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Review

Hyperlipidemia in children

Brian W. McCrindle*

Division of Cardiology, Department of Pediatrics, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8

Received 31 December 2004; received in revised form 31 December 2004; accepted 18 January 2005

Available online 17 February 2005

Abstract Hyperlipidemia in children has emerged as an increasingly prevalent risk factor in children, concomitant with the worldwide epidemic of obesity. Hyperlipidemia can alter vascular endothelial function and impair some of its pro-fibrinolytic and anti-thrombotic regulatory properties, as well as initiate the atherosclerotic process. There are strong links between vascular changes and hyperlipidemia in children, both from pathologic and non-invasive assessment studies. More severe lipid abnormalities in children are related to primary familial dyslipidemias. Current recommendations for screening begin with assessment of family history for cardiovascular disease or events or parental hyperlipidemia. High-risk individuals merit more intensive investigation and intervention. While fat-restricted diets have been shown to be safe in children, lipid-lowering is modest. Those with more severe lipid abnormalities may meet criteria for drug therapy, and the statin agents commonly used in adults are increasingly being used in high-risk children, with similar efficacy and safety, although long-term concerns remain.

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* Tel.: +1 416 813 7610; fax: +1 416 813 7547.
E-mail address: brian.mccrindle@sickkids.ca.

There is an epidemic of overweight and metabolic syndrome worldwide, and consequently there is increasing medical focus on the issue of hyperlipidemia. Studies have documented the increasing prevalence of overweight and obesity in children and adolescents, with a concomitant increase in the prevalence of cardiovascular risk factors [1–4]. The evidence is now strong for a link between lipid abnormalities and cardiovascular disease in children. While the cornerstone of management of lipid abnormalities has focused on a fat and cholesterol-restricted diet, other dietary controversies have arisen. A proportion of children with clinically important hyperlipidemia will meet the (adult) criteria for lipid-lowering drug therapy. There is now increasing evidence from clinical trials regarding the safety and effectiveness of these drugs in children. This review will discuss the relationship between hyperlipidemia and thrombosis, mechanisms of hyperlipidemia, as well as clinical assessment and management strategies for hyperlipidemia during childhood.

The link between thrombosis, fibrinolysis and hyperlipidemia

Hyperlipidemia promotes functional abnormalities and structural vascular wall injury. This is primarily mediated through the many functions of the endothelium. An intact and healthy endothelium is a smooth surface that participates in the regulation of blood flow, as well as having properties that are anti-inflammatory, anti-thrombotic and pro-fibrinolytic. Many of these functions are mediated through oxidation sensitive mechanisms which influence the bio-availability of nitric oxide [5].

Much of the focus on the link between thrombosis and atherosclerosis has been related to atherosclerotic plaque rupture or hemorrhage with luminal thrombosis [6–9]. These events result in acute coronary syndromes, and both platelets and clotting factors have a role in this dynamic response. However, children rarely have these advanced atherosclerotic lesions. Nonetheless, children with dyslipidemia have been shown to have impaired fibrinolytic activity. Albisetti and colleagues studied 36 children with asymptomatic dyslipidemia and 26 control subjects with venous occlusion stress testing [10]. They noted that children with dyslipidemia at baseline had decreased levels of tissue plasminogen activator, reflecting decreased fibrinolytic capacity. They also had significantly increased levels of plasminogen, alpha2 macroglobulin and fibrinogen. These

abnormalities were felt to reflect the presence of endothelial dysfunction. Studies in adults have shown that treatment of hyperlipidemia with the hydroxymethylglutaryl (HMG) CoA reductase inhibitors or “statins” can significantly decrease thrombus formation and improve the fibrinolytic profile [11]. This is manifest by decreased plasminogen activator inhibitor 1 and decreased tissue plasminogen activator antigen levels. A study by Joukhar and colleagues showed that treatment with various statins significantly reduced plasma levels of prothrombin fragment 1+2 and von Willibrand factor antigen [12]. These studies suggest that there may be a link between hyperlipidemia, endothelial dysfunction and abnormalities in thrombosis and fibrinolysis in children.

The atherosclerotic process in children and adolescents

There is a growing body of evidence that the atherosclerotic process begins in youth and progresses dependent on the presence of traditional cardiovascular risk factors. Newman and colleagues reported a pathologic study of 30 young adults, and noted that the percent total surface involvement of the aorta with fatty streaks was linearly correlated with pre-mortem determinations of low density lipoprotein (LDL) cholesterol levels [13]. A pathologic study by Napoli and colleagues showed that in normal cholesterolemic young children, the rate of accumulation of abdominal aortic fatty streaks was significantly greater in those children with who had been born to a hypercholesterolemic mother [14]. This study suggests some possibility of environmental prenatal programming towards endothelial dysfunction. A further study by Berenson and colleagues showed that the presence of fibrous plaque lesions increased with age, and was directly correlated with traditional cardiovascular risk factors [15]. However, they also showed that the level of involvement increased exponentially with an increasing number of cardiovascular risk factors.

Noninvasive in vivo markers of atherosclerosis have been used to examine the pediatric population. Children with familial hypercholesterolemia have been shown to have abnormal endothelial function as assessed by provocative maneuvers inducing vasodilatation of the brachial artery detected with vascular ultrasound imaging [16–19]. Hyperlipidemia in children has also been shown to result in abnormalities of carotid intima–media thickness, distensibility and compliance by vascular

ultrasound [20–25]. Electron beam computed tomography has shown that children and young adults with hyperlipidemia have increased levels of coronary artery calcification [26]. Thus, it appears that hyperlipidemia in children and adolescents is directly related to both pathologic changes and functional abnormalities which are predictive of progression to manifest atherosclerotic cardiovascular disease in adulthood.

Mechanisms of dyslipidemia

Lipid abnormalities can be classified as either being primary or secondary. Primary dyslipidemias are due to defects in the metabolic pathways induced by genetic abnormalities. The commonest primary dyslipidemia is familial hypercholesterolemia [27–29]. It is primarily associated with elevations of LDL, although elevated triglycerides and low high density lipoprotein (HDL) are sometimes seen. Familial hypercholesterolemia is inherited as an autosomal dominant with a gene frequency of 1:250 to 1:500 in the general population. It is associated with a markedly increased risk of premature cardiovascular disease. The underlying functional abnormality is a defect in the LDL receptor or in the LDL receptor recognition protein apolipoprotein B. This results in a failure of LDL to be cleared from the circulation. The degree of increased risk of premature cardiovascular disease is quite striking. McCrindle and colleagues noted in 40 children age 10 to 17 years that 30 of the fathers were affected [30]. Of these, 57% had had a myocardial infarction at a median age of 39 years, with 3 of the fathers having died at their initial event. A study of 1034 children with familial hypercholesterolemia by Wiegman and colleagues showed that children with an LDL level above 240 mg/dL had a 1.7 times higher risk of having a parent who had premature cardiovascular disease [31]. In addition, they showed that children with an additional low HDL level of below 40 mg/dL or an elevated lipoprotein (a) level above 300 mg/L had a 1.8 times higher risk of having a parent with premature cardiovascular disease.

Familial combined hyperlipidemia is characterized by elevations of LDL, elevated triglycerides and decreased HDL, or both [32]. It is inherited as an autosomal dominant, and many phenotypes may be present within a given family pedigree. It is caused by an overproduction of very low density lipoprotein (VLDL), reduced free fatty acid trapping, and decreased clearance of chylomicrons and remnants. It is associated with a moderately increased risk of premature cardiovascular disease.

Dysbetalipoproteinemia is characterized by both elevated cholesterol and triglycerides [33]. It is inherited as an autosomal recessive with a gene frequency of 1:5000 in the general population. Physical manifestations are common with the presence of palmar crease xanthoma, tuberous and tuberoeruptive xanthomata and an association with a moderately increased cardiovascular risk. It is associated with a particular polymorphism of the apolipoprotein E.

Familial hypoalphalipoproteinemia is characterized by the isolated finding of a low HDL level [34,35]. Its inheritance is an autosomal dominant and is associated with a mild to moderately increased cardiovascular risk. It is caused by decreased production of HDL or a mutation in the apolipoprotein A1 surface protein of HDL.

A larger proportion of the less severe dyslipidemias are related to secondary causes. These include the use of medications, such as corticosteroids and anabolic steroids, and isotretinoin. Endocrinopathies, such as diabetes, hyper- and hypothyroidism and hypercortisolism, also cause lipid abnormalities. Hyperlipidemia is a feature of biliary obstruction and biliary cirrhosis, and chronic renal failure and nephrotic syndrome.

The most prevalent secondary cause of hyperlipidemia is overweight and obesity. This is becoming of increasing concern as the prevalence of overweight and obesity has reached epidemic proportions in the general population. The lipid abnormalities associated with overweight are characterized by a lipid triad, which includes elevated triglycerides, low HDL and the presence of abnormalities in the composition and structure of LDL, such that it becomes a smaller, denser and more atherogenic particle [36,37]. These abnormalities lead to an increased risk of atherosclerosis in and of themselves, but often obesity is associated with more general abnormalities characterized by the metabolic syndrome. In addition to dyslipidemia, this includes insulin resistance with type 2 diabetes and hypertension [38].

Assessment of lipid abnormalities

It is important in the assessment of dyslipidemia to characterize whether it is related to a primary or a secondary cause. A detailed history should be obtained to determine the presence of any medical conditions and the use of medications. A detailed review of systems should be pursued in order to determine any symptoms that may suggest a

secondary cause. A personal risk assessment includes an evaluation of dietary behaviour and intake. Quantification of both active and sedentary pursuits should be obtained. Use and exposure to cigarette smoke, both among the patient, the family members and peers, should be elicited. A detailed family history should be obtained to determine the presence of cardiovascular risk factors, hyperlipidemia and premature cardiovascular disease or events. A careful physical examination should include assessment of height, weight and body mass index, plotted on standardized growth charts. Attention to accurate assessment of blood pressure is necessary. The remainder of the physical examination should be directed towards eliciting signs suggestive of secondary causes. Often screening blood work should be obtained to assess for the presence of diabetes, thyroid abnormalities and hepatic or renal dysfunction.

Screening and management recommendations

Current guidelines regarding screening and management for hyperlipidemia in children and adolescents are derived from a report of an Expert Panel of the National Cholesterol and Education Program (NCEP), published in 1992 [39]. The panel recommended two approaches. The first approach is a population-based approach aimed at lowering the average population cholesterol levels. They recommended no dietary restrictions under the age of 2 years. Following this, a prudent diet was recommended to be gradually introduced, which maintained adequate nutrients and calories and ideal body weight, while reducing the proportion of caloric intake from total fat to 30% or less, saturated fat to 10% or less, and cholesterol intake to less than 300 mg/day.

In addition, an individual approach was advocated in order to identify high-risk individuals over the age of 2 years (Fig. 1) The initial screening involved an assessment of family history. A high-risk history was defined as the presence of a parent with a cholesterol level above 240 mg/dL, a parent or grandparent with a documented premature cardiovascular disease event, or a parent or grandparent with diagnosed or treated cardiovascular disease morbidity. If the family history was unavailable and other risk factors or conditions were present, this was also felt to identify a high-risk individual. If the risk assessment revealed parental hyperlipidemia, an assessment of total blood cholesterol in the child was

advocated. If the family history was positive for cardiovascular disease, a fasting lipoprotein analysis was recommended. For those for whom total blood cholesterol was measured, the level was then stratified into three categories. If the single level was above 200 mg/dL, or the average of two levels was above 170 mg/dL, a fasting lipoprotein profile was recommended. A fasting lipoprotein profile includes assessment of total cholesterol, LDL, HDL and triglyceride levels. It was recommended that it be repeated and the average LDL levels then stratified into three risk categories. An acceptable level was defined as less than 110 mg/dL, borderline 110 to 130, and high above 130 mg/dL. For those with high LDL levels an evaluation for primary and secondary causes was recommended and a more rigorous fat and cholesterol restricted diet started.

Since the publication of these guidelines, a number of their limitations have been highlighted. Numerous studies have noted that initiation of screening with family history may be inadequate to identify a significant proportion of the population with elevated LDL levels [40]. The cut-points used to determine risk categories are derived from population-based percentiles and may not bear a direct relationship to the actual disease process. There was no consideration given to variation in the LDL levels by race, gender, age and level of sexual maturation. The recommendations also failed to recognize the overall lower risk evident in females. Finally, the guidelines were published at a time when the epidemic of overweight and obesity was not yet obvious, and the guidelines do not address a role for screening for elevated non-HDL cholesterol, low HDL and high triglycerides.

Dietary therapy

Because of its presumed safety, lipid-lowering dietary therapy has been advocated as the cornerstone of management. The focus has been on a fat and cholesterol-restricted diet, although numerous dietary supplements have also been variously advocated. The safety of the fat and cholesterol-restricted diet was investigated in a large multi-institutional, randomized clinical trial [41]. This trial enrolled 663 children with mild to moderate hypercholesterolemia who did not meet criteria for drug lipid-lowering therapy. They were randomized to either a usual care group or an intervention characterized by intensive diet education aimed at reducing the proportion of caloric intake from total fat to less than 28%, saturated fat to less than 8% and cholesterol to less than 150 mg/day. Over a 3-

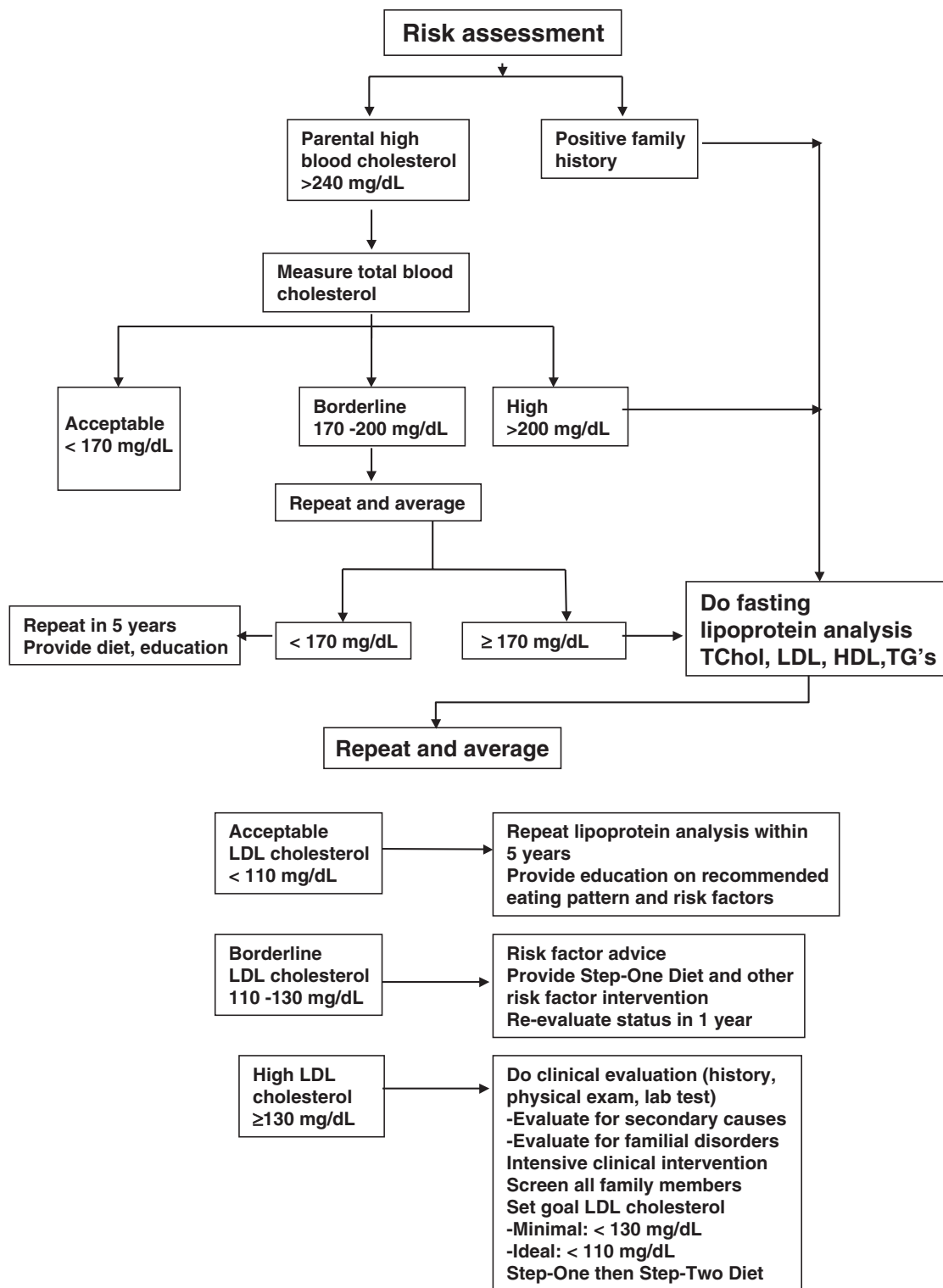


Figure 1 Screening and management algorithm from the NCEP Expert Panel 1992 [39]. HDL, high density lipoprotein; LDL, low density lipoprotein; NCEP, National Cholesterol Education Program; TChol, total cholesterol; TG, triglycerides.

year period the LDL level was reduced from 131 to 119 mg/dL in the usual care, and 131 to 115 mg/dL in the diet intervention group. A further study extended the results to up to 7 years of follow-up and showed maintenance of the intervention [42].

No abnormalities were detected with regards to growth and sexual maturation, psychologic testing or any nutritional safety parameters. A randomized trial of a fat restricted diet was also performed in 1062 infants 7 months of age who were randomized

to either a control diet versus a dietary intervention aimed at altering the dietary fat composition ratio and cholesterol to less than 200 mg/day [43,44]. At 5 five years of age, compared to controls males had an LDL level that were 15 mg/dL lower, with females having levels 6 mg/dL lower.

Other forms of dietary interventions have been recommended. Gylling and colleagues performed a randomized cross over clinical trial using a dietary fat replacement with a sitostanol ester margarine [45]. They noted a 15% reduction in LDL levels in 15 children with familial hypercholesterolemia. Some alternative or complimentary medicines have been variously advocated for treatment of hyperlipidemia. McCrindle and colleagues performed a randomized, double-blind, placebo-controlled clinical trial of garlic extract therapy in 30 children with familial hyperlipidemias [46]. They noted no significant effect on any lipid profile parameter or any other cardiovascular risk factor.

Drug therapy

The report of the Expert Panel of the NCEP also recommended criteria for initiation of lipid-lowering drug therapy [39]. They recommended that

this be only considered in children over the age of 10 years and only after an adequate trial of 6 to 12 months of the fat-restricted diet. Drug therapy was recommended if the LDL level remained above 190 mg/dL, or above 160 mg/dL together with a positive family history of premature cardiovascular disease or the presence of two or more other risk factors in the patient.

Several classes of drugs are available for the management of dyslipidemia (Table 1). The bile acid binding resins have been felt to be preferred in the pediatric age group as they are not systemically absorbed. The act to bind bile salts within the intestinal lumen and prevent their enterohepatic reuptake thus removing this cholesterol-derived product from the cholesterol pool. This leads to an upregulation of LDL surface receptors on hepatocytes and increased clearance of LDL from the circulation. Bile acid binding resins are available in both a powder and tablet formulation. They are usually dosed starting at 4 to 5 g/day, and titrated up to a maximum of about 20 g/day. However, they are associated with very poor palatability, leading to very poor compliance. Gastrointestinal side effects are common and, in addition, there is concern that they may increase triglyceride levels and may interfere with the absorption of fat-

Table 1 Clinical studies of efficacy of drug therapy for hyperlipidemia in children and adolescents

Study	Drug	Dose	Change in lipoprotein profile (%)			
			Tchol	LDL	HDL	Triglycerides
<i>Bile acid binding resins</i>						
Tonstad et al. [48]	Cholestyramine	8 g/day	-12	-17	NS	NS
McCrindle et al. [30]	Cholestyramine	8 g/day	-7 to -11	-10 to -15	+2 to +4	+6 to +9
Tonstad and Ose [49]	Colestipol	2 to 12 g/day	-17	-20	-7	-13
McCrindle et al. [50]	Colestipol	10 g/day	-7	-10	+2	+12
<i>HMG CoA reductase inhibitors (statins)</i>						
Ducobu et al. [60]	Simvastatin	20-40 mg/day	-26	-37	+23	-9
De Jongh et al. [55]	Simvastatin	10-40 mg/d	-31	-41	+3	-9
Knipscheer et al. [52]	Pravastatin	5 mg/day	-18	-23	+4	+2
		10 mg/day	-17	-24	+6	+7
		20 mg/day	-25	-33	+11	+3
		40 mg/day	-17	-21	+9	-18
Lambert et al. [53]	Lovastatin	10 mg/day	-17	-21	+9	-18
		20 mg/day	-19	-24	+2	+9
		30 mg/day	-21	-27	+11	+3
		40 mg/day	-29	-36	+3	-9
Stein et al. [54]	Lovastatin	10 mg/day	-13	-17	+4	+4
		20 mg/day	-19	-24	+4	+8
		40 mg/day	-21	-27	+5	+6
Firth et al. [61]	Fluvastatin	20-80 mg/day	-24	-30	-2	-15
McCrindle et al. [51]	Atorvastatin	10-20 mg/day	-30	-40	+6	-13
<i>Other agents</i>						
Wheeler et al. [57]	Bezafibrate	10-20 mg/day	-22	NC	+15	-23
Colletti et al. [56]	Niacin	500-2200 mg/day	-13	-17	+4	+13
McCrindle et al. [50]	Pravastatin and colestipol	Pravastatin 10 mg/day with colestipol 5 g/day	-13	-17	+4	+8

HDL, high density lipoprotein; LDL, low density lipoprotein; TChol, total cholesterol.

soluble vitamins and some medications. The amount of LDL lowering with the bile acid binding resins is modest at best and in studies in the pediatric population has ranged to a 13% to 20% average LDL lowering [30,47–50].

Newer agents aimed at the intestine include a newer bile acid binding agent called colesevelam. This is felt to be a more potent binding agent with fewer adverse effects. It results in similar lipid lowering as other bile acid binding agents; however, it is felt to have no effect on triglycerides or drug or vitamin absorption. A newer class of drugs are the direct intestinal cholesterol absorption inhibitors. These are felt to result in lowering of LDL levels by about 20%. They have been advocated for use as an adjunct to the statins in order to more successfully achieve LDL target levels. However, no pediatric studies have yet been performed.

The cornerstone of the lipid-lowering therapy in adults has rested with the HMG CoA reductase inhibitors or statins. The use of these drugs has resulted in important reductions in overall cardiovascular morbidity and mortality. These agents act by inhibiting the rate-limiting step in endogenous cholesterol synthesis. In response to this, there is an upregulation of LDL receptors to draw cholesterol into the depleted intracellular pool and promote LDL clearance from the circulation. Several agents are available and some good short-term, randomized clinical trials have been performed in the pediatric population [51–55]. The magnitude of LDL lowering is significantly greater than with the bile acid binding resins and they are often associated with increases in HDL levels as well.

In considering the use of the statins in the pediatric population the choice of statin is usually a matter of personal preference (Table 2). The statin is usually started at the lowest dose given at bedtime, with monitoring of creatinine kinase and liver transaminases. Patients must be advised about the use of the medication in pregnancy and the possibility of drug interactions. Patients who develop muscle cramps should be advised to discontinue the medication.

Niacin and nicotinic acid may infrequently be used for management of hyperlipidemia in children and adolescents. Its effect is primarily to lower LDL and triglycerides, to raise HDL and to lower lipoprotein (a). The mechanism of action relates to decreasing hepatic production and release of the VLDL. When initiating therapy, a lower dose is preferred with up-titration to a therapeutic dose of 2 to 6 g/day. Adverse effects are significant, and include flushing, glucose intolerance, myopathy, gastrointestinal symptoms, hyperuricemia, and rarely fulminant hepatic failure. Only one study of

their use in children has been reported and, because of tolerance and safety concerns, they are not routinely used [56].

The fibric acid derivatives or fibrates are effective in both lowering triglycerides and raising HDL. These are useful drugs in treating primary hypertriglyceridemia. The mechanism of action is complex. Adverse effects include gastrointestinal complaints, cholelithiasis, liver function abnormal-

Table 2 Guidelines for the use of HMG CoA reductase inhibitors (statins) in children and adolescents

Patient selection

1. Use the current criteria of the Expert Panel of the NCEP for drug initiation.
2. Factors that may lower the age at which to start a statin include higher LDL levels, males, greater family history of premature cardiovascular disease and the presence of other risk factors.
3. Include the preferences of patient and family in the decision-making.
4. In general, do not start before the age of 10 years in males, and preferably after onset of menses in females.

Initiation and titration

1. The choice of the particular statin is a matter of preference.
2. Start with the lowest dose given once a day at bedtime. Measure creatine kinase (CK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
3. Instruct the patient to report all potential adverse effects, especially muscle cramps, immediately. Advise female patients about concerns regarding pregnancy, and the need for appropriate contraception if warranted. Advise about drug interactions.
4. After 6 weeks, measure fasting lipoprotein profile, CK, ALT and AST.
 - threshold for worrisome level of CK—10 times the upper limit of normal
 - threshold for worrisome level of ALT, AST—3 times the upper limit of normal
 - target levels for LDL—desirable <130 mg/dL, ideal <110 mg/dL
5. If target LDL levels are achieved and there are no laboratory abnormalities, continue therapy and recheck in 12 weeks, then 6 months.
6. If laboratory abnormalities are noted or symptoms are reported, temporarily withhold the drug and repeat the bloodwork in about 2 weeks. When abnormalities return to normal, the drug may be restarted with close monitoring.
7. If target LDL levels are not achieved, increase the dose by one increment (usually 10 mg), and repeat the bloodwork in 6 weeks. Continue stepped titration up to maximum recommended dose until target LDL levels are achieved, or there is evidence of toxicity.

Monitoring

1. Monitor growth, sexual maturation and development.
2. Monitor fasting lipoprotein profile, CK, ALT and AST every 6 months.
3. Monitor compliance with lipid-lowering dietary and drug therapy. Serially assess for other risk factors.

ities and myopathy. These adverse effects are less prevalent than with the statins; however, the risk of myopathy is substantially increased when the fibrates are combined with the statins or in the presence of renal insufficiency. Only one pediatric study has been reported [57]. Their use is generally limited to those with only extreme elevations of triglycerides who are at risk for pancreatitis.

Therapeutic impact on the atherosclerotic disease process

Clearly the widespread advocacy for screening and management of hyperlipidemia in children should be based on documentation of a direct impact on the disease process itself. Since the likelihood of a cardiovascular event or manifest cardiovascular disease is extremely uncommon in this age group, this evidence has been lacking. However, recent studies have used the noninvasive markers to document some vascular impact. de Jongh and colleagues in a randomized clinical trial of simvastatin showed that flow-mediated dilatation of the brachial artery as assessed by vascular ultrasound was markedly improved in children with familial hypercholesterolemia treated with 40 mg of simvastatin [58]. Engler and colleagues also performed a double-blind, randomized cross over clinical trial of vitamin C 500 mg and vitamin E 400 units/day for 6 weeks, and showed normalization of flow-mediated dilatation of the brachial artery in 15 children with familial hyperlipidemias [59]. While preliminary, these studies provide some important and promising evidence to advocate for screening and management of lipid abnormalities in children and adolescents.

Summary

The link between hyperlipidemia and the atherosclerotic process in children and adolescents has been established. Given the epidemic of overweight and associated cardiovascular risk factors, a strong imperative is present for implementation of a screening and management program. There has been a limited success in using fat and cholesterol-restricted diets to manage hyperlipidemia. It is likely that the focus of dietary management should shift to the prevention and treatment of overweight and obesity. Pediatric clinical trials of lipid-lowering drug therapy are suggesting similar effectiveness and safety to that observed in the adult population. Early

evidence has shown that therapy can improve endothelial function in hyperlipidemic children. This may suggest a translation into prevention or slowed progression of atherosclerotic cardiovascular disease into adulthood.

References

- [1] Eisenmann JC. Secular trends in variables associated with the metabolic syndrome of North American children and adolescents: a review and synthesis. *Am J Human Biol* 2003;**15**:786-94.
- [2] Tremblay MS, Willms JD. Secular trends in the body mass index of Canadian children. *Can Med Assoc J* 2000;**163**: 1429-33.
- [3] Gidding SS, Bao W, Srinivasan SR, Berenson GS. Effects of secular trends in obesity on coronary risk factors in children: the Bogalusa Heart Study. *J Pediatr* 1995;**127**: 868-74.
- [4] Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents. Findings from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2003;**157**:821-7.
- [5] Napoli C, Lerman LO. Involvement of oxidation-sensitive mechanisms in the cardiovascular effects of hypercholesterolemia. *Mayo Clin Proc* 2001;**76**:619-31.
- [6] Falk E, Fernandez-Ortiz A. Role of thrombosis in atherosclerosis and its complications. *Am J Cardiol* 1995;**75**: 3B-11B.
- [7] Libby P. The interface of atherosclerosis and thrombosis: basic mechanisms. *Vasc Med* 1998;**3**:225-9.
- [8] Ruberg FL, Loscalzo J. Prothrombotic determinants of coronary atherothrombosis. *Vasc Med* 2002;**7**:289-99.
- [9] Sambola A, Osende J, Hathcock J, Degen M, Nemerson Y, Fuster V, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. *Circulation* 2003;**107**:973-7.
- [10] Albisetti M, Chan AK, McCrindle BW, Wong D, Monagle P, Andrew M. Impaired fibrinolytic activity is present in children with dyslipidemias. *Pediatr Res* 2004;**55**:576-80.
- [11] Dangas G, Badimon JJ, Smith DA, Unger AH, Levine D, Shao JH, et al. Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile. *J Am Coll Cardiol* 1999;**33**:1294-304.
- [12] Joukhadar C, Klein N, Prinz M, Schrolnberger C, Vukovich T, Wolzt M, et al. Similar effects of atorvastatin, simvastatin and pravastatin on thrombogenic and inflammatory parameters in patients with hypercholesterolemia. *Thromb Haemost* 2001;**85**:47-51.
- [13] Newman III WP, Freedman DS, Voors AW, Gard PD, Srinivasan JL, Cresanta JL, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. *N Engl J Med* 1986;**314**:138-44.
- [14] Napoli C, Glass CK, Witztum JL, Deutsch R, D'Armiento FP, Palinski W. Influence of maternal hypercholesterolemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. *Lancet* 1999;**354**:1234-41.
- [15] Berenson GS, Srinivasan SR, Bao W, Newman III WP, Tracy WA, 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.

- [16] Urbina EM, Brinton TJ, Elkasabany A, Berenson GS. Brachial artery distensibility and relation to cardiovascular risk factors in healthy young adults (The Bogalusa Heart Study). *Am J Cardiol* 2002;**89**:946-51.
- [17] Mietus-Snyder M, Malloy MJ. Endothelial dysfunction occurs in children with two genetic hyperlipidemias: improvement with antioxidant vitamin therapy. *J Pediatr* 1998;**133**:35-40.
- [18] Sorensen KE, Celermajer DS, Georgakopoulos D, Hatcher G, Betteridge DJ, Deanfield JE. Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein(a) level. *J Clin Invest* 1994;**93**:50-5.
- [19] Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;**340**:1111-5.
- [20] Tonstad S, Joakimsen O, Stensland-Bugge E, Leren TP, Ose L, Russell D, et al. Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects. *Arterioscler Thromb Vasc Biol* 1996;**16**:984-91.
- [21] Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intima-media thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation* 2001;**104**:2815-9.
- [22] Sanchez A, Barth JD, Zhang L. The carotid artery wall thickness in teenagers is related to their diet and the typical risk factors of heart disease among adults. *Atherosclerosis* 2000;**152**:265-6.
- [23] Kieltyka L, Urbina EM, Tang R, Bond MG, Srinivasan SR, Berenson GS. Framingham risk score is related to carotid artery intima-media thickness in both white and black young adults: the Bogalusa Heart Study. *Atherosclerosis* 2003;**170**:125-30.
- [24] Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study). *Am J Cardiol* 2002;**90**:953-8.
- [25] Riley WA, Freedman DS, Higgs NA, Barnes RW, Zinkgraf SA, Berenson GS. Decreased arterial elasticity associated with cardiovascular disease risk factors in the young. *Bogalusa Heart Study. Arteriosclerosis* 1986;**6**:378-86.
- [26] Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA, et al. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. *J Am Coll Cardiol* 1996;**27**:277-84.
- [27] Kwiterovich Jr PO. Identification and treatment of heterozygous familial hypercholesterolemia in children and adolescents. *Am J Cardiol* 1993;**72**:30D-7D.
- [28] Kwiterovich Jr PO. Pediatric implications of heterozygous familial hypercholesterolemia. Screening and dietary treatment. *Arteriosclerosis* 1989;**9**:1111-20.
- [29] Tonstad S. Stratification of risk in children with familial hypercholesterolemia with focus on psychosocial issues. *Nutr Metab Cardiovasc Dis* 2001;**11**(Suppl. 5):64-7.
- [30] McCrindle BW, O'Neill MB, Cullen-Dean G, Helden E. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr* 1997;**130**:266-73.
- [31] Wiegman A, Rodenburg J, de Jongh S, Defesche JC, Bakker HD, Kastelein JJP, et al. Family history and cardiovascular risk in familial hypercholesterolemia. Data in more than 1000 children. *Circulation* 2003;**107**:1473-8.
- [32] Cortner JA, Coates PM, Liacouras CA, Jarvik GP. Familial combined hyperlipidemia in children: clinical expression, metabolic defects, and management. *J Pediatr* 1993;**123**:177-84.
- [33] Mahley RW, Huang Y, Rall Jr SC. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. *J Lipid Res* 1999;**40**:1933-49.
- [34] Calabresi L, Franceschini G. High density lipoprotein and coronary heart disease: insights from mutations leading to low high density lipoprotein. *Curr Opin Lipidol* 1997;**8**:219-24.
- [35] Vega GL, Grundy SM. Hypoalphalipoproteinemia (low high density lipoprotein) as a risk factor for coronary heart disease. *Curr Opin Lipidol* 1996;**7**:209-16.
- [36] Brinton EA. Lipid abnormalities in the metabolic syndrome. *Curr Diabetes Rep* 2003;**3**:65-72.
- [37] Ruotolo G, Howard BV. Dyslipidemia of the metabolic syndrome. *Curr Cardiol Rep* 2002;**4**:494-500.
- [38] Cruz ML, Goran MI. The metabolic syndrome in children and adolescents. *Curr Diabetes Rep* 2004;**4**:53-62.
- [39] 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.
- [40] Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Serum total cholesterol screening for the detection of elevated low-density lipoprotein in children and adolescents: the Bogalusa Heart Study. *Pediatrics* 1990;**85**:472-9.
- [41] Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. *JAMA* 1995;**273**:1429-35.
- [42] Obarzanek E, Kimm SY, Barton BA, Van Horn LL, Kwiterovich Jr PO, Simons-Morton DG, et al. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). *Pediatrics* 2001;**107**:256-64.
- [43] Rask-Nissila L, Jokinen E, Ronnema T, Viikari J, Tammi A, Niinikoski H, et al. Prospective, randomized, infancy-onset trial of the effects of a low-saturated-fat, low-cholesterol diet on serum lipids and lipoproteins before school age: the Special Turku Coronary Risk Factor Intervention Project (STRIP). *Circulation* 2000;**102**:1477-83.
- [44] Kaitosaari T, Ronnema T, Raitakari O, Tavia S, Kallio K, Volanen I, et al. Effect of 7-year infancy-onset dietary intervention on serum lipoproteins and lipoprotein subclasses in healthy children in the prospective, randomized Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study. *Circulation* 2003;**108**:672-7.
- [45] Gylling H, Siimes MA, Miettinen TA. Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia. *J Lipid Res* 1995;**36**:1807-12.
- [46] McCrindle BW, Helden E, Conner WT. Garlic extract therapy in children with hypercholesterolemia. *Arch Pediatr Adolesc Med* 1998;**152**:1089-94.
- [47] Tonstad S, Sivertsen M, Aksnes L, Ose L. Low dose colestipol in adolescents with familial hypercholesterolaemia. *Arch Dis Child* 1996;**74**:157-60.

- [48] Tonstad S, Knudtson J, Sivertsen M, Refsum H, Ose L. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996;**129**:42-9.
- [49] Tonstad S, Ose L. Colestipol tablets in adolescents with familial hypercholesterolaemia. *Acta Paediatr* 1996;**85**:1080-2.
- [50] McCrindle BW, Helden E, Cullen-Dean G, Conner WT. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. *Pediatr Res* 2002;**51**:715-21.
- [51] McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003;**143**:74-80.
- [52] Knipscheer HC, Boelen CC, Kastelein JJ, van Diermen DE, Groenemeijer BE, van den EA, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res* 1996;**39**:867-71.
- [53] Lambert M, Lupien PJ, Gagne C, Levy E, Blauchman S, Langlois S, et al. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. Canadian Lovastatin in Children Study Group. *Pediatrics* 1996;**97**:619-28.
- [54] Stein EA, Illingworth DR, Kwiterovich Jr PO, Liacouras CA, Siimes MA, Jacobson MS, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999;**281**:137-44.
- [55] de Jongh S, Ose L, Szamosi T, Gagne 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.
- [56] Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL, Newburger JW. Niacin treatment of hypercholesterolemia in children. *Pediatrics* 1993;**92**:78-82.
- [57] Wheeler KA, West RJ, Lloyd JK, Barley J. Double blind trial of bezafibrate in familial hypercholesterolaemia. *Arch Dis Child* 1985;**60**:34-7.
- [58] de Jongh S, Lilien MR, op't RJ, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002;**40**:2117-21.
- [59] Engler MM, Engler MB, Malloy MJ, Chiu EY, Schloetter MC, Paul SM, et al. Antioxidant vitamins C and E improve endothelial function in children with hyperlipidemia: Endothelial Assessment of Risk from Lipids in Youth (EARLY) Trial. *Circulation* 2003;**108**:1059-63.
- [60] Ducobu J, Brasseur D, Chaudron JM, Deslypere JP, Harvengt C, Muls E, et al. Simvastatin use in children. *Lancet* 1992;**339**:1488.
- [61] Firth JC, Marais AD, Byrnes P, Fuller CA, Bonnici F. Fluvastatin in heterozygous familial hypercholesterolemia. *Cardiol Young* 2000;**10**(Suppl. 2):35 [abstract].