pISSN: 2234-8646 eISSN: 2234-8840
http://dx.doi.org/10.5223/pghn.2014.17.2.85
Pediatr Gastroenterol Hepatol Nutr 2014 June 17(2):85-92

Review Article

PGHN

Dyslipidemia in Children and Adolescents: When and How to Diagnose and Treat?

Jung Min Yoon

Department of Pediatrics, Konyang University College of Medicine, Daejeon, Korea

Recently, the incidence and prevalence of obesity and dyslipidemia are increasing. Dyslipidemia is associated with significant comorbidities and complications, and with cardiovascular risk factors (obesity, diabetes mellitus, hypertension and smoking). The main objectives of this article are that describe the prevalence of dyslipidemia in Korean children and adolescents and review the diagnosis and management of dyslipidemia in children and adolescents.

Key Words: Dyslipidemias, Obesity, Diagnosis, Treatment

INTRODUCTION

With socioeconomic development and the rapid increase of obesity for the past 20 years, the obesity rate has increased nearly 10-fold in children and adolescents [1,2]. Data from the Organization for Economic Co-operation and Development (OECD) indicate that obesity rate of Korea is low among OECD countries, but growing more and more recently. Approximately 4% of the Korean adults are obesity, and about 30% are overweight. OECD estimate that the rate of overweight will increase by 5% within the next 10 years. The obesity rate of children is relatively high, especially in Korean boys. Fig. 1 shows the past and projected rates of overweight and obesity for Korean individuals aged 3-17 years.

The hypercholesterolemia was associated with cardiovascular disease (CVD). Atherosclerotic plaque is associated with the elevation of non-high density lipoprotein cholesterol (HDL-C) [3]. As the number of risk factors in CVD increased, the severity of asymptomatic coronary and aortic atherosclerosis was increased in youth [4]. Dyslipidemia is associated with cardiovascular risk factors (obesity, diabetes mellitus [DM], hypertension and smoking) [3,5]. Dyslipidemia is associated with carotid artery elasticity, intima-media thickness and brachial flow-mediated dilatation from childhood to adulthood [6,7].

Therefore, the main objectives of this article are that describe the prevalence of dyslipidemia in Korea and review the diagnosis and management of dyslipidemia in children and adolescents.

Received : May 17, 2014, Revised : June 10, 2014, Accepted : June 18, 2014

Corresponding author: Jung Min Yoon, Department of Pediatrics, Konyang University Hospital, 158, Gwanjeodong-ro, Seo-gu, Daejeon 302-718, Korea. Tel: +82-42-600-9230, Fax: +82-42-600-9090, E-mail: ruleout@empal.com

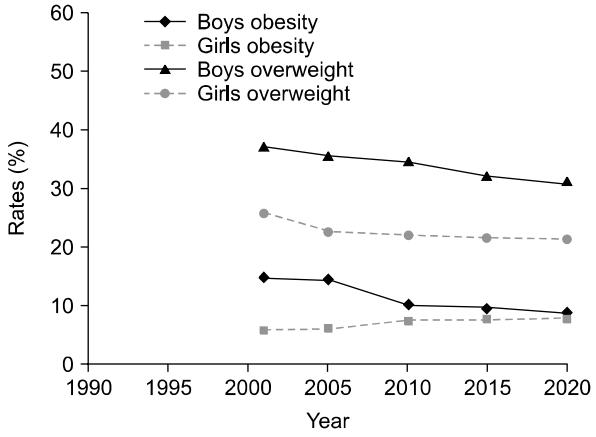

Fig. 1. Past and projected rates of child obesity and overweight, age 3-17 years, in Korea.

PREVALENCE OF DYSLIPIDEMIA IN KOREA CHILDREN AND ADOLESCENTS

According to the 2012 report by Yang et al. [8], 19.7% of children and adolescents in Korea (age 10-18 years) have at least 1 abnormal lipid profiles. The authors studied to identify a reference value for each serum lipid concentration of children and adolescents in Korea (2,363 people, age 10-18 years) using data from the Korea National Health and Nutrition Examination Survey (KNHANES) IV (2007-2009). According to cutoff points and guideline of the American Heart Association (AHA) and National Cholesterol Education Program (NCEP), the prevalence of high low-density lipoprotein cholesterol (LDL-C) was 6.5%, that of high triglycerides (TG) was 4.7%, and that of low HDL-C was 7.1%. Totally, approximately 0.41% of study group were potentially possible for pharmacologic treatments [8].

In the study by Kim et al. [9], the dyslipidemia is increased with increasing body mass index (BMI) in male and female. The total cholesterol (TC) level was significantly increased with increasing BMI, especially in male. In this study, the prevalence of dyslipidemia was 25.2% in boys and 21.7% in girls and the more the frequency of dyslipidemia increased in overweight and obesity. The independent predictors of dyslipidemia were age and overweight /obesity in boys and girls.

Recently, the prevalence of dyslipidemia (in individuals, aged over 20 years) was increased from 32.4% in 1998 to 42.6% in 2001 and 44.1% in 2005. In 1998, KNHANES data, the prevalence of dyslipidemia was 47% in 2001 and 61% in 2005 [10]. The mean LDL-C level is increasing over time and the prevalence of high TG ($>$110 mg/dL) and low HDL-C ($<$40 mg/dL) increased by 6.2% and 10.5% in Korean children and adolescents [11]. However, increases in prevalence of dyslipidemia and abdominal obesity in Korea, whereas in the United States (US), decreases in low HDL cholesterolemia and high blood pressure contributed to a decreased prevalence. According to the 2012 report by Kit et al. [12], among youths aged 6-19 years in 1988-1994 and 2007-2010, there were a decrease in mean TC (from 165 to 160 mg/dL; p $<$0.001) and a decrease in the incidence of elevated TC (from 11.3% to 8.1%; p=0.002). Mean HDL-C significantly increased between 1988-1994 and 2007-2010, but the prevalence of low HDL-C did not change.

DIAGNOSTIC CRITERIA FOR DYSLIPIDEMIA

The plasma levels of lipids and lipoproteins are influenced by various metabolic, genetic, and environmental factors. The lipid concentration is influenced by age, sex, and ethnicity. In 2011, the US National Institutes of Health Heart, Lung, and Blood Institute (NHLBI) experts revised the lipid cutoff values based on US normative data, categorized as the acceptable, borderline, and high [13]. Table 1 shows the more information.

The cut-off levels for LDL-C and TC according to the NCEP, American Academy of Pediatrics and NHLBI guidelines are similar. But, HDL-C $<$35 mg/dL and TG $>$150 mg/dL be regarded the abnormal in children and adolescents in AHA guideline [14]. In KNHANES-IV, the cutoff points for TC ($>$ 200 mg/dL) and LDL-C ($>$130 mg/dL) are equivalent to the 95th percentile of Korean children and adolescents. For HDL-C, the cut-off point of $<$40 mg/dL which corresponds to the 10th percentile is

Table 1. Acceptable, Borderline-high, and High Plasma Lipid and Lipoprotein Ranges for Children and Adolescents

Category	Acceptable (mg/dL)	Borderline (mg/dL)	High (mg/dL)
TC	<170	170-199	≥200
LDL-C	<110	110-129	≥130
Non-HDL-C	<120	120-144	≥145
TG (y)			
0-9	<75	75-99	≥100
10-19	<90	90-129	≥130
HDL-C	>45	40-45	<40

TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides. Modified from the article of Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute (Pediatrics 2011;128(Suppl 5):S213-56) [13].

Table 2. Selective Lipid Screening in Children and Adolescents

Recommendations for fasting lipid profile screening in children and adolescents (aged 2-18 years)
① A family history of myocardial infarction, stroke, peripheral arterial disease or treatment for these disorders (interventional catheterization or surgery) prior to age 55 years in men or age 65 years in women in parents or grandparents
② A family history of elevated TC (>240 mg/dL)
③ An unobtainable family history
④ Another cardiovascular risk factor, including hypertension, diabetes mellitus, cigarette smoking, or obesity (BMI ≥ 95th percentile)

TC: total cholesterol, BMI: body mass index.

considered abnormal. However, the cutoff point for TG (>130 mg/dL) is equivalent to around the 80-85th percentile [8,15]. This is a low cutoff point; therefore, according to AHA guidelines, the cutoff point for TG (>150 mg/dL) is reasonable for Korean children and adolescents.

LIPID SCREENING FOR DYSLIPIDEMIA

There was two major approach for diagnosis of dyslipidemia, namely, screening in the selected population and general population. Traditionally, screening in high-risk children has been recommended because of multiple risk factors and the family history of CVD or the presence of hypercholesterolemia. With obesity, type 2 DM, and metabolic syndrome increasing in children and adolescents, the target of screening is likely to be expanded to other factors, such as non-HDL, elevated TG, elevated apo B (reflected increasing LDL particles), hyperglycemia and insulin resistance, and hypertension.

SELECTIVE SCREENING

As the guidelines of the AHA and NCEP, the current recommendations for screening are based on the family history or the risk factor of CVD and dyslipidemia (Table 2). In selective screening, fasting lipid panels should be assessed in children aged over 2 years with risk factors. Fasting TC, TG and HDL-C should be checked. The LDL-C is calculated using the Friedewald equation: LDL-C=TC (HDL-C+TG/5). If TG is >400 mg/dL, this formula cannot be used. The sensitivity of assays to determine LDL-C concentrations is lower than that obtained using the Friedewald equation. The direct LDL-C assays were limited in dyslipidemia screening of children [16]. Non-HDL-C is atherogenic and the better predictor of dyslipidemia in adult, but is also related to non-lipid cardiovascular risk factors in adulthood [17].

UNIVERSAL SCREENING

The 2011 NHLBI guidelines additionally recommend "universal screening" [13]. In 2010, the results of the Coronary Artery Risk Detection in Appalachian Communities project indicated that the selective screening would have missed many with significant dyslipidemia and failed to detect the genetic dyslipidemias which require pharmacologic treatment. The universal screening would enable for proper intervention and prevention of future atherosclerotic disease [18].

Cholesterol levels are reasonably consistent over 2 years of age. Cholesterol levels are not routinely measured before the age of 2 years because no formal treatment is recommended for this age group. Ten years of age (range, 9-11 years) has been proposed as an appropriate time to check the lipid profile [19].

Because TC and LDL-C level reduced by 10-20% during adolescence [13], children at risk for familial dyslipidemia should ideally be screened before adolescence (age 2 and 10 years). If results during puberty are normal, blood checking should be repeated on the end of puberty (age 16 years in girls and 18 years in boys). In universal screening, non-fasting TC and HDL-C can be checked, which this is meaningful in children than a fasting lipid profile.

MANAGEMENT OF DYSLIPIDEMIA

Current guidelines recommend dietary modification and lifestyle changes as the first therapy for dyslipidemia. The lifestyle change and diet therapy must be emphasized with appropriate levels in terms of patient education. This is an essential point, although is often forgotten by medical doctors. If the family does not change in life style and dietary habit, the obesity will not improve unless the community provides appropriate intervention.

If these fail, then the medications should be considered. The main target of management is LDL-C and TG. The algorithm of diagnosis and treatment in pediatric dyslipidemia is shown in Fig. 2.

LIFESTYLE CHANGES

The primary treatment for dyslipidemia in children and adolescents is lifestyle changes, primarily dietary, and increased physical activity. The increasing of physical activity are correlated with decreased body fat and BMI, higher HDL-C levels, lower TC, TG and LDL-C levels, decreased insulin resistance and lower blood pressure in childhood and adolescence [13]. Children and adolescents should be encouraged the moderate and vigorous physical activity every day. Sedentary time for watching television, internet, and playing video games should be reduced as much as possible (＜2 hours/day) [13].

DIETARY TREATMENT

The NCEP experts recommend dietary treatment aged over 2 years [13]. The first approach to therapy for children with dyslipidemia is a modified diet containing decreased amounts of cholesterol, total fat, saturated and trans-fat. The intake of simple sugars

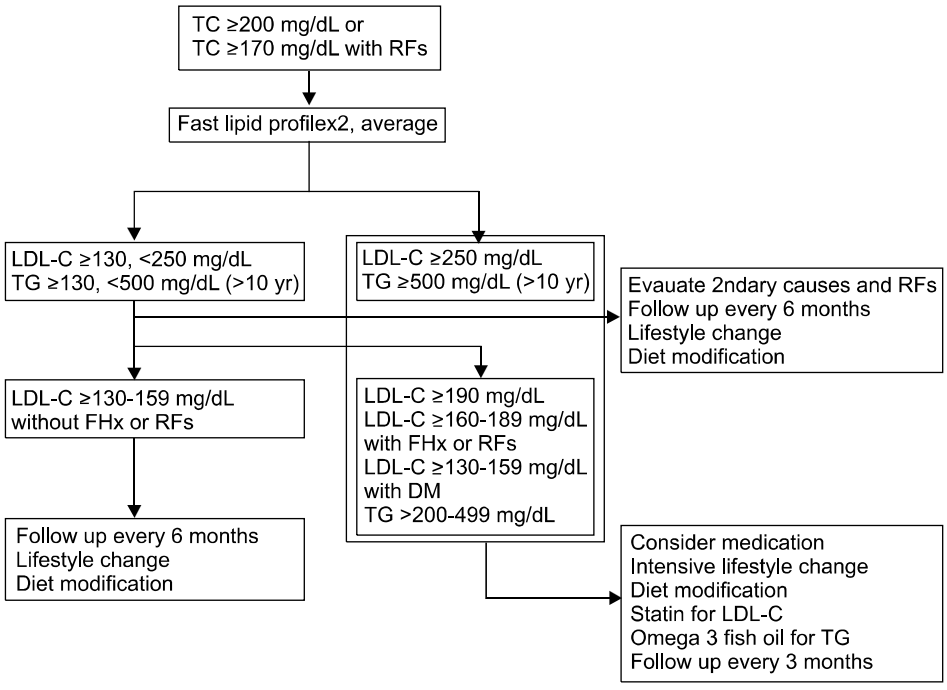

Fig. 2. Diagnostic and management algorithm for pediatric dyslipidemia. TC: total cholesterol, RFs: risk factors, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides; FHx: family history, DM: diabetes mellitus. Adapted from the article of Lim (Ann Pediatr Endocrinol Metab 2013;18: 1-8) [19].

Table 3. American Heart Association Step I and Step II Diets

Nutrient	Step I diet	Step II diet
Total fat (total daily calories, %)	<30	<30
Saturated fatty acids (%)	<10	<7
Polyunsaturated fatty acids (%)	≤10	≤10
Cholesterol (daily intake, mg)	<300	<200
Carbohydrates (total daily calories, %)	50-60	50-60
Protein (total daily calories, %)	10-20	10-20

is decreased and that of complex carbohydrates are increased. The limiting protein intake is not recommended. Adequate calories should be provided to maintain the normal development and growth.

If the fasting lipid profile shows that TC, TG or LDL-C is high or HDL-C is low, a repeat profile is obtained after 3 weeks. If dyslipidemia persists (Fig. 2), the evaluation of secondary causes in dyslipidemia is needed and dietary treatment is initiated. The recommended diet includes the limitation of saturated fat intake to <10% of the total calories, and decreasing of cholesterol intake to <300 mg/day [20]. After Step I diet is initiated, and the fasting lipid panel is rechecked in 6-8 weeks. If the dyslipidemia not corrected, the Step II diet is begun. Table 3 shows a comparison of AHA Step I and Step II diets.

The Cardiovascular Health Integrated Lifestyle Diet (CHILD)-1 diet by the NCEP pediatric panel is as follows: total fat (25-30% of total daily calories); saturated fat (8-10% of daily kcal/estimated energy requirements); avoiding trans-fat, <300 mg/day from cholesterol; dietary fiber (14 g/1,000 kcal); fat-free unflavored milk; limiting sodium intake and sweetened juice (no added sugar) <120 mL/day. The CHILD-2 diet is consisted with CHILD-2-LDL and CHILD-2-TG. The CHILD-2 diet recommends: 25-30% of total calories from fat; <7% from saturated fat; <10% from monounsaturated fat; and avoiding trans-fat. The CHILD-2-LDL recommends: plant sterol and stanol esters up to 2 g/day; water-soluble fiber psyllium, dose of 6 g/day (2-12 years) and 12 g/day (>12 years). The CHILD-2-TG recommends: decreasing sugar and sugar-sweetened beverages; replacing simple with complex carbohydrates; and increasing dietary fish to increase omega-3 fatty acid intake [13].

PHARMACOLOGIC TREATMENT

When to initiate medication?

Pharmacologic treatment of dyslipidemia is recommended in children aged ≥10 years with fail to the diet treatment and lifestyle changes after 6-12 months. Pharmacologic treatment for lower LDL-C is started in children without other CVD risk factors if the LDL-C is persistently ≥190 mg/dL despite a dietary intervention. Pharmacologic treatment is started, if the post-dietary LDL-C is ≥160 mg/dL with an at least 1 risk factors for CVD, a family history of CVD or metabolic syndrome. In children with DM, the medication should be considered when LDL-C is ≥ 130 mg/dL [13,14,21,22].

The six main classes of dyslipidemia therapy in children: the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statins), bile acid sequestrants (cholestyramine and colestipol), cholesterol absorption inhibitor, niacin (nicotinic acid), fibric acid derivatives and omega-3 fatty acids. Each drug is described below.

3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statins)

HMG-CoA reductase inhibitor (statins) are the most commonly used medication to treat the dyslipidemia in children and adults. Statins can competitively inhibit HMG-CoA reductase which the first enzyme of the HMG-CoA reductase pathway. By inhibiting HMG-CoA reductase, the statins block the pathway of cholesterol synthesis in the liver. Atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin are currently approved by the US Food and Drug Administration for adolescents. Side effect of statin is limited and does not affect the growth or pubertal maturation. The increasing in liver enzyme up to 3 times the normal level has been reported in adolescents treated with simvastatin (40 mg/day) and atorvastatin (20 mg/day) [23,24]. Although rare, the asymptomatic increasing (over

10-fold) of creatine kinase (CK), has been reported in adolescents treated statins [25]. Liver function tests and CK assessment is recommended every 3-4 months in children. Because the cholesterol synthesis takes place mostly at night, the statin is usually taking at night for maximize their effect.

Bile acid sequestrants (cholestyramine and colestipol)

The cholestyramine and colestipol are bile acid binding resins, as bile acid sequestrants. This medication can bind the bile salt in the gastrointestinal (GI) tract and prevent the reuptake. This medication leads to depletion of bile salts and increased conversion of cholesterol to bile in the liver. The decreasing cholesterol level in hepatocytes leads to up-regulation of LDL-C receptor and increased clearance of LDL from the circulation [26]. Because the bile acid sequestrants are stayed in the GI tract, there was no systemic side-effects. But, the adverse GI effects such as gas, bloating, constipation, and cramps are common and the compliance is poor with interruption rates ranging from 20% to 30%. This agent can bind fat soluble vitamins. This effect would result in a vitamin deficiency, and so checking blood levels and possible supplementation has been suggested.

Cholesterol absorption inhibitors (ezetimibe)

Cholesterol absorption inhibitor is newly developed medication which inhibiting the uptake of cholesterol. This blocks the uptake of cholesterol, thereby reducing the incorporation of cholesterol esters into chylomicron particles. This medication can decrease cholesterol absorption and decrease cholesterol delivery to the liver. The net result is a reduction in circulating LDL particles. This drug class is approved in children aged >10 years, as an adjuvant to statins. Co-administration of ezetimibe with the simvastatin is well tolerated, safe and resulted in higher LDL-C decrease compared with the simvastatin alone in adolescents (aged 10-17 years) with familial hypercholesterolemia studied as long as 53 weeks [27].

Niacin (nicotinic acid)

Niacin (vitamin B3) acts by decreasing the hepatic production and release of very-low-density lipoprotein (VLDL). This agent can reduce the LDL-C and TG levels and this is the most potent HDL-C enhancer; however, this is of limited use because the significant side effect. The most common side effects are hepatic failure, hyperglycemia, flushing, myopathy, hyperuricemia, and gastrointestinal issues. Colletti et al. [28] reported that six children (29%) had reversible dose-related elevations of serum aminotransferase levels and the niacin threatment was stoped in 8 children (38%) because of flushing, GI trouble, headache, or elevated aminotransferase levels.

Fibric acid derivatives

The fibric acid derivatives (gemfibrozil and fenofibrate) are usually used to treat hypertriglyceridemia in adult. This can reduce the hepatic production of TG by increasing oxidation of fatty acids in the muscle and liver and can reduce the rate of hepatic lipogenesis. This is also believed to increase HDL-C through a complex mechanism regulated by the nuclear transcription activator, peroxisome proliferator-activated receptor-α [29]. Fibric acid derivatives agents mainly affect TG and HDL-C. Although rare, rhabdomyolysis and myopathy may occur, particularly when used with a statin.

Omega-3 fatty acids

The omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) have been studied for effect of reducing TG level in adult. In adult, omega-3 fatty acids (2-4 g/day) reduced TG levels (30-40%) and increased HDL-C (6-17%) [13]. The typical dose of omega-3 fish oils (1 g per capsule) is 1-4 g/day; its side effect is intermittent gastrointestinal issues.

CONCLUSION

Obesity in current society is not a medical issue, but also socioeconomic issue. In this article, I reviewed the prevalence of dyslipidemia in children and adolescents as well as the diagnosis and man-

agement of dyslipidemia. The prevalence of obesity and dyslipidemia are increasing, and this condition is associated with significant comorbidities and complications. Pediatricians should be aware of the diagnosis and management of dyslipidemia. Such attention and aggressive management of dyslipidemia will enable prevention of type 2 DM or CVD in adulthood.

REFERENCES

1. Park YS, Lee DH, Choi JM, Kang YJ, Kim CH. Trend of obesity in school age children in Seoul over the past 23 years. Korean J Pediatr 2004;47:247-57.
2. Kim YS, Park MJ. Time trend in height, weight, BMI and waist circumference of Korean adolescents; from the Korean National Health and Nutrition Examination Survey (KNHNES), 1998, 2001 and 2005. J Korean Soc Pediatr Endocrinol 2007;12:142-9.
3. McGill HC Jr, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol 2000; 20:1998-2004.
4. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-6.
5. McGill HC Jr, McMahan CA, Zieske AW, Malcom GT, Tracy RE, Strong JP. Effects of nonlipid risk factors on atherosclerosis in youth with a favorable lipoprotein profile. Circulation 2001;103:1546-50.
6. Li S, Chen W, Srinivasan SR, Bond MG, Tang R, Urbina EM, et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. JAMA 2003;290:2271-6.
7. Juonala M, Viikari JS, Rönnemaa T, Marniemi J, Jula A, Loo BM, et al. Associations of dyslipidemias from childhood to adulthood with carotid intima-media thickness, elasticity, and brachial flow-mediated dilatation in adulthood: the Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2008; 28:1012-7.
8. Yang S, Hwang JS, Park HK, Lee HS, Kim HS, Kim EY, et al. Serum lipid concentrations, prevalence of dyslipidemia, and percentage eligible for pharmacological treatment of Korean children and adolescents; data from the Korea National Health and Nutrition Examination Survey IV (2007-2009). PLoS One 2012; 7:e49253.
9. Kim SH, Ahn BC, Joung H, Park MJ. Lipid profiles and prevalence of dyslipidemia in korean adolescents. Endocrinol Metab 2012;27:208-16.
10. Lee MH, Kim HC, Ahn SV, Hur NW, Choi DP, Park CG, et al. Prevalence of dyslipidemia among Korean adults: Korea National Health and Nutrition Survey 1998-2005. Diabetes Metab J 2012;36:43-55.
11. Lim S, Jang HC, Park KS, Cho SI, Lee MG, Joung H, et al. Changes in metabolic syndrome in American and Korean youth, 1997-2008. Pediatrics 2013;131:e214-22.
12. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. JAMA 2012;308:591-600.
13. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(Suppl 5):S213-56.
14. Kavey RE, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K; American Heart Association. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation 2003;107:1562-6.
15. Lim JS. The current state of dyslipidemia in Korean children and adolescents and its management in clinical practice. Ann Pediatr Endocrinol Metab 2013;18: 1-8.
16. Yu HH, Markowitz R, De Ferranti SD, Neufeld EJ, Farrow G, Bernstein HH, et al. Direct measurement of LDL-C in children: performance of two surfactant-based methods in a general pediatric population. Clin Biochem 2000;33:89-95.
17. Srinivasan SR, Frontini MG, Xu J, Berenson GS. Utility of childhood non-high-density lipoprotein cholesterol levels in predicting adult dyslipidemia and other cardiovascular risks: the Bogalusa Heart Study. Pediatrics 2006;118:201-6.
18. Ritchie SK, Murphy EC, Ice C, Cottrell LA, Minor V, Elliott E, et al. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. Pediatrics 2010;126:260-5.
19. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ 2007;335:599.
20. Gidding SS, Dennison BA, Birch LL, Daniels SR,

Gillman MW, Lichtenstein AH, et al; American Heart Association; American Academy of Pediatrics. Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association. Circulation 2005;112: 2061-75.
21. Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122:198-208.
22. Kwiterovich PO Jr. Recognition and management of dyslipidemia in children and adolescents. J Clin Endocrinol Metab 2008;93:4200-9.
23. de Jongh S, Ose L, Szamosi T, Gagné C, Lambert M, Scott R, et al; Simvastatin in Children Study Group. 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.
24. 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.
25. Avis HJ, Vissers MN, Stein EA, Wijburg FA, Trip MD, Kastelein JJ, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2007;27:1803-10.
26. Shepherd J, Packard CJ, Bicker S, Lawrie TD, Morgan HG. Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. N Engl J Med 1980; 302:1219-22.
27. van der Graaf A, Cuffie-Jackson C, Vissers MN, Trip MD, Gagné C, Shi G, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. J Am Coll Cardiol 2008;52:1421-9.
28. Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL, Newburger JW. Niacin treatment of hypercholesterolemia in children. Pediatrics 1993;92:78-82.
29. Auwerx J, Schoonjans K, Fruchart JC, Staels B. Transcriptional control of triglyceride metabolism: fibrates and fatty acids change the expression of the LPL and apo C-III genes by activating the nuclear receptor PPAR. Atherosclerosis 1996;124(Suppl):S29-37.