**Abstract**

Atherosclerosis begins in childhood. Not uncommonly, the first presentation of atherosclerosis is sudden cardiac death. It therefore makes sense that risk-factor modification to prevent the development or delay the onset of atherosclerosis needs to begin early in life. Dietary intervention is the key component for the primary prevention of hyperlipidaemia. However, if diet and lifestyle fail to correct hyperlipidaemia, drug therapy may have to be considered. All children and adolescents with high-risk lipid disorders such as familial hypercholesterolaemia (FH), those with diabetes mellitus or other cardiovascular disease risk factors or with a family history of premature coronary artery disease should be considered for lipid-lowering therapy if diet and lifestyle intervention are ineffective. There are now numerous studies that have documented the safety and efficacy of statin therapy in both children and young adults. Based on these studies, it is now recommended that statin therapy be initiated in all male FH children from the age of ten years and at the onset of menses in females with FH. The initiation of statin therapy could be considered even earlier in FH children at high risk.

**Introduction**

Atherosclerosis begins in childhood. Several studies, such as the PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study and the Bogalusa study, have demonstrated that fatty streaks occur in the aorta and coronary arteries within the first few decades and that much more advanced lesions are present in a significant portion of adolescents and young adults. These studies have also demonstrated that the major traditional risk factors for atherosclerosis and cardiovascular disease, namely hyperlipidaemia, hypertension, cigarette smoking, obesity and diabetes mellitus, are strongly associated with the presence and extent of arterial lesions. It is estimated that 75% to 90% of the current cardiovascular disease epidemic is related to these risk factors.

Atherosclerosis is now the leading cause of death worldwide, not only in developed countries but also in developing countries. In South Africa, cardiovascular disease is second only to HIV as the major cause of death. We are therefore facing a ‘double burden’ of disease – HIV on the one hand and, with rapid urbanisation and lifestyle change, an emerging epidemic of cardiovascular disease on the other.

Not uncommonly, the first presentation of atherosclerosis is sudden cardiac death. It therefore makes sense that risk-factor modification to prevent the development or delay the onset of atherosclerosis needs to begin early in life.

**Diet and lifestyle**

Dietary intervention is the key component for the primary prevention of hyperlipidaemia. Reduced intake of saturated fat and cholesterol lowers total and LDL cholesterol. Controlling calorie intake and restricting carbohydrate and refined sugar intake are also important in the prevention of hypertriglyceridaemia and obesity. However, implementing dietary changes in young children and adolescents has been controversial, as there has been a concern that diets low in cholesterol and saturated fat might interfere with normal sexual maturation. There is no evidence for this, however, and two recent studies, the STRIP (Special Turku Coronary Risk Factor Intervention Project) study and the DISC (Dietary Intervention Study in Children) study, have shown that dietary intervention with restriction of fat and cholesterol is both safe and effective when applied from as young as seven months of age in children at risk for hypercholesterolaemia.

This is supported by the recent Consensus Statement from the American Heart Association on dietary recommendations for children and adolescents. These recommendations stress a diet high in fruit and vegetables, whole grains, beans, fish and lean meat, and emphasise reduced intake of saturated and trans-fatty acids, cholesterol and added sugar. The Guidelines also emphasise energy intake and physical activity appropriate for the maintenance of a normal, healthy weight for height (see Table 1).

Adherence to a healthy diet can reduce LDL cholesterol levels by 12% to 16%. Such a diet also reduces the risk of obesity, which is becoming epidemic worldwide, even in children.
Table I: AHA paediatric dietary strategies for individuals aged >2 years: Recommendations to all patients and families

- Balance dietary calories with physical activity to maintain normal growth.
- 60 minutes of moderate to vigorous play or physical activity daily.
- Eat vegetables and fruits daily, limit juice intake.
- Use vegetable oils and soft margarines low in saturated fat and trans fatty acids instead of butter or most other animal fats in the diet.
- Eat whole grain breads and cereals rather than refined grain products.
- Reduce the intake of sugar-sweetened beverages and foods.
- Eat more fish, especially oily fish, broiled or baked.
- Use non-fat (skim) or low-fat milk and dairy products daily.
- Reduce the intake of sugar-sweetened beverages and foods.
- Eat whole grain breads and cereals rather than refined grain products.
- Use vegetable oils and soft margarines low in saturated fat and trans fatty acids.
- Eat vegetables and fruits daily, limit juice intake.
- Eat more fish, especially oily fish, broiled or baked.
- Use non-fat or low-fat dairy products as sources of calcium and protein.
- Pay attention to portion size; serve portions appropriate for the child’s size and age.
- Use non-fat or low-fat dairy products as sources of calcium and protein.
- Limit snacking during sedentary behaviour or in response to boredom and, in particular, restrict use of sweet/sweetened beverages as snacks (e.g. juice, soda, sports drinks).
- Limit sedentary behaviours, with no more than one or two hours per day of video screen/television time and no television in children’s bedrooms.
- Allow self-regulation of total caloric intake in the presence of normal BMI or weight for height.
- Have regular family meals to promote social interaction and role model food-related behaviour.

Lipid-lowering drug therapy

Drug therapy for hyperlipidaemia in children and adolescents has been controversial. However, recent clinical trials have shown that effective lowering of LDL cholesterol in children with familial hypercholesterolaemia or those with severe hyperlipidaemia is both safe and effective and can delay or even prevent the onset of atherosclerosis. The AHA has recently issued a scientific statement highlighting this new evidence supporting drug therapy for the treatment of hyperlipidaemia in children and adolescents at high cardiovascular risk.

All children and adolescents with high-risk lipid disorders such as familial hypercholesterolaemia, those with diabetes mellitus or other cardiovascular disease risk factors, or a family history of premature coronary artery disease should be considered for lipid-lowering therapy if lifestyle intervention is ineffective.

a) Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is a common genetic disorder affecting approximately 1:500 persons or 10 million people worldwide. In South Africa, probably because of a founder effect, the condition is even more highly prevalent in the Afrikaner, Jewish and Asian populations, with an estimated gene frequency of 1:80 to 1:100. There are probably more than 100 000 affected persons in South Africa, the vast majority undiagnosed and untreated. The diagnosis of FH can by and large be made clinically. There is usually a family history of premature coronary artery disease, one parent will have hypercholesterolaemia and may well have the clinical signs of FH, namely arcus cornealis and thickening of the tendo-Achilles (see Figures 1 and 2).
intima-media thickness is significantly increased by the age of 12 years.\textsuperscript{13} Myocardial ischaemia and coronary artery stenosis have also been well documented in young adults with heterozygous FH.

The risk of a fatal or non-fatal cardiovascular event by age 60 years in FH subjects is at least 50% in men and about 30% in women. In young adults with FH and aged 20 to 40 years, the relative risk of a fatal coronary event is increased 100-fold\textsuperscript{10} This should be compared to other “traditional” risk factors, such as hypertension and smoking, which only increase the relative risk by about three- to fivefold.

Importantly, risk estimates for a standard cardiovascular event using risk charts such as the Framingham risk score seriously underestimate risk in subjects with FH. These charts should not be used if the total cholesterol is $> 7.25 \text{mmol/l}$.

b) Other causes of high risk hyperlipidaemia in children and adolescents

A number of conditions other than genetic lipid disorders, such as FH associated with hyperlipidaemia, can also place a child at high risk for atherosclerosis. These conditions include diabetes mellitus, organ transplantation, HIV infection, connective tissue disease and chronic kidney disease.\textsuperscript{8}

More than 50% of mortality in diabetic patients is related to coronary artery disease (CAD) and, for this reason, diabetes mellitus is now considered a CAD risk equivalent. Dyslipidaemia should therefore be looked for in all young diabetics, especially those with microalbuminuria or proteinuria. If dietary therapy and improved glycaemic control do not correct the dyslipidaemia, lipid-lowering drug therapy should be considered.

Up to 50% of HIV-infected children treated with highly active antiretroviral (HAART) therapy develop lipid abnormalities, most commonly an increase in total and LDL cholesterol levels.\textsuperscript{14} This is seen particularly with the use of the protease inhibitors. In HIV-infected adults, lipoprotein abnormalities have been shown to be associated with an increased risk for cardiovascular disease, and the same probably holds true for children.

Lipid abnormalities are also commonly observed in paediatric patients following all types of solid organ transplantation, in children with connective tissue diseases such as systemic lupus erythematosis (SLE), and in those with kidney diseases such as nephrotic syndrome.

Drug therapy with retinoids, which are commonly used for the treatment of acne, can also elevate total cholesterol and triglyceride levels, although this reverses when therapy is discontinued.

Important secondary causes of hyperlipidaemia are shown in Table III. These need to be considered in all children and adolescents with hyperlipidaemia.

Obesity and overweight should prompt the need for a lipogram in children and adolescents. These children should also be screened for other components of the metabolic syndrome (elevated blood pressure, elevated triglycerides, low HDL cholesterol and high fasting glucose levels). The metabolic syndrome predisposes to type 2 diabetes mellitus and has recently been shown to predict cardiovascular disease in adults, increasing the risk approximately 15-fold.\textsuperscript{15} Diet and lifestyle interventions therefore need to be instituted early and aggressively in such children.

### Table III: Causes of secondary hyperlipidaemia

| Category                        | Causes                                                                 |
|---------------------------------|------------------------------------------------------------------------|
| Endocrine disorders             | - Diabetes mellitus                                                   |
|                                 | - Hypothyroidism                                                       |
|                                 | - Cushing’s syndrome                                                    |
|                                 | - Acromegaly                                                           |
| Renal disease                   | - Nephrotic syndrome                                                   |
|                                 | - Chronic renal failure                                                |
|                                 | - Post-renal transplantation                                           |
| Hepatobiliary disease           | - Cholestasis                                                          |
|                                 | - Primary hepatocellular carcinoma                                     |
| Dysproteinemia                  | - Multiple myeloma                                                     |
|                                 | - Systemic lupus erythematosan                                        |
| Drug therapy                    | - Thiazide diuretics                                                   |
|                                 | - ‘B’-adrenergic blockers                                               |
|                                 | - Oral contraceptives                                                  |
|                                 | - Retinoids                                                            |
|                                 | - ‘HAART’                                                              |
| Miscellaneous                   | - Alcohol                                                              |
|                                 | - Anorexia nervosa, bulimia                                            |
|                                 | - Lipodystrophy                                                        |
|                                 | - Glycogen storage diseases                                            |

* = common

### Which drug to use?

Until recently, only dietary intervention and/or bile acid-binding resins, e.g. cholestyramine, were recommended for the treatment of FH in children, but efficacy and compliance were both very poor. The HMG CoA reductase inhibitors or statins work by inhibiting the rate-limiting enzyme, HMG CoA reductase, for the endogenous synthesis of cholesterol. This leads to the depletion of the intracellular cholesterol pool, which triggers an upregulation of LDL surface receptors, leading to increased clearance of LDL from the circulation. Statin therapy has resulted in significant reductions in cardiovascular and all-cause mortality in adults at risk for, and with, manifest cardiovascular disease and are now also the preferred agent for treating hypercholesterolaemia in children and adolescents who meet the criteria for drug therapy.\textsuperscript{5,18} Adverse effects are uncommon or even rare, but include infrequent gastro-intestinal upset, elevation of liver enzymes, myalgia and, very rarely, rhabdomyolysis. However, on the basis of current evidence, the risk of liver- or muscle-related adverse events is so small that this is not a reason to withhold statin therapy in high-risk children and adolescents, especially those with FH. Randomised control trials of up to four years in children have shown that statin therapy does not impair growth or sexual development.\textsuperscript{16,17} The safety of statin therapy during pregnancy is uncertain, however, and statin therapy should therefore be discontinued during pregnancy.

There are now numerous studies that have documented the safety and efficacy of statin therapy in both children and young adults. Based on these studies, the AHA now recommends initiating treatment with statin therapy in childhood at the age of ≥ 10 years in males and at the onset of menses in females. However, the initiation of statin therapy should be considered even earlier in FH children at ‘high risk’.\textsuperscript{5,18} (See Table IV.)
Table IV: High-risk conditions in children with FH

- High levels of LDL cholesterol, particularly exceeding 6 mmol/l
- Male gender
- A family history of very early onset coronary disease – in the third or fourth decade of life or earlier
- Current cigarette smoking or passive smoke exposure
- Low HDL-cholesterol levels of <1 mmol/l
- Presence of hypertension
- Presence of overweight or obesity and aspects of the metabolic syndrome
- Presence of other conditions associated with increased atherosclerotic risk, such as diabetes, HIV infection, connective tissue disease

How low to go?

Few studies have addressed the goal of LDL cholesterol in young children. However, more aggressive LDL cholesterol reduction has recently been shown to delay the progression of and even cause the regression of early atherosclerosis as assessed by carotid intima-media thickness in children with FH.11

In my opinion, the LDL cholesterol goals of therapy should be the same in children as in adults, namely an LDL cholesterol of below 3 mmol/l in most and a more aggressive goal of < 2.5 mmol/l in those with established cardiovascular disease (coronary artery disease, carotid plaque or peripheral vascular disease) or those with multiple other CAD risk factors (diabetes, smoking).

High-dose statin therapy may be required to achieve these goals. The efficacy of the different statins currently available in South Africa is shown in Table V.

Statin therapy alone may not always achieve these goals. Further reduction in LDL cholesterol could be achieved with the addition of a cholesterol-absorption inhibitor, such as ezetimibe, which will reduce the LDL cholesterol consistently by another 16% to 20%, with minimal adverse effects. A better-tolerated bile acid resin than cholestyramine, namely colesvelam, is currently undergoing clinical trials in children with FH and could be another option in the future in combination with statin therapy.

Carotid artery plaque has been shown to be present in about 10% of children with FH compared to no plaque in unaffected siblings. A recent study has also shown that introducing statin therapy early in young patients with FH can significantly delay the progression of atherosclerosis.12 This study supports the concept of initiating statin therapy for those with FH in childhood.

In my opinion, we should adopt ‘the younger the better’ option rather than ‘later but greater’ if we want to reduce the high cardiovascular morbidity and mortality associated with FH.13 We should not wait until the basin overflows, but should rather just ‘turn off the tap’.

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