Dyslipidemia in Children & Adolescents: Study, Diagnosis & Management

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]. The obesity rate of children is relatively high, especially in boys. 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 to describe the prevalence of dyslipidemia in children and adolescents attending our outpatient department and review the diagnosis and management of dyslipidemia in these.

PREVALENCE OF DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS:
According to the 2012 report by Yang et al. [8], 19.7% of children and adolescents in our hospital (age 10-18 years) have at least 1 abnormal lipid profiles.

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 failed to detect the genetic dyslipidemias which require pharmacologic treatment [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 our 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.

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, categorised as the acceptable, borderline, and high [10]. 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 [11].

SCREENING GUIDELINES:
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. 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 children screening of children [12].

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 [14]. The 2011 NHLBI guidelines additionally recommend “universal screening” [10]. 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 [14].

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 [15].

Because TC and LDL-C level reduced by 10-20% during adolescence [10], 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: 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 [10]. 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) [10].

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 transfat. The intake of simple sugars 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.

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-2-2-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, with an at least 1 risk factor for CVD, a family history of CVD or metabolic syndrome. In children with DM, the medication should be considered when LDL-C ≥160 mg/dL with an at least 1 risk factor for CVD, a family history of CVD or metabolic syndrome. In adolescents (aged 10-17 years) with familial hypercholesterolemia studied as long as 53 weeks [22].

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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 [21]. 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 poor with compliance 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 [22].

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. [23] reported that six children (29%) had reversible dose-related elevations of serum aminotransferase levels and the niacin treatment was stopped in 8 children (38%) because of flushing, GI trouble, headache, or elevated aminotransferase levels.

Fibrin acid derivatives:
The fibrin 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 [24]. Fibrin acid derivatives agents mainly affect TG and HDL-C. Although rare, rhombodomylosis 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 ef- fect of reducing TG level in adult. In children, omega-3 fatty acids (2-4 g/day) reduced TG levels (30-40%) and increased HDL-C (6-17%) [10]. The typical dose of omega-3 fish oils (1 g per capsule) is 1-4 g/day; its side effect is intermittent increased HDL-C (6-17%) [10]. The typical dose of omega-3 fish oils (1 g per capsule) is 1-4 g/day; its side effect is intermittent increased HDL-C (6-17%) [10]. The typical dose of omega-3 fish oils (1 g per capsule) is 1-4 g/day; its side effect is intermittent increased HDL-C (6-17%) [10].

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