REVIEW ARTICLE

Atherosclerosis in Children and Adolescents

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ABSTRACT Being an old disease, atherosclerosis is now considered as the leading cause of death in industrial countries and in some developing countries, and a steady increase of the proportion of death from cardiovascular disease is seen every where. In the USA death from cardiovascular disease rose from 14% of all death in 1937 to 54% in 1968. Although clinical manifestations of atherosclerosis usually occur at adult age, its pathogenesis has been shown to start at early life. Fatty streak has been shown in not less than 5% of apparently normal children below 1 year of age. We discuss in considerable details the risk factors for atherosclerosis and the role of pediatrician in controlling this disease. Algorithm of screening and diagnosis of high risk children and adolescents for atherosclerosis, as well as the basis of its management are also discussed. Step care dietetic program is very important, although use of certain drugs is warranted in selected cases. **[Paediatr Indones 1997; 37: 45-60]**

Introduction

Atherosclerosis is a very old disease, having been identified even in the mummies of ancient Egypt. In the latter half of this century, this disease and its complications have caused up to 50% of deaths in the western world. A child born today is up to 500 times more likely to die from the complication of atherosclerosis than from congenital heart disease. Although the clinical manifestations usually present in the middle and late adult life, the risk factors for atherogenesis are often present in childhood and early histopathological changes can be found in large arteries in the first decade of life.[1]

Virchow postulated in 1862 that lipid infiltration into the arterial wall was the prime cause of atherosclerotic lesions. This hypothesis was fortified by Anitschkow in 1913, who demonstrated that a diet with unnaturally high cholesterol level induced

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atherosclerosis in rabbits and that correction of the diet caused the lesions to regress.[4] Monckeberg in 1915, reported examining coronary arteries of 140 combat soldiers who died as a consequence of injuries sustained in World War I. The soldiers had a mean age of 27.7 years, and 65 of the 140 had raised atherosclerotic plaques in the coronary arteries. This was followed by Zinserling in 1925 who found fatty streaks in the autopsy of subjects up to 15 years of age. In 1952, investigators at Louisiana State University School of Medicine found fatty streaks lesion in the aortas of young autopsied persons in New Orleans. Subsequently Holman and colleagues in 1958 reported the finding of young autopsied, 1 to 69 years of age suggested that all subjects 3 years of age and older had at least minimal fatty streaks, the earliest grossly recognizable lesion of atherosclerosis (70%-80%). Advanced study (1960) revealed that aortic fatty streaks were presents in many children under the age of 3 years and in all children over 3 years old, while fatty streaks were rare in the coronary arteries before the age of 10 years but more frequent in the second decade of life. Furthermore, fatty streaks have been shown to present in 90% or more after the age of 20 years, and fibrous plaques were more frequent in the third decade. Study by World Health Organization group in five cities in Europe performed fatty streaks and fibrous plaques in the coronary arteries as early as the 10- to 14- year age group.[3]

Detailed report about the occurrence of atherosclerosis in children was found in the autopsy of young soldiers killed in action in Korea. The average age in 200 cases was 22.1 years, and over 77.3% of them had evidence of atherosclerosis in their coronary arteries.[2,7] Since that time, Stary and colleagues have demonstrated a very high incidence of lipid laden macrophages in the intima of the aorta and coronary arteries of young American children killed in motor accidents, with over 50% of children aged 10-14 having some evidence of early atherosclerosis.[1] Other investigators have found fatty streaks in aortas in children age 3 years,[5,6,8] 10-14 years, and the most frequently in the age of 20 years.[5] The early signs of disease identified in these autopsy studies almost certainly represent the same pathological process that causes late morbidity and mortality. The presence of atheroma in young people has been correlated with a high level of low density lipoproteins and with cigarette smoking, both of which are known to be important risk factors for late cardiovascular death.[1] The recent prospective study by Klag and colleagues, which demonstrated that serum cholesterol levels in late teenage years were strongly predictive of cardiovascular morbidity and mortality in middle age, is further evidence that the presence of risk factors in the pediatric age range is important in determining the later development of occlusive vascular disease.[9] Strong and colleagues, reported that atherosclerosis began in childhood (since infant as fatty streaks), and progresses further in adolescence and young adulthood, while clinical manifestations usually occur in the middle age or older as coronary heart disease.[7]

It is clear that atherosclerotic lesions have begun since childhood,[8-12] and will developed as a permanent lesion in adolescence. The changes of the vascular need a long period of time,[2,10] and it cause a significant coronary dysfunction after age 40 or older

before the first clinical manifestations occur as angina pectoris, myocardial infarction, or sudden death.[5,10]

The role of pediatric cardiologist is important in the prevention of coronary heart disease, although it is still in debate. Most experts consider that prevention of coronary heart disease during infant is needed if there is family history of hypercholesterolemia; eventhough, most of the experts believe that diet intervention, regular physical activity and cessation of smoking, is still recommended to lower atherosclerosis process.[13]

Definition

Atherosclerosis is a diseases primarily of the elastic arteries (aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e. g., coronary and popliteal arteries).[5] The basic lesion is fatty streaks that are not raised and thus do not cause any disturbances in blood flow, and it may be precursor atheromatous plaque. Fatty streaks are composed of lipid-filled foam cells, T lymphocytes, extracellular lipid, proteoglicans, collagen, and elastic fibers. "Streaks" begins as multiple yellow, flat spots less than 1 mm in diameter that coalesce into elongated streaks, 1 cm long or may be longer.[14] Table 1 depicts the percentage of fatty streaks in the aortic wall.

Table 1. Percentage of fatty streak in aorta[15]

Age	Cases	% of affected aorta
Still birth	9	0
1 week	11	0
1-12 mos	16	5
1-5 yrs	13	5
6-10 yrs	10	5
11-15 yrs	7	10
16-20 yrs	12	10

Atheromatous lesions, or atheromatous plaques, consist of a raised focal plaque within the intima, having a core of lipid (mainly cholesterol and cholesterol esters) and is covered by fibrous cap. Plaques appear white to whitish yellow and impinge on the arterial lumen, varying in size from 0.3-1.5 cm but may coalesce to form larger masses. The centers of plaques contain a yellow, grumous debris, called an atheroma.[14]

Atheroma derived from the Greek word for *gruel*.[5,14] Atheromas are sparsely distributed at first, but as the disease advances, they become more and more numerous, sometimes covering the entire circumference of severely affected arteries. As the plaques increase in size, they progressively encroach on the lumen of the artery as well as on the subadjacent media.

Consequently, in small arteries, plaques are occlusive, comprimising blood flow to distal organs and causing ischemic injury, but in large arteries they are destructive, weakening the affected vessel wall, causing aneurysms or rupture or favoring thrombosis. Moreover, extensive atheromas are friable, often yielding emboli of their grumous contents into distal circulation (atheroemboli), most commonly noted in the kidney.[14]

Atherosclerotic plaques have three principal components: (1) cells, including smooth muscle cells, macrophages, and leukocytes ; (2) connective tissue extracellular matrix, including collagen, elastic fibers and proteoglycans; and (3) intracellular and extracellular lipid deposits.[14]

Epidemiology

Death from cardiovascular disease in the United States rose from 14% of all deaths in 1937 to 54% in 1968. Almost all cases being related to atherosclerosis . But in the late 1960's and by 1975 the rate shown a statistically significant influenced by changes in diet, life style, better control of hypertension and improved therapy for myocardial infarction and other complication of ischemic heart disease.[14]

Epidemiologic studies also indicate that increased age, male gender, and certain genetic factors increase the risk of atherosclerosis. Death rates from ischemic heart disease are significantly higher in men. Familial predisposition factors is most likely polygenic, particularly, hyperlipidemia (including genetic defects in lipoprotein metabolism), hypertension and diabetes trend to be familial. Although the aforementioned factors are unchangeable in an individual, other risk factors, particularly diet, lifestyle, and personal habits important in the pathogenesis and progression of this disease.[14]

Atherosclerosis may be seen during childhood as a result of certain very rare disorders such as progeria and some of the genetic mucopolysaccharidoses. Accelerated vascular aging may also accompany juvenile diabetes or hypothyroidism.[2]

Genetically transmitted hyperlipidemias are also encountered in childhood. Of the five recognized (Table 2), only types II and IV are important in childhood. Although it is estimated that only 1-5% of the overall population has genetic hyperlipidemia, this group accounts for approximately 1/3 of the coronary artery disease manifested clinically before 50 years of age.[2] Gofman described a method for characterizing the lipoproteins of blood serum by ultracentrifugation. Frederickson et al suggested a system for classifying the hyperlipoproteinemias using Roman numerals I through V:[2]

Type I hyperlipoproteinemia occurs in childhood as abdominal colic. Eruptive xanthomas on the abdomen, buttocks and mucous membranes, or lipemia retinalis, are present. This disorder has not been found to predispose to early vascular disease.

Type II, the most common of the hyperlipoproteinemias, is also known as familial hyper-β-lipoproteinemia, familial hypercholesterolemia, .and familial xanthomatosis. This disease characterized by elevated serum cholesterol levels and an increased (-lipoprotein band on electrophoresis. Patients with the rare homozygous form of this disorder usually develop xanthomas on the extensor tendons of the hand, the Achilles tendon, and the tibial tuberosities early in life. Clinically evident coronary artery disease may also occur in early childhood, often by 10 years of age.

Type III is a rare disorder inherited as an autosomal recessive. It occurs primarily in obese adults with glucose intolerance. Type IV is often associated with obesity, hyperuricemia, glucose intolerance, and premature atherosclerosis. It may be secondary to diabetes mellitus, hyperthyroidism, dysglobulinemia, obstructive liver disease, or the nephrotic syndrome. Type V, has all the clinical manifestations of Type I except that it occurs in adults.

Table 2. The Frederick-Lees classification of hyperlipopreteinemias[2,14]

Type	Lipoprotein abnormality	Prevalence 0-19 years (percent)	Clinical features			
			Cororany arteries	Peripheral arteries	Xanthomas	Others
I	Chylomicron	0	0	0	0	Abdominal pain
IIa	β-Lipoprotein	67	+	?	+	Aortic stenosis
IIb	pre-β and β-lipoprotein	3				
III	abnormal β-lipoprotein	1	+	+	+	
IV	pre-β-lipoprotein	28	+	+	0	Often obese
V	Chylomicron + pre-β-lipoprotein	1	?	?	0	

Risk Factors

Epidemiologic studies showed that risk factors associated with coronary artery and aortic atherosclerosis.[7] The risk factors that predispose to atherosclerosis and ischemic heart disease have been identified by means of a number of prospective studies in

well defined population groups, most notably the famed Framingham Study (Massachusetts) (e.g., the Multiple Risk Factor Intervention Trial [MRFIT])[17] Of the various risk factors, four are most significant: (1) hyperlipidemia, (2) hypertension, (3) cigarette smoking, and (4) diabetes.[18,19]

Moderate consumption of coffee and alcohol, marital status, and family size (possible indicators of emotional stress) are apparently unrelated to excess risk.[2] Goldstein and colleagues, added other risk factor, who demonstrated that 50% of survivors of acute myocardial infarction under 60 years were hyperlipemic when studied approximately 3 months after the attack. One-half of this group were found to be from families with genetically dominant hyperlipemias. Two disorders characterized by Goldtein, familial hypercholesterolemia and familial mixed hyperlipidemia (increased cholesterol and triglycerides), were associated with premature coronary artery disease in family members.[2] Measurements of high density lipoprotein (HDL) fractions by either ultracentrifugation or by selective lipoprotein precipitation are generally available and useful to clinicians. Elevation of HDL cholesterol is inversely correlated with coronary artery disease and levels of HDL are widely variant in childhood. Therefore, evaluation of pediatric hypercholesterolemia should include determinations of both low and high density lipoprotein cholesterol.[2]

Table 3. Risk factors for atherosclerosis

MAJOR	MINOR
▪ Hyperlipidemia	▪ Obesity
▪ Hypertension	▪ Physical inactivity
▪ Cigarette smoking	▪ Male sex
▪ Diabetes mellitus	▪ Family history
	▪ Increase of age
	▪ Stress (type A personality)
	▪ Oral Contraceptive
	▪ High intake of carbohydrate
	▪ Hyperhomocystinemia

Lipid Biochemistry

Lipid normally function as building blocks and fuels in the human body. Cholesterol are necessary components of cell membranes and associates structures like myelin and are needed as well for hormone synthesis. triglycerides are a major source of energy. Lipoproteins are spherical particles with a surface composed of free cholesterol, phospholipids, and protein, and a core containing predominantly cholesterol esters and triglycerides.[6] More than 95% of all plasma lipids after absorption are as lipoproteins, containing triglycerides, phospholipids, cholesterol and protein. Protein in compound are approximately one forth to one third from total constitution, the remnant is lipid. The rate of lipoproteins total concentrations in plasma are (700 mg/ dl, and can be divided into each concentration such as: [27]

	mg/dl
Cholesterol	180
Phospholipid	160
Triglyceride	160
Protein	200

Lipoproteins Classifications

Lipoproteins are categorized into four major classes on the basis of their density, which are measured by ultracentrifugation.

Chylomicron

Chylomicrons are large triglyseride-rich particles produced in the intestine and are carried by lymph through the thoracic duct to the venous system. The primary apoproteins in chylomicrons are apoproteins B and C-II (the latter is responsible for triggering the action of lipoprotein lipase in the capillary endothelium of adipose tissue). The main function of chylomicrons is to deliver dietary triglycerides to adipose and other tissue.[6]

1. Very low density lipoprotein (VLDL, pre-beta-lipoprotein), contains high level of triglycerides and moderate level of phospholipid and cholesterol. [6,17,25,26]
2. VLDL transports triglycerides, which are synthesized primarily in the liver and to a lesser extent, in the intestine. VLDL contains apoproteins B100 and E. In the fasting state, most plasma triglycerides are carried by VLDL to adipose and other tissues.[6]
3. Low density lipoprotein (beta-lipoprotein), contains a few triglycerides but high percentage of cholesterol. [6,17,25,26] LDL is the major cholesterol carrying lipoprotein in

plasma, it delivers cholesterol to hepatocytes and peripheral cells for synthesis of cell membranes and steroid hormones. Apoprotein B100, contained in LDL particles, is responsible for binding to the LDL receptor. The plasma level of LDL cholesterol is directly associated with the risk of coronary disease.[6]

4. High density lipoprotein (alpha-lipoprotein), contains approximately 50% of protein with a fewer level of lipid. [6,17,25,26]

HDL serves as an acceptor of lipid, especially free cholesterol, from various tissues. It is produced directly by the liver and the intestine and derived as well from chylomicron and VLDL catabolism. The major proteins of HDL are apoprotein A-I and A-II. HDL cholesterol acts as a mechanism for the removal of cholesterol from various tissues; its plasma level is inversely related to the risk of coronary artery disease.[6]

Lipoprotein Synthesis

Most of lipoproteins are endogenous synthesized in the liver. In fact that most of phospholipids, cholesterol and triglycerides (only chylomicron) are produced in the liver. But, fewer high density lipoproteins are synthesized in intestine epithelial during the fatty acids absorption.[27]

Lipoproteins Function

Principally, the plasma lipoproteins function are lipid transport to all of the body. Mainly triglycerides are synthesized in the liver and are transported to adipose and other peripheral tissues in the form of very low density lipoprotein. Low density lipoprotein is the remnant of very low density lipoproteins after they losses their triglycerides to adipose tissues, leaving high cholesterol levels and phospholipids in low density. Inversely, high density lipoprotein transport cholesterol to the liver and other peripheral tissues, so that this lipoprotein type is important in the role of atherosclerosis prevention.[27]

Pathogenesis

There have been some theories of atherogenesis that were proposed by experts, such as:[12,14,21,25,28]

1. Thrombogenic theory (Carl von Rokitansky,1844)
2. Imbibition theory (Rudolf Virchow, 1853)
3. Primary medial weakness (Thoma, 1883)
4. Monoclonal proliferation (Benditt & Benditt, 1973)
5. Response to injury (Ross & Glomset, 1976)

Response to injury hypothesis of atherosclerosis is now widely held. This theory

states that atherosclerosis lesions is initiated as a response to various form of injury to arterial endothelium.[14,25,28,29]

The injury postulated is a form of endothelial dysfunction without necessary denudation, which increases permeability to plasma constituents, including lipids, and permits blood monocytes and eventually platelets to adhere to endothelium. Monocytes adhere and subsequently enter the intima, transform into macrophages, and accumulate lipid to become foam cells, contributing to the evolution of the lesions, the earliest lesion of atherosclerotic is so called as fatty streaks.[14,25,28,29] Factors released from activated platelets at the surface or monocytes than cause migration of smooth muscle cells (SMC) from media into the intima, followed by proliferation and synthesis of extracellular matrix components by SMCs, leading to the accumulation of collagen and proteoglycans. Single injurious events can be followed by restoration of endothelial function and regression of the lesions. Repeated or chronic injury, however, results in the development of an atheromatous plaque, probably by permitting continuing increased permeability, ingress of monocytes, or perhaps platelets interactions.[14,25,28,29] The current trend is to consider atherosclerosis as a chronic inflammatory response of the vascular wall to a variety of initiating events that can occur early in life.[14,29]

Laboratory Examination

Screening

Expert Panel of National Cholesterol Education Program (EPNCEP) recommends selective screening of children and adolescents with a family history of premature cardiovascular disease (or at least one parent with high serum cholesterol).

- Children and adolescents whose parents or grandparents at age 55 or less (for men) and 65 years or less (for women) were found to have coronary atherosclerosis following angiography or underwent balloon angioplasty or coronary artery bypass surgery.
- Children and adolescents whose parents or grandparents at age 55 or less (for men) and 65 years or less (for women) had documented myocardial infarction, angina pectoris, peripheral vascular or cerebrovascular disease or sudden cardiac death.
- The offspring of a parent who has been found to have high total cholesterol (240 mg/dL or higher)
- Children and adolescents whose parental or grandparent history is unobtainable, particularly patients with other risk factors.

The recommendations of selective screening are somewhat controversial, but some investigators have recommended.

Total cholesterol level or lipoprotein profile

The experts from NCEP have recommended testing vary according to the reasons:[10]

- At least one parent has a high blood cholesterol, the initial step is a measurement of total cholesterol.
- For children who have a family history of premature cardiovascular disease, a lipoprotein analysis is recommended.
- Measurements of cholesterol and lipoproteins
- Total cholesterol and LDL cholesterol levels are not measured before the person is age 2, and no treatment si recommended before that age.
- The child does not have to be fasting for measurement of total cholesterol
- A lipoprotein analysis is obtained after an overnight fast of 12 hours. Total cholesterol, HDL cholesterol and triglyseride level are measured. LDL cholesterol level is then estimated by the *Friedewald formula:*

LDL cholesterol = total cholesterol - HDL cholesterol - (triglyseride : 5)

This formula is not accurate if the child is not fasting, if the triglyseride level is above 400 mg/dL, or if chylomicrons or dysbetalipoproteinemia is present.

Classification

Depending on the total cholesterol and LDL cholesterol levels, patients are categorized as acceptable, borderline and high.

- Acceptable : If total cholesterol levels < 170 mg/dL; borderline: 170-199 mg/dL; and high > 200 mg/dL.
- For those who had lipoprotein analysis done: Regardless of indication, a lipoprotein analysis should be repeated and the average LDL cholesterol levels. The patients is then categorized as acceptable (LDL cholesterol < 110 mg/dL); borderline (110-129 mg/dL), and high (>130 mg/dL).

Non invasive method for testing endothelial dysfunction in children has been developed with high resolution ultrasound imaging, with a 7.0 MHz linear array transducer.[20] Mahoney and colleagues, have used electron beam computed tomography as a sensitive, noninvasive method for detecting coronary artery calcification, a marker of the atherosclerotic process.[24]

Diagnosis

Atherosclerotic lesion begins in childhood and progresses further irreversible lesions in adolescents. The clinical features of atherosclerotic lesions in childhood does not appear, and culminates in clinical disease in middle age or later. Clinical evaluation, i.e, history (risk factor, family history), physical examination (hypertension, obesity) and other laboratory testing are important to establish the diagnosis. See Figure 1.

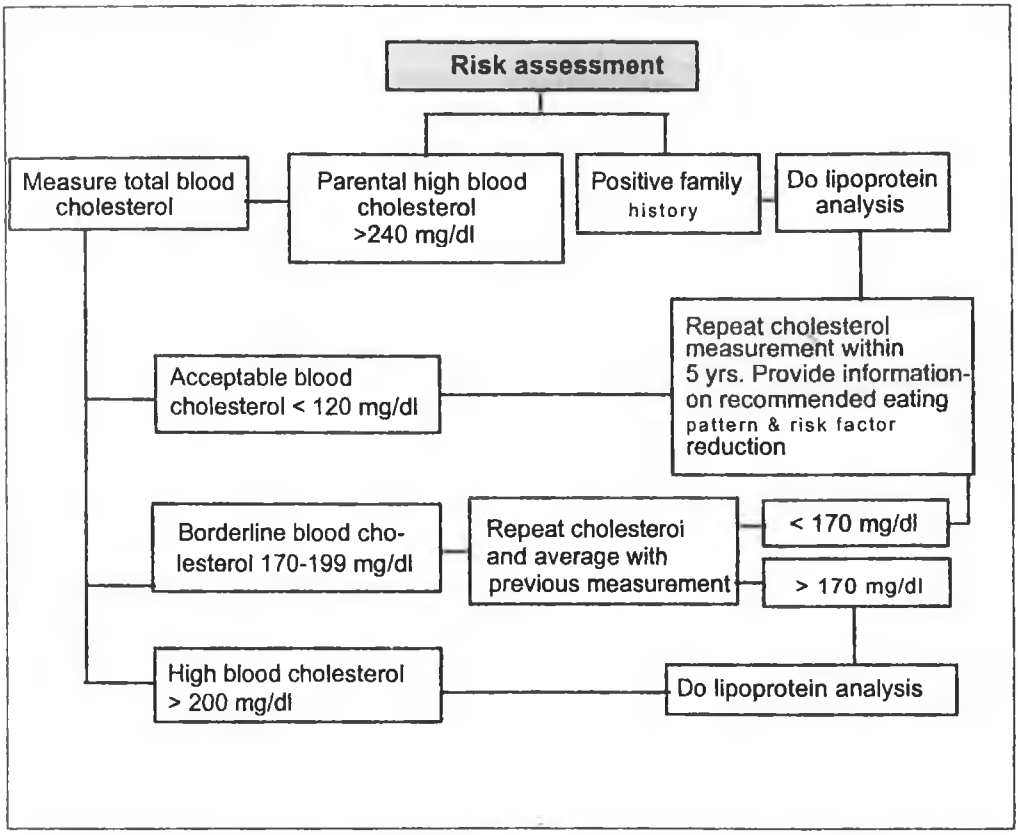

Figure 1. Eisk assessment recommended by the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, National Cholesterol Education Program (NIH Publication No. 91-2732, September 1991).

Management

Atherosclerotic lesions start to develop in childhood and progress to irreversible lesions in adulthood. High levels of total cholesterol, LDL, and VLDL and low levels of HDL are correlated with an increased risk for coronary heart disease in adolescents and young adults. Irreversible atherosclerosis may already exist by the fourth decade of life, efforts to lower serum cholesterol levels in children have been made in the hope of preventing or retarding the progress of atherosclerosis.[5,10] Most of experts suggested that dietary modification/intervention,[2,5,8,10,11,13,23,26-30] and lowering risk factors (ces- sation of cigarette smoking, regular physical activity)[2,6,10,13] are still recommended. The pediatricians is faced with several problems simultaneously: the diet composition for the infant, child, and adolescents, the diagnosis and treatment of the child with a family history of early atherosclerotis.[30]

Expert Panel of National Cholesterol Education Program/ EPNCEP (June 1993), has recommended two complementary approaches, to lower blood cholesterol levels for children and adolescents.[10]

1. **Population approach:** For children older than 2, the following are recommended:
   a. Nutritional adequacy should be achieved by eating a wide variety of foods
   b. Adequate calories should be provided for normal growth and development.
   c. The following pattern of nutrient intake is recommended (Step-1 Diet, Table 7): saturated fatty acid (SFA) less than 10% of total calories, total fat not more than 30% of total calories, and dietary cholesterol less than 300 mg per day. Children younger than age 2 may require a higher percentage of calories from fat.
2. **Personal approach:** To identify and treat children and adolescents who are at high risk for having high cholesterol levels.

Table 4. Causes of secondary hypercholesterolemia[10]

Exogenous Causes
- Drugs: corticosteroids, isotretinoin (Accutane), thiazides, anticonvulsants, (β-blockers, anabolic steroids, certain oral contraceptives, alcohol, obesity

Obstructive Liver Diseases
- Biliary atresia
- Biliary cirrhosis

Endocrine and Metabolic Disorders
- Hypothyroidism, diabetes mellitus, lipodystrophy, idiopathic hypercalcemia, glycogen storage disease, sphingolipidoses

Chronic Renal Diseases
- Nephrotic syndrome

Miscellaneous Causes
- Anorexia nervosa, progeria, collagen diseases
- Klinefelter syndrome

Dietary therapy

Dietary therapy is the primary approach for the treatment of high blood cholesterol level in children and adolescents.[8] Diet therapy is prescribed in two steps that reduce theintake of saturated fatty acids and cholesterol.[8,10]

1. *The Step One Diet* (Table 5) contains the same nutrient intake recommended in the population approach to lowering cholesterol.
2. If the Step One Diet (Table 5) for 3 months fails to achieve the minimal goals of therapy, the *Step Two Diet* is prescribed.

Table 5. Nutrient composition of Step One and Step Two diets

Nutrient	Step One Diet	Step Two Diet
Total fat (% total calories)	<30%	<30%
▪ Saturated fatty acid (SFA)	<10%	<7%
▪ Polyunsaturated fatty acid (PUFA)	<10%	<10%
▪ Monounsaturated fatty acids (MUFA)	10-15%	10-15%
Carbohydrates (% of total calories)	50-60%	50-60%
Protein (% of total calories)	10-20%	10-20%
Cholesterol (per day)	<300 mg	<200 mg
Total calories	To achieve and maintain desired weight	

Drug treatment

The Expert Panel recommend drug therapy in children ages 10 years and older if after an adequate trial of diet therapy (6 months to 1 year).[8,10]

1. LDL cholesterol remains 190 mg/dL or higher, or
2. LDL cholesterol remains 160 mg/dL or higher and
   - There is a family history of premature cardiovascular disease (before age 55 in men and before age 65 in women), or
   - Two or more other cardiovascular disease risk factors (such as HDL cholesterol below 35 mg/dL, cigarette smoking, high blood pressure, obesity or diabetes) are present.

For children and adolescents with hypercholesterolemia, only the bile acids sequestrants (cholestyramine, colestipol) are recommended. This drugs increase excretion of bile acids in stool and increase LDL receptor activity. Niacin, HMG CoA (3-hydroxy-3 methylglutaryl-coenzyme A) reductase inhibitors (lovastatin, pravastatin), probucol, fibric acid derivates (gemfibrozil, clofibrate) are not recommended as routine drugs for use in children and adolescents,[8,10] with an exception to this rule may be considered

for a child or adolescents who does not have an adequate response to diet plus administration of bile sequestrants.[8] However, in certain cases, when children have extremely high LDL cholesterol levels, we may decide to initiate drug therapy at a younger age.[8]

Table 6. Cut-points of total and LDL-cholesterol for dietary intervention in children and adolescents with a family history of hypercholesterolemia or premature cardiovascular disease[8,10,23]

Category	Total cholesterol (mg/dl)	LDL- cholesterol (mg/dl)	Dietary intervention
Acceptable	<170	<110	Recommended population eating pattern
Borderline	170-199	110-120	Step One diet prescribed Other risk factor intervention
High	>200	>130	Step One diet prescribed, then Step Two diet if necessary Other risk factor intervention

Table 7. Summary of major drugs for consideration

Drug	Reduce CHD risk	Long-term safety	Maintaining adherence	LDL-cholesterol lowering, %	Special precautions
Cholestyramine, colestipol	Yes	Yes	Requires considerable educaion	15-30	Triglycride >
Nicotinic acid	Yes	Yes		15-30	Hyperuricemia
Lovastatin	Not proven	Not established		25-45	Liver function
Gemfibrozil	Not proven	Preliminary evidence	Relatively easy	5-15	LDL>
Probucol	Not proven	Not established	Relatively easy	10-15	HDL<

Table 8. Drugs highly effective in lowering LDL cholesterol

Drug	Starting dose	Maximum dose	Usual time & frequency	Side effects	Special precautrions
Cholestyramin, colestipol	4 g b.i.d. 5 g b.i.d.	24 g/day 30 g/day	Twice daily within an hour, of major meals	Upper/lower GIT	Dosing schedule of co-adminstered drugs
Nicotinic acid	100-250 mg as single dose	3 g/d	Three times a day with meals	Flushing, upper GIT and hepatic	Uric acid, liver function, glucose
Lovastatin	20 mg once daily with evening meal	80 mg/d	Once (evening) or twice daily	GI tract, hepatic, muscle pain	Liver function, creatinine kinase, lens

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