS correlated with 24-hour systolic blood pressure values and 24-hour pulse pressure. A stepwise regression analysis revealed the pulse pressure to be a predictor of the carotid IMT.

IMT in Kawasaki Disease

Recent investigations showed an increased intima-media thickness after Kawasaki disease. One study included 20 adolescents after Kawasaki disease with coronary artery lesions and 20 sex- and age-matched controls. The values of the IMT were significantly higher in patients after Kawasaki disease whereas there was no difference regarding blood pressure, serum lipids, or BMI. The authors conclude that this finding is likely to be secondary to the changes in arterial walls after a diffuse vasculitis involving non-coronary arteries.⁷

The second study enrolled 26 patients after Kawasaki disease with coronary artery aneurysms, 24 patients after Kawasaki disease with normal coronary arteries and 22 healthy age-matched children.¹⁶ In both patient groups the IMT was significantly increased compared with the control group, and the carotid

IMT correlated significantly with the level of LDL-cholesterol in all subjects studied.

In both investigations the importance of a lifelong follow-up of children after Kawasaki disease has been emphasised. Even if visible vascular changes during the acute phase of the illness predominantly involve the coronary arteries, a generalised vasculitis may be responsible for permanent endothelial damage.

IMT in Diabetes Mellitus

Numerous studies have addressed vascular changes in type 1 diabetes mellitus. The largest investigation was conducted in 142 American children and adolescents and revealed a significantly increased IMT compared with healthy controls. The mean carotid IMT was significantly higher in persons with a diabetic complication (including hypertension, retinopathy, or microalbuminuria). In male subjects but not in female subjects, HDL-cholesterol and the LDL/HDL ratio were correlated with carotid IMT.⁸

In contrast to these findings, one further study failed to find any significant influence of diabetic parameters on the IMT in 52 patients with type 1 diabetes mellitus.¹⁷

The IMT measurement as a diagnostic tool for monitoring appropriate therapeutic measures was studied in two investigations. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed, in 1,229 adult patients with type 1 diabetes mellitus, that the progression of the IMT increase may be delayed by aggressive treatment.¹⁸ Six-hundred and eighteen patients were randomly assigned to receive intensive diabetes treatment (group 1) and 611 patients received conventional treatment (group 2). After six years, a significantly decreased progression of IMT was observed in group 1. The progression of IMT was associated with age, systolic blood pressure, smoking, the ratio of LDL- to HDL-cholesterol, urinary albumin excretion rate and with the mean glycosylated haemoglobin (HbA_{1c}) value during the mean duration of the trial.

In children, a case report of a boy with insufficiently controlled type 1 diabetes mellitus and an IMT comparable to a 50- to 60-year-old healthy adult has

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been published. After 41 months of intensive treatment, the IMT decreased significantly.¹⁹ Thus, an increased IMT may be reversible by appropriate and aggressive metabolic control of type 1 diabetes mellitus.

Concluding, the measurement of IMT offers several advantages for the assessment of cardiovascular risk in children and adolescents. It is non-invasive and not time consuming and therefore easy to perform in an out-patient clinic setting. When an appropriate analysing system is applied, the results are reliable and the inter-observer variability is low. IMT values reflect the vascular status in children in the same

manner as has been proven to occur in adults. Especially in patient groups with an increased risk of atherosclerosis, IMT measurement allows the identification of patients with a special risk of cardiovascular disease on an individual basis. This would modify clinical management. Subjects with an increased risk and signs of atherosclerosis should be treated more aggressively. Optimising the metabolic state and accompanying dietary modifications and exercise performance would be the treatment strategy in these cases. Conversely, children with normal IMT may be followed sequentially with less aggressive intervention. ■

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