ARTICLE

Cardiovascular risk factors in Australian children: hypertension and lipid abnormalities

SUMMARY

In children, cardiovascular risk factors are often overlooked but play an important role in later adult cardiovascular health. Lifestyle management and tackling childhood obesity are important, however some children will develop hypertension and dyslipidaemia which requires treatment.

Non-drug treatment should be tried first. Antihypertensive drugs should be reserved for those with secondary hypertension, end-organ damage and those who have not responded to lifestyle measures.

Drug treatment of raised concentrations of low-density lipoprotein cholesterol should be reserved for older children with familial hypercholesterolaemia, very high cholesterol, or those with multiple risk factors for premature coronary artery disease, who do not respond to dietary change.

Introduction

Autopsy studies have found that atherosclerosis occurs in children. Its extent is associated with many of the traditional risk factors for coronary artery disease – lipid abnormalities, hypertension, exposure to cigarette smoke and obesity.[1,2] Several studies have shown, in otherwise healthy children, an association between these risk factors and reduced endothelial function or increased arterial stiffness and wall thickness.[3]

Children with inherited dyslipidaemia, type 1 diabetes and chronic renal dysfunction have impaired vascular function, arterial wall thickening and an increased risk of premature coronary artery disease. Overweight and obese children may have lipid abnormalities, hypertension and insulin resistance. As obesity tends to continue through childhood, these risk factors may be present throughout life. Although it is unclear if obesity in childhood increases the risk of adult coronary artery disease, independent of adult obesity, there is considerable evidence of an adverse effect of obesity on the vascular structure and function of children.

These studies have led to recommendations for the management of cardiovascular risk factors in children who are at increased risk of premature coronary artery disease and in those who are overweight or obese. Although the management is based on lifestyle modification, drugs are increasingly being used for dyslipidaemia and high blood pressure in children.

Screening

Although excellent guidelines exist for cardiovascular risk management in adult Australians[4] there is no equivalent Australian document for children. There are population differences in Australian children which make it prudent to offer some local modifications to the screening and treatment guidelines produced in North America.

High blood pressure

The National High Blood Pressure Working Group in the USA has made recommendations regarding hypertension in children. It suggests opportunistic screening of blood pressure in **all** children older than three years. Children younger than three years should be screened if they have additional risk factors for hypertension such as prematurity or very low birth weight, congenital heart disease, recurrent urinary tract infection or renal disease or are being treated with drugs known to raise blood pressure.[5]

It has yet to be shown that a program of regular childhood screening of blood pressure reduces the risk of adult hypertension or cardiovascular disease. However, measuring blood pressure should be part of the routine physical examination. As high blood pressure in childhood is strongly associated with high body mass, a case can be made for regularly assessing blood pressure in overweight and obese children and in those with a high risk for premature coronary artery disease (Box 1).

Blood pressure should be measured in the right arm, after five minutes of quiet rest, using an appropriately sized cuff (cuff bladder width ≥40% and length 80–100% of the mid-arm circumference). The blood pressure should be considered within the percentiles based on gender, age and height (calculated from www.cdc.gov/growthcharts), with reference to US

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Box 1 Suggested groups for regular surveillance of blood pressure in childhood

All adolescents (>12 years)

All children irrespective of age with:

- body mass index >85th percentile
- increased risk of hypertension
- increased risk of premature coronary artery disease – inherited dyslipidaemia, diabetes, chronic kidney disease
- 'repaired' congenital or acquired heart disease

normative data (available at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf).

Dyslipidaemia

The National Cholesterol Education Program produced guidelines for the screening of dyslipidaemia and acceptable levels for cholesterol in American children in 1992.[6] It recommended cholesterol testing in children with a family history of premature coronary artery disease or high cholesterol (Table 1). Recent guidelines from the American Academy of Pediatrics have widened the indications for, and lowered the age of, cholesterol testing.[7] They recommend a fasting lipid profile for children 2–10 years old, with retesting after 3–5 years if the results are normal. The recommendations are to screen:

- all children with a positive family history of dyslipidaemia or premature coronary artery disease
- any child whose family history is unknown
- all overweight and obese children
- all children with other cardiovascular risk factors such as hypertension, cigarette smoking or diabetes mellitus.

One potential rationale for early childhood lipid testing is that lipoprotein levels tend to track from childhood into adult life.[8-10] Serial correlations of lipids over time vary significantly between different studies and also depend upon the type of lipid followed. For total and low density lipoprotein (LDL) cholesterol, approximately 40–55% of children with high concentrations will go on to have elevated levels as young adults. Detection of lipid abnormalities in young children could prompt the changes in lifestyle that will be required throughout life. However, both universal and targeted lipid testing in children still result in a high false-positive rate for adult dyslipidaemia.

In contrast, screening based only on the child's family history may suffer from inaccurate or incomplete information and relies on adult family members having their cholesterol measured. However, more rigorous assessment of family history combined with cholesterol testing in adults, to detect those with significant elevations of LDL, should improve the identification of children at highest risk of future coronary artery disease, namely those with inherited dyslipidaemias such as familial hypercholesterolaemia.

Overweight and obese children commonly have lipid abnormalities, particularly reduced concentrations of high density lipoprotein (HDL) cholesterol and high triglycerides.[11] However, screening of overweight and obese children does not improve the specificity for elevated adult LDL.[9] Although the majority of overweight and obese children with low concentrations of HDL become adults with low concentrations, testing these children will not detect most of the people who have reduced concentrations of HDL in adulthood.

For overweight and obese children, with or without high triglycerides and reduced HDL, the approach to treatment is weight management via changes in diet and physical activity. It is uncertain, particularly in the case of young children, that knowing their lipid profile will lead to a greater motivation to implement such changes. In the majority of overweight and obese children, lifestyle changes may be undertaken without testing their lipids.

In Australia, we suggest that screening for cholesterol abnormalities be reserved for older children (>10–12 years) with a positive family history of dyslipidaemia or premature coronary artery disease, or with other cardiovascular risk factors including overweight or obesity.

Management

Whenever possible management should begin with non-drug treatment.

Hypertension

When hypertension is confirmed in a child (repeated valid blood pressure measurements >95th percentile) the clinical history and examination should consider

Table 1 Classification of cholesterol levels in children and adolescents from families with hypercholesterolaemia or premature cardiovascular disease [6]

CATEGORY	TOTAL CHOLESTEROL (mmol/L)	LDL CHOLESTEROL (mmol/L)
Acceptable	<4.4	<2.8
Borderline	4.4–5.1	2.8–3.3
High	≥5.2	≥3.4

possible secondary causes (see Box 2). Specialist referral is indicated for further evaluation and management.

Non-drug treatment

A large number of studies have shown that diet and physical activity are safe and effective in reducing blood pressure in children.[5] This approach is appropriate for all children with hypertension associated with being overweight or obese. Lifestyle modifications within the whole family are central to the non-drug treatment of hypertension. Although it is difficult to achieve, weight loss is associated with substantial reductions in blood pressure (up to 8–12 mmHg). Mild salt restriction ('no added salt') may produce further small reductions in blood pressure (1–3 mmHg). Referral to a paediatric dietitian is indicated in very young children or in those with severe obesity.

Drug treatment

The long-term cardiovascular benefits of antihypertensive drugs in children are not known and their effects on growth and development are also unknown. However, many classes of antihypertensive drugs have been shown to be safe and effective in lowering blood pressure in children. The indications for antihypertensive treatment in children with blood pressure above the 95th percentile include:

- severe symptomatic hypertension
- secondary hypertension
- presence of other risk factors for premature coronary artery disease (diabetes mellitus, chronic renal disease, inherited dyslipidaemia)
- persistent hypertension despite an adequate trial of non-drug therapy **plus** evidence of end-organ damage.

Factors such as dosing frequency, formulation (availability of a suspension for young children) and the presence of comorbid conditions will have an important impact on the choice of drug. Children should be started on the lowest recommended dose and the dose gradually increased until the desired blood pressure is attained (<95th percentile or <90th percentile in the presence of end-organ damage). A second class of drug may be added if the highest maximal dose is reached or if adverse effects develop on higher doses of the first drug. Of the commonly used antihypertensive drugs, ACE inhibitors and calcium channel blockers are contraindicated in pregnancy; they should therefore be used with caution in females of reproductive age. Contraception should be discussed before prescribing.

Dyslipidaemia

The long-term effects of treating childhood dyslipidaemia are uncertain.

Non-drug treatment

Lifestyle modifications within a whole family are central to the non-drug treatment of dyslipidaemia and hypertension

Diet and increased physical activity are important components of the management of lipid abnormalities in children. They are recommended in all children with borderline or high concentrations of total or LDL cholesterol and in the obese with low concentrations of HDL cholesterol and high triglycerides. Lifestyle modifications within a whole family are central to the non-drug treatment of dyslipidaemia.

Diets with reduced saturated fat and cholesterol may lower total cholesterol by between 5 and 10%. Increasing the intake of soluble fibre and the use of plant sterol or stanol margarines may produce further modest reductions (5–10%) in LDL concentrations. Although short-term data indicate that plant sterols and stanols are safe, long-term studies on their safety in children are required, in relation to decreased absorption of beta carotene and fat-soluble vitamins.

We are unaware of any randomised controlled trials of fish oil supplementation in paediatric dyslipidaemia.

Box 2 **Further evaluation of children with hypertension**

Exclusion of white-coat hypertension

24-hour ambulatory blood pressure monitoring when white-coat hypertension is suspected or when there has been a poor response to therapy

Evaluation for secondary causes

Indications

- <8 years
- extreme blood pressure elevation (>99th percentile + 5 mmHg)
- signs or symptoms of a secondary cause
- failure to respond to therapy

Tests (as determined by detailed history and examination)

- urine – urinalysis, catecholamines, steroids, protein
- blood – chemistry, renin, catecholamines
- renal ultrasound
- renovascular imaging
- echocardiogram – aortic coarctation

Evaluation for end-organ damage

- echocardiogram – left ventricular hypertrophy
- retinal examination

Drug treatment

The guidelines of the American Academy of Pediatrics suggest considering drug treatment in children eight years or older with LDL concentrations of 4.9 mmol/L or more, or 4.1 mmol/L or more in the presence of at least two other risk factors for coronary artery disease. Treatment should also be considered if there is a family history of premature coronary artery disease or an LDL concentration of 3.3 mmol/L or more in the presence of diabetes.[7] Younger children with homozygous familial hypercholesterolaemia and dramatic elevations in LDL concentrations (>12 mmol/L) will also require drug treatment. A proportion of children with homozygous familial hypercholesterolaemia will require plasmapharesis to lower LDL cholesterol.

HMG CoA reductase inhibitors (statins) are currently the first-line drugs for elevated cholesterol in children. In randomised controlled trials in children, statins have resulted in reductions in total (15–30%) and LDL cholesterol (20–40%). Small improvements have also been observed in HDL cholesterol (3–10%). These trials have demonstrated the short-term safety of statins in children, with rare cases of elevations in liver transaminases and creatine kinase. In general, the lower end of the dose range for adults results in substantial reductions in cholesterol in children, with a relatively smaller incremental benefit from higher doses. Children should be monitored for muscle cramping and periodically have blood collected for liver enzymes and creatine kinase.

Bile acid binding resins and niacin may produce effective cholesterol lowering but current preparations are limited by their adverse effect profile. Ezetimibe, a cholesterol-absorption inhibitor, may reduce LDL concentrations by 20% and it is commonly used in adults in combination with statins. Its use in children requires further investigation.

Familial hypercholesterolaemia

Lifestyle modification alone is unlikely to lower LDL sufficiently in patients with heterozygous familial hypercholesterolaemia. However, the specific age to start drug treatment is uncertain. Arterial wall thickness in children with heterozygous familial hypercholesterolaemia begins to diverge from unaffected siblings at around 12 years. A number of randomised clinical trials have shown the short-term safety and efficacy of statins (cholesterol lowering of 20–50%) in these children, even when started between eight and ten years.[12,13] However, evidence for their long-term safety is lacking. Our practice is to exercise caution and reserve statin therapy for older children (>12 years).[14] It may be appropriate to delay statin therapy for longer in girls, until an age when discussions about reproduction and contraception can occur, as statins are contraindicated in pregnancy. A strong family history of premature coronary artery disease, unusually high cholesterol (>9 mmol/L after conservative measures) or a rapid progression in surrogate measures of atherosclerosis (for example ultrasound measurement of carotid arterial wall thickness) may lower the age threshold for therapy.

Conclusion

Cardiovascular risk factors are increasing in children, particularly those who are overweight or obese, which may have an adverse effect on long-term cardiovascular health. The mainstay of management is diet and increased physical activity. Drug treatment of high blood pressure should be reserved for children with secondary hypertension or those with end-organ damage who do not respond to lifestyle measures. Statin treatment of high concentrations of LDL cholesterol should be reserved for older children with familial hypercholesterolaemia, very high cholesterol, or those with multiple risk factors for premature coronary artery disease, who do not respond to dietary change. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Most obese children have high concentrations of high density lipoprotein.

6. Unlike adults, weight loss does not reduce blood pressure in children.

Answers on page 71

REFERENCES

1. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. JAMA 1990;264:3018-24.
2. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-6.
3. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003;290:2277-83.
4. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Position Statement on Lipid Management - 2005. Heart Foundation of Australia. www.heartfoundation.org.au/SiteCollectionDocuments/The-lipid-position-statement.pdf [cited 2012 Mar 6]
5. 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(2 Suppl 4th Report):555-76.
6. American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992;89:525-84.

7. Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122:198-208.
8. Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. Am J Epidemiol 1991;133:884-99.
9. Magnussen CG, Raitakari OT, Thomson R, Juonala M, Patel DA, Viikari JS, et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. Circulation 2008;117:32-42.
10. Lauer RM, Lee J, Clarke WR. Factors affecting the relationship between childhood and adult cholesterol levels: the Muscatine Study. Pediatrics 1988;82:309-18.
11. Jago R, Harrell JS, McMurray RG, Edelstein S, El Ghormli L, Bassin S. Prevalence of abnormal lipid and blood pressure values among an ethnically diverse population of eighth-grade adolescents and screening implications. Pediatrics 2006;117:2065-73.
12. de Jongh S, Ose L, Szamosi T, Gagné C, Lambert M, Scott R, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation 2002;106:2231-7.
13. Rodenburg J, Vissers MN, Wiegman A, van Trotsenburg AS, van der Graaf A, de Groot E, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. Circulation 2007;116:664-8.
14. Ayer JG, Sullivan DR, Sholler GF. Lipid abnormalities in children: should we be doing more? Med J Aust 2009;190:107-8.