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Prevention of atherosclerosis and drug treatment of high-risk lipid abnormalities in children and adolescents

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Abstract

Objective: To discuss risk factors of atherosclerosis in pediatrics, dietary and physical activity guidelines, and, mainly, drug treatment of high-risk lipid abnormalities.

Sources: Data were obtained from articles indexed in MEDLINE, published over the last 5 years.

Summary of the findings: Children with severe dyslipidemia or additional risk factors such as family history of early cardiovascular disease or other signs of metabolic syndrome may need treatment with hypolipidemic drugs. New recommendations from the U.S. guidelines indicate drug treatment before the age of 10 years according to the magnitude of the additional risk factors for cardiovascular disease. Pediatricians should know when to diagnose dyslipidemia, when to indicate drug treatment and which medication can be used in children and adolescents with the least risk or harm to their development.

Conclusions: The first-line treatment of dyslipidemia consists of lifestyle changes, focusing on prevention. Children with high-risk lipid abnormalities should be considered for drug treatment. Decisions to be made together with the parents must be evaluated taking into consideration risks and benefits of the medication to the patient.

J Pediatr (Rio J). 2009;85(1):6-14: Atherosclerosis, hypercholesterolemia, lipids, medication, pediatrics.

Introduction

Atherosclerosis is a silent disease that starts in childhood and develops during adolescence and adulthood, causing cardiovascular disease in adults or elderly people.[1-3] The disease was early detected in fetuses of hypercholesterolemic mothers.[1] The pathogenesis of atherosclerotic disease involves the inflammatory and immune systems. Oxidized low-density lipoprotein cholesterol (LDL-C) accumulates underneath the vascular endothelial cells, resulting in filiform fatty deposits within the vascular intima, which will be covered by a fibrous coat (plaque). This plaque, depending on its stability, may cause ischemic and thrombotic events, such as coronary heart disease and acute myocardial infarction, respectively.[4]

Studies on atherosclerosis began through autopsies of young individuals killed in combat. In individuals at mean age 22 years, 45% of the autopsies showed evidence of coronary atherosclerosis, and 5% of these at a severe stage.[2] Pathological and epidemiological studies correlate atherosclerotic lesions and the following risk factors: lipid profile abnormalities, hypertension, hyperglycemia, and obesity.[5-9]

A study involving adolescents showed that modifiable risk factors, such as age, sex, LDL-C levels, high-density lipoprotein cholesterol (HDL-C), triglycerides, smoking, blood pressure, and obesity, are related to atherosclerotic lesions in the coronary and aorta arteries at different grades. These risk factors tend to become more and more important, since they tend to persist and, typically, get worse as age advances.[1]

Raitakari et al.[6] followed up 2,229 young adults, aged between 24 and 49 years, who had previously participated in

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Table 1 - Lipid profile for children over 2 years old and adolescents, according to the I Directive on the Prevention of Atherosclerosis in Childhood and Adolescence[13]

Lipoproteins (mg/dL)	Desirable	Borderline	High
TC	< 150	150-169	> 170
LDL-C	< 100	100-129	≥ 130
HDL-C	≥ 45	-	-
TG	< 100	100-129	≥ 130

HDL-C = high-density lipoprotein cholesterol fraction; LDL-C = low-density lipoprotein cholesterol fraction; TC = total cholesterol; TG = triglycerides.

a study of risk factors for atherosclerosis during childhood, at the age of 3-9 years. The authors assessed LDL-C levels, systolic blood pressure and smoking, linking these risk factors to the carotid artery intima-media thickness obtained by ultrasonography at adult life. A linear regression analysis was performed, with correction for age, sex and current risk factors, and a strong association between risk factors at adolescence and an increase in carotid intima-media thickness was found at adult life.[6] Risk factors found at adolescence have higher predictive value than those analyzed on imaging examination at adult life, highlighting the importance of risk factors at early ages.[6-9] Family history of hypercholesterolemia and cardiovascular disease stands as an important risk factor, which is directly related to lipoprotein levels in children.[10] A Brazilian study identified that, by dividing the obese children by tertiles of homeostasis model of insulin resistance (HOMA-IR), 41.2% of the patients in the first tertile showed more than two risk factors for cardiovascular disease.[11]

Increased LDL-C levels may be secondary to inadequate eating habits and lifestyle and/or may occur due to changes in the lipid metabolism resulting from genetic factors. The main representative of lipid metabolic changes in childhood and adolescence is familial hypercholesterolemia. It is characterized by high levels of total and LDL cholesterol, family history of hypercholesterolemia and early death of first-degree relatives due to cardiovascular disease.[12]

Considering the increase in the prevalence of childhood obesity, and the consequent increase in the risk of cardiovascular events in a younger population, a new discussion with regard to drug treatment in this population deserves special attention.

Lipid abnormalities

Table 1 shows lipid profile normal values, for children aged 2 years or over, currently adopted by the Brazilian Society of Pediatrics and the Brazilian Society of Cardiology. Serum cholesterol measurements and fractions should be performed after 12 h of fasting.

The first pediatric joint statement was issued in 1992 by the National Cholesterol Education Program (NCEP)[14] and points out two ways of detecting dyslipidemias in children and adolescents. One of them mentions that children with family history of early cardiovascular disease should measure their total cholesterol serum levels and fractions. Family history is defined as parents or grandparents age 55 or younger with evidence of atherosclerosis: peripheral vascular disease, cerebrovascular disease, undergone coronary artery surgical procedure, victim of acute myocardial infarction or sudden cardiac death. The other one mentions that children with parental history of hypercholesterolemia (total cholesterol level ≥ 240 mg/dL) should measure their total cholesterol level. If cholesterol level is borderline (between 170 and 200 mg/dL), cholesterol measurement should be repeated. If two measurements of total cholesterol are ≥ 170 mg/dL, or the first measurement is ≥ 200 mg/dL, children should have their serum cholesterol fractions measured. Because of individual variations, serum cholesterol measurements and fractions should be assessed twice in the same clinical laboratory to confirm diagnosis of dyslipidemia.

In 2005, in Brazil, the Brazilian Society of Cardiology and other civil societies, such as the Brazilian Society of Pediatrics, created the I Directive on the Prevention of Atherosclerosis in Childhood and Adolescence.[13] Analysis of lipid profile is recommended in children: 1) whose parents or grandparents have a history of atherosclerosis at age 55 years or younger; 2) whose parents have total cholesterol ≥ 240 mg/dL; 3) who present additional risk factors such as hypertension, obesity, smoking, or consumption of saturated and/or trans fat- rich foods; 4) who use corticosteroids or have diseases that develop along with dyslipidemia (AIDS, hyperthyroidism, lupus, chronic renal disease, anorexia nervosa); and 5) who show clinical manifestations of dyslipidemia (xanthoma, xanthelasma, corneal arcus, recurrent abdominal pain, pancreatitis). This guideline recommends lipid profile collection [triglycerides, total and LDL cholesterol, very low-density lipoprotein cholesterol (VLDL-C) and HDL-C] for all children with the above-mentioned characteristics, after 12 h of fasting, in a reliable clinical laboratory.[14]

Recommendation for reassessment and treatment is limited to those with borderline (110 to 129 mg/dL) or high (≥ 130 mg/dL) LDL-C.[13,15]

Dietary guidelines

Prevention

The population-based approach in the guidelines recommends that children over 2 years old adopt a fat and cholesterol-restricted diet which proves appropriate to support their growth and development, in addition to maintaining a "desirable" body weight. Daily recommendation for the general population consists in consuming 300 mg/dL of cholesterol and, at most, 30% of the total energetic value in fat, while only 10% of this value can consist of saturated fat. Currently, consumption of trans fat, which is found in the hydrogenated fat used in the manufacturing of industrialized products, is restricted.[16] Its consumption is directly related to increased concentrations of small-sized LDL-C, which present higher atherogenic risk than the large-sized LDL-C.[16] The American Heart Association (AHA) recommends that the trans fat content in a diet be up to 1% of the total energetic value of lipids.[16]

Dietary recommendations include consumption of omega-3-rich fish, two portions a week, since it is associated with reduced risk of sudden death following - and death due to - coronary heart disease in adults.[16]

Treatment

Dietary guidelines from the NCEP[14] for children with high LDL-C include: consumption of 200 mg/dL of daily cholesterol and saturated fat at a maximum of 7% of its total energetic value.[13] The amount of trans fat consumed should be the same as that recommended for the general population. A double-blinded, randomized, placebo-controlled trial of docosahexaenoic acid (omega-3) in 20 hyperlipidemic children showed favorable and significant changes in the distribution of lipoprotein subclasses, with an increase in larger lipoproteins and a reduction in smaller and more atherogenic lipoproteins.[17] Hypertriglyceridemic children benefit from the consumption of omega-3, and supplementary medication should be considered if the therapeutic amount is not achieved.

Physical activity recommendations

Time spent in front of TV, video games and computer should be limited to 2 h/day to prevent atherosclerosis, in addition to encouraging pleasing physical activity for 30 min/day, 3 to 4 times a week.[14] A Brazilian study found prevalence of sedentary lifestyle in over 70% of the overweight children and adolescents.[11]

Physical activity seems to act on lipid profile; however, it is extremely difficult to methodologically assess physical activity in children and adolescents. Aerobic activity seems to be related to a decrease in the levels of triglycerides, total and LDL cholesterol, as well as to an increase in HDL-C levels.[2,18,19] Although these changes are of a modest nature, physical activity brings additional benefits, such as a reduction in body mass index, in blood pressure, and, consequently, a decrease in cardiovascular disease.[19,20]

Drug treatment of dyslipidemia

Joint statement

The NCEP[14] recommended drug treatment for children over 10 years old with LDL-C ≥ 190 mg/dL, whose cholesterol levels remained high despite of dietary treatment for 6 to 12 months. The NCEP also considered treatment for those children with LDL-C ≥ 160 mg/dL with two or more risk factors for cardiovascular disease or with family history of early cardiovascular disease. Bile resins were considered first-line drugs because they were nonabsorbable.[13]

According to the Brazilian directive[13] all children with LDL-C > 130 mg/dL should be followed up. First-line treatment should always be dietary treatment. Medication should be restricted to children over 10 years old who present persistently high LDL-C levels, regardless of nutrition orientation. LDL-C reference values for intervention with lipid-lowering drugs depend on current risk factors, such as family history and magnitude of LDL-C elevation. Drug treatment has been indicated preferably in higher risk situations and situations in which one fails to change lifestyle in order to achieve LDL-C ideal (< 110 mg/dL) or acceptable (110 to 130 mg/dL) levels.[14]

Clinical trials

Primary dyslipidemia

Interventional studies in children with primary dyslipidemia were important to demonstrate drug safety, no interference with children's growth and development, and, mainly, reversion of functional vascular abnormalities by drug treatment. Dirisamer et al.[12] carried out a study with 20 adolescents, aged between 10 and 17 years, with diagnosis of familial hypercholesterolemia on simvastatin treatment for 1 year. LDL-C levels were reduced in 30% among those children receiving 5 mg/day, 30% among those receiving 10 mg/day, and 36% among those receiving 20 mg/day. Two patients showed raised creatine kinase enzymes and transaminases (alanine aminotransferase and aspartate aminotransferase). Side effects occurred during the first 4 weeks of treatment and disappeared up to the seventh day, and none of the patients had to be weaned off the treatment because of the side effects.[10]

A randomized, double-blinded, placebo-controlled trial, with a 2-year follow-up, of patients aged 8-18 years, with diagnosis of familial hypercholesterolemia, administering a dose of 20 mg to patients under 14 years old and 40 mg to those over 14 years old, demonstrated a reduction of 24.1% in LDL-C levels. As for drug safety, the authors analyzed educational level, growth and development, as well as pubertal

stage and endocrine function, and no significant differences were found between intervention and control groups. The most important finding of this study was the reduction in carotid intima-media thickness among the patients who received pravastatin, identifying that the atherosclerotic lesions in these children were reversible.[21]

Another prospective study with 35 children aged between 4.1 and 18.5 years, with familial hypercholesterolemia, on pravastatin, showed a reduction of 33% in LDL-C levels after 1-year follow-up with doses of 10 to 60 mg. The use of pravastatin proved safe and well-tolerated even in those patients under 8 years old, and the patients did not present changes in growth patterns, delay in pubertal development or changes in testosterone and estradiol levels.[22] A total of 54 female adolescents with familial hypercholesterolemia were randomized in a multi-center placebo-controlled trial, with initial dose of 20 mg of lovastatin for 4 weeks, progressing to 40 mg for an additional 20-week period, in a total of 24 weeks of follow-up. Lovastatin was well-tolerated, and the mean reduction in LDL-C level was 27%.[23]

Another randomized, double-blinded, placebo-controlled study, with 186 patients with familial hypercholesterolemia, aged 8-18 years, was carried out using pravastatin during a mean period of 4.5 years at a dose of 20 mg for children under 14 years old and 40 mg for those over 14 years old. LDL-C levels decreased in 29.2% of the patients, and there was a reduction in carotid intima-media thickness among the patients who received pravastatin.[24] Thus, the use of statins in primary dyslipidemias seems scientifically safe; however, their use should always be evaluated against the balancing of costs and benefits to young patients.

Secondary dyslipidemia

Metabolic syndrome (MS) is a nutrition disorder that occurs in developed and developing countries with high prevalence in the adult population and a growing trend toward the pediatric population.[25-27] Prevalence of MS in American adolescents was identified in 6.8% of the overweight adolescents and in 28.7% of the obese adolescents.[28] A Brazilian study with obese children demonstrated the prevalence of MS to be 17.3% of the obese children aged between 7 and 10 years.[11]

MS is a complex disorder characterized by a set of cardiovascular risk factors usually related to central fatty deposits and insulin resistance. The disease components found in adults include: central obesity, hypertriglyceridemia, reduced serum HDL-C levels, high blood pressure, and high fasting glycemia.[29] Obesity is a severe risk factor for the development of dyslipidemia. Although criteria for the diagnosis of this syndrome in children and adolescents are yet to be defined, values of glucose, insulin resistance, triglycerides, C-reactive protein, interleukin-6, and systolic blood pressure raise significantly as obesity increases, along with a reduction in serum HDL-C and adiponectin levels.[30] MS is associated with the development of metabolic and cardiovascular diseases, such as atherosclerosis and type 2 diabetes mellitus.[31-33]

A 25 to 30-year follow-up study of 814 children, initial age between 5 and 19 years, demonstrated that 3.9% of the children showed prevalence of MS in childhood; 69% of these children had persistent MS throughout the study period, compared to 24% of them who did not have MS in childhood.[32]

The Bogalusa Heart Study demonstrated that obese school children are 2.4 to 7.1 times more likely to show high levels of total cholesterol, LDL-C and triglycerides, and 12.6 times more likely to have hyperinsulinemia.[5] A Brazilian study found that overweight children and adolescents are 2.8 times more likely to develop dyslipidemia.[34]

Sun et al.[35] demonstrated that children with high blood pressure are at greater risk of developing systemic hypertension, as well as MS, at adulthood. Recently, the risk for MS could be identified in the first decade of life through the early measurement of body mass index and waist circumference at 6 years old.[36]

Studies of drug treatment in children with MS are rare in the literature. A hybrid, multi-center, randomized, double-blinded, placebo-controlled study used atorvastatin therapy in 187 children aged 10-17 years, with diagnosis of primary dyslipidemia or severe hypercholesterolemia (defined as LDL-C ≥ 190 mg/dL). Among the patients on atorvastatin, 60% achieved LDL-C levels < 130 mg/dL, whereas none of the patients in the control group achieved this target LDL-C level after a 6-month follow-up. Therapy was well-tolerated and no side effects were observed regarding growth and development patterns.[37]

Some individuals have conditions favorable to the development of high-risk lipid abnormalities. These conditions include: diabetes mellitus, chronic renal disease, heart transplant, Kawasaki disease, congenital heart disease, chronic inflammatory disease, cancer, and AIDS.[38]

Type 1 diabetes is a metabolic disease characterized by a deficiency in insulin secretion causing hyperglycemia, which is associated as a primary factor in the development of atherosclerosis. It is a chronic renal disease that causes cardiac abnormalities, such as pericarditis, arrhythmias and ventricular dysfunction, which, in addition to uremia and hypertension, will increase the risk of developing atherosclerosis. Heart transplant children have some degree of atherosclerosis in the coronary arteries during the first year after transplantation. Another disease that causes coronary changes, the Kawasaki disease, also predisposes children to early atherosclerotic disease. Systemic lupus erythematosus and rheumatoid arthritis are chronic inflammatory diseases associated with atherosclerosis because of the inflammation itself (which is part of the pathophysiology of atherosclerotic disease), as well as the corticoid therapy used for its treatment. Congenital

heart diseases that cause coronary abnormalities and obstructive lesions are also related to early atherosclerosis. Children who survive cancer have lower ventricular mass index, along with a decrease in growth hormone levels, causing the development of obesity, insulin resistance, type 2 diabetes mellitus, with consequent MS.[38,39]

Another risk group for early atherosclerotic disease is the HIV-infected children who use protease inhibitors. Cross-sectional studies have shown an association of these drugs with hypercholesterolemia and hypertriglyceridemia.[40] Studies examining the incidence of hypercholesterolemia in children on protease inhibitors observed a raise in cholesterol levels throughout the treatment.[41] In the first prospective, longitudinal study to examine the inhibiting effects of protease on the HIV-infected pediatric population, in addition to the 13% who presented lipid profile changes, 13% developed hypercholesterolemia due to the treatment.[42]

The manual for the treatment of AIDS-related dyslipidemia in adults recommends pravastatin or atorvastatin for patients with triglycerides between 200 and 500 mg/dL and gemfribozil for those with triglycerides > 500 mg/dL. Simvastatin and lovastatin should be avoided because of drug interaction with antiretroviral therapy.[43] Prospective studies showed effectiveness and safety in the use of statins (pravastatin, atorvastatin, simvastatin, and fluvastatin) and fibrates (bezafibrate, gemfribozil, fenofibrate, and ciprofibrate) for patients on antiretroviral therapy, with no changes in the levels of cluster of differentiation 4, viral load, creatine kinase, and transaminase, suggesting no interaction with the antiretroviral therapy.[44,45]

In view of the foregoing, it becomes evident that prevention of atherosclerosis and its repercussions on the cardiovascular system should begin in childhood. It seems that dietary treatment is not enough to stop disease progression in severe cases, highlighting the need for drug therapy associated with a dietary treatment to halt disease progression.

New recommendations for drug treatment of children and adolescents with dyslipidemia

Some theories claim that pediatric treatment is not as effective or safe to reduce morbidity and mortality in adults as suggested. However, the 1992 statement does not take into account high-risk children with family history of parents with early cardiovascular disease and/or hypercholesterolemia, the ones who can benefit from drug treatment at an early age. Additionally, drug treatment is based only on LDL-C levels and does not take into account other risk factors for atherosclerotic disease.

The drug treatment proposed by the I Directive on the Prevention of Atherosclerosis in Childhood and Adolescence, although considering statins as the drug of choice, takes into account only the LDL-C level, disregarding the level of other abnormalities, such as reduced HDL-C, hypertriglyceridemia and other changes related to obesity and MS.[14] Thus, the criteria to indicate drug treatment in the prevention of atherosclerotic disease in high-risk children and adolescents need to be revised.[46]

McCrindle et al.[2] have recently established new recommendations to start high-risk dyslipidemic children on drug treatment. Lipid profile should be assessed in children with family history and/or in overweight and obese children. In the latter, additional MS components should be assessed, such as insulin resistance, type 2 diabetes mellitus, hypertension, and central obesity.

The criteria for drug treatment remain the same as those from the 1992 statement. Statins remain first-line drugs. In some cases, treatment can be considered before the age of 10 years. Children with lipid profile abnormalities combined with additional risk factors can present a reduced cut point for serum LDL-C level to start drug therapy. Risk factors are as follows:

- positive family history of early cardiovascular disease or event;
- association of low HDL-C level with increased levels of triglycerides and small-sized LDL-C particles;
- association between overweight or obesity and MS signs;
- presence of other medical condition associated with increased risk of atherosclerosis, such as diabetes, AIDS, systemic lupus erythematosus, organ transplant, or cancer;
- presence of hypertension;
- smoking and second-hand smoking;
- presence of other markers of increase in homocysteine and C-reactive protein.

Drugs used in the treatment of dyslipidemia

Bile resins

Bile resins reduce the absorption of bile acids from the intestine and increase the expression of hepatic LDL-C receptors, lowering serum cholesterol. They may increase triglyceride levels, interfere in the absorption of fat-soluble vitamins, and often cause gastrointestinal side effects. Reduction in serum LDL-C levels varies from 13 to 20%, and doses vary from 2 to 12 g/day.[2,4,14] Although bile resins are a class of first-line drugs in the treatment of dyslipidemia according to the 1992 statement, in practice, bile resins are not well-tolerated and some patients complain of the bad taste, contributing to their low effectiveness.[2,4,14]

Statins

Statins reduce cholesterol synthesis by inhibiting the enzyme HGM-CoA reductase, controlling a step of cholesterol synthesis. This decrease in intracellular sterol causes the

LDL-C receptor gene to increase the number of LDL-C receptors and, consequently, to reduce circulation of this lipoprotein.[2,4]

Side effects of statins include hepatotoxicity with increase in transaminases (usually transitory), miotoxicity with myalgia and/or rarely with rhabdomyolysis, and teratogenicity. Female adolescents on statin therapy should be guided regarding contraceptive methods. Other drug interactions may occur with increased risk of toxicity (macrolides, antifungals, protease inhibitors, calcium channel blockers, cyclosporine, and decrease in serum statin levels, such as rifampicin, barbiturates and carbamazepine). Their effectiveness and safety in children and adolescents is similar to that found in adults.[2]

There are four statins currently approved by the Food and Drug Administration (FDA) in the United States for clinical use: simvastatin, lovastatin, atorvastatin, and pravastatin. Dose of simvastatin is 10 to 40 mg/day; lovastatin is 10 to 40 mg/day; atorvastatin is 10 to 20 mg/day; and dose of pravastatin is 20 mg/day for children aged 8-13 years and 40 mg/day for those aged 14-18 years.[4] Reduction in LDL-C levels varies from 21 to 41%.[2] Rosuvastatin, a new statin, proved to be effective and safe in the treatment against hyperlipidemia in adults with primary dyslipidemia, though studies with children are currently lacking.[47-49]

Nicotinic acid

Nicotinic acid is a soluble vitamin, whose action remains under study, which lowers triglycerides and LDL-C levels and raises HDL-C levels. It is rarely used for treatment in the pediatric population because of the high incidence of adverse effects, such as diarrheic disease, and other more severe side effects, such as glucose intolerance, myopathy, hyperuricemia and fulminant liver failure.

Fibrates

Fibrates are fibric acid derivatives, with a complex mechanism of action, which decrease triglyceride levels and increase HDL-C levels. They can also reduce LDL-C levels. Dose of bezafibrate varies from 10 to 20 mg/day, and its side effects include: high transaminases and creatine kinase enzymes, myopathy, and rhabdomyolysis, particularly when in combination with statins. This class of drugs can be used preferentially in children with severe increase in triglycerides and at high risk of developing pancreatitis (triglycerides ≥ 400 mg/dL).[2,4,14,50]

Inhibitors of cholesterol absorption

Selective inhibitors of cholesterol absorption are new agents that lower lipid levels. Ezetimibe reduces LDL-C levels in 20% and triglycerides in 5%; causing a slight increase in HDL-C level (1%). It is used preferentially in combination with statins in children with severe hyperlipidemia who do not respond to statin monotherapy. Their use in children over 10 years old has already been approved in the United States for patients with severe hypercholesterolemia at doses of 10 mg/day.[2,14]

Statin treatment

The AHA[2] developed a manual to guide the use of statins in children, whose summary is found in Table 2. Recommendations include the NCEP's selection criteria (age and serum LDL-C concentration) and can be influenced by the presence and magnitude of additional risk factors for cardiovascular disease, as well as by the presence of cutaneous xanthomas. It is important to ask the opinion of the parents and family when deciding on the treatment. Generally, treatment should not begin before the age of 10 in boys and before menarche in girls; Tanner stage of pubertal development equal to or greater than II must be achieved. Liver disease, renal failure, myopathy, and pregnancy are contraindications for statin treatment.[2,51]

Patients on statin treatment should be monitored regarding growth (height, weight, body mass index), sexual maturation and development (Tanner stage of pubertal development). Biochemical laboratory measurements (creatine kinase, alanine aminotransferase and aspartate aminotransferase) should be performed every 3 or 6 months. Diet should be monitored, stimulating low lipid content and highlighting the importance of a healthy diet to the success of the treatment. Children should be advised of additional risk factors, such as weight gain, smoking and sedentary lifestyle.[2] Some studies have demonstrated safety and effectiveness of statin treatment in children; however, due to the lack of long-term studies, these recommendations should be used carefully.

Final considerations

The pediatrician plays a crucial role in the prevention and treatment of atherosclerosis. Keeping a healthy lifestyle should be encouraged from childhood as the basis of the prevention of atherosclerotic disease and its comorbidities, which have affected the population at an earlier age.

Evidence from studies on the drug treatment of children with primary dyslipidemia shows safety and effectiveness similar to that found in the treatment of adults. Dated statements show limitations, mainly because they could not approach the recent childhood overweight and obesity epidemic. These new recommendations include additional risk factors involved in the pathophysiology of atherosclerosis. They point out that drug treatment should be used only in children with high-risk lipid abnormalities, or other associated high-risk conditions that do not respond to changes of lifestyle, and should not be used as first-line treatment.

Conclusions

It is important to highlight that drug treatment should be used only in patients with severe lipid abnormalities, in

Table 2 - Indication and monitoring of statin use in dyslipidemic children and adolescents according to the AHA[2]

1) Statins are first-line drugs in the treatment of dyslipidemia. Decision on which statin to be used is based on the experience and/or preference of the professional.

2) Start with the lowest dose a day, before going to bed. Perform serum creatine kinase, ALT and AST measurements.

3) Guide patients on adverse affects, especially myopathies. If myopathy occurs, evaluate its relation with physical activity; withdraw medication and perform serum creatine kinase measurement. Treatment can be resumed when symptoms and laboratory changes disappear.

4) Alert adolescents to the use of contraceptive methods.

5) Alert to drug interactions, especially with cyclosporine, fibrates, niacin, erythromycin, azole antifungals, nefazodone, and protease inhibitors.

6) After 4 weeks, monitor serum creatine kinase, AST and ALT measurements, and compare them to baseline levels. Serum creatine kinase levels 10 times higher than the upper limit should be investigated (take into account the impact of physical activity), as well as ALT and AST three times higher than the upper limit. The minimum acceptable LDL-C concentration should be less than 130 mg/dL, and the ideal concentration should be less than or equal to 110 mg/dL.

7) If the desirable LDL-C concentration is achieved and no laboratory changes are observed, continue treatment and monitor biochemical examinations every 8 weeks and, subsequently, every 3 months.

8) If laboratory abnormalities or symptoms are observed, withdraw medication temporarily and repeat exams in 2 weeks. If biochemical parameters return to normal values, statin therapy can be resumed along with monitoring.

9) If LDL-C concentration does not meet the goal, double the dose used and repeat laboratory exams in 4 weeks. Increase the dose continuously up to the maximum dose recommended until LDL-C achieves the desirable levels, and, mainly, if no clinical or laboratory evidence of toxicity is observed.

AHA = American Heart Association; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

patients with high-risk conditions who did not meet their lipid-lowering goals through diet and lifestyle approaches, or when these changes are not directly related to the patient's lifestyle. Pediatricians should use their scientific knowledge to improve the quality of life of their patients, always keeping in mind the binomial benefits/risks for the pediatric patient in the short, medium and long term.

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