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Invited Paper

Raising heart-healthy children

ALBERT P ROCCHINI

CS Mott Hospital, University of Michigan Medical Center, Ann Arbor, Michigan, USA

Abstract The current article will describe how the cardiovascular risk factors of obesity, increased blood pressure, hyperlipidemia, cigarette smoking, poor physical fitness and prenatal environment impact the development of cardiovascular disease and what types of therapy can be used in the pediatric patient to modify them.

Key words childhood smoking, cholesterol, hypertension, obesity, perinatal cardiovascular risk.

Coronary artery disease has its origin in childhood.[1,2] Epidemiological and clinical studies in adults with coronary heart disease have made it possible to develop lists of risk factors that can help to identify individuals susceptible to the development of coronary heart disease. The risk factors that have been identified include obesity, increased blood pressure, hyperlipidemia, cigarette smoking, poor physical fitness and prenatal environment. The current article will describe how these risk factors impact the development of cardiovascular disease and what types of therapy can be used in the pediatric patient to modify them.

Obesity

Obesity is a complex and difficult clinical problem. It is the most prevalent and serious nutritional disease in the developed world. Childhood obesity is known to exert a major impact on cardiovascular risk. We have documented that 97% of obese children have four or more of the following risk factors: elevated blood pressure, elevated serum triglyceride levels, decreased high density lipoprotein (HDL) cholesterol levels, increased total cholesterol levels, diminished work capacity, hyperinsulinemia, insulin resistance and a strong family history of coronary heart disease.[3] For over 70 years, it has been recognized that hypertension is common in obese individuals. We have observed that obese adolescents have a blood pressure distribution that is skewed to the right.[4] The mean blood pressure for the group is greater than one standard deviation to the right of the mean blood pressure for the general population. We have also demonstrated that although obese adolescents have a blood pressure distribution that is skewed to the right of normal, following weight loss this distribution no longer differs from the general population.[4] In the same study, we also demonstrated that the method by which weight loss is produced was important in determining the degree of blood pressure reduction. Although weight loss in general results in a drop in resisting systolic and diastolic blood pressure and heart rate, the greatest decrease in resting systolic blood pressure and heart rate is observed when weight loss is incorporated with physical conditioning.

Another major cardiovascular risk factor associated with obesity is an abnormal lipid profile.[5] When children and adult subjects are stratified for fatness, there is a direct significant relationship between lipid levels and obesity. The primary cause of hypertriglyceridemia in children who are free from other diseases is obesity. In addition, obesity is frequently associated with a significant depression in HDL cholesterol. We have demonstrated that, as with blood pressure, lipid abnormalities are markedly improved in obese adolescents following weight loss and that a weight-loss program that incorporates exercise along with caloric restriction produces the most favorable effects on lipids.[4] We and others have determined that the lipid abnormalities observed in obese adolescents are directly associated with hyperinsulinemia and insulin resistance.[5] Insulin resistance, in our study, was assessed in obese adolescents by measuring both fasting insulin and whole body glucose uptake during euglycemic hyperinsulinemia clamp. Using a step-wise multiple regression analysis, we have documented that whole body glucose uptake, that is, insulin sensitivity, was the most important determinant for triglyceride level, low density lipoprotein (LDL) and HDL cholesterol in our obese patients. Fasting insulin level was also directly correlated to total cholesterol and inversely to HDL cholesterol level. The mechanism whereby insulin resistance leads to these lipid abnormalities has not been completely

Correspondence: Albert P Rocchini, CS Mott Hospital, University of Michigan Medical Center, Box 0204, Ann Arbor, MI 48109, USA. Email: < rocchini@umich.edu >

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characterized. There is evidence to suggest that two of the ways in which hyperinsulinemia elevates triglycerides are through enhanced hepatic very low density lipoprotein synthesis and through a defect in very low density lipoprotein (VLDL) removal. An increased rate of degradation of the apoprotein A1 (the major lipoprotein in HDL cholesterol) is believed to be a major cause for the reduced level of HDL cholesterol observed in many insulin-resistant subjects.

Another important cardiovascular risk factor that we have found associated with obesity is the development of cardiac hypertrophy. We have observed that, compared to non-obese adolescents, obese adolescents have a significant increase in left ventricular mass (Fig. 1). The increase in left ventricular mass is probably the result of the elevated blood pressure and the increased cardiac output and stroke volume that accompany obesity.

Treatment modalities used in obese children and adolescents can be characterized into one of a combination of six basic approaches: (i) caloric restriction; (ii) increase physical activity; (iii) habit pattern changes based on social learning theory; (iv) anoretic drugs; (v) therapeutic starvation; and (vi) intestinal bypass surgery. Certainly, drug therapy, starvation and surgery are unacceptable treatment strategies for the majority of children. However, a practical weight-loss program can be developed for the child. We believe that in order to assess the child's ability to comply with a weight-loss program, it is advisable to use a trial diet for 2–3 weeks. If the child is successful with this diet, that is, losing at least 0.5–1 kg in 2–3 weeks, he or she is likely to benefit from a weight-loss program. If, however, the child is unsuccessful, the family and child should be counselled and asked to return in 3–6 months or sooner if there is a change in attitude towards a weight-loss program. The weight-loss program that we use consists of three components: (i) diet; (ii) behavior change; and (iii) exercise. The caloric requirements necessary for a child to lose 0.5–1 kg per week are determined by reducing the current level of calories by 209–419 J/day. We believe that an adolescent weight-reduction diet should not contain less than 5013 J/day, because if diet is more deficient in kilojoules than this then it may provide inadequate vitamins and nutrients to promote normal growth and development. However, kilojoule levels should never exceed 10 443 J/day, because the child is unlikely to take the diet seriously if allowed too large a caloric intake. An exchange-type diet is our best recommendation, because it teaches the child the essentials of good nutrition and gets them actively involved in determining their own diet. The behaviour change component of the program includes hourly classes that are maintained weekly for at least 20–30 weeks and then every other week until the child has maintained a goal weight for at least 1 month. These classes center on nutrition education, record keeping, stimulus control for restricting the external cues that set the occasion for eating and reinforcement of altered behaviour. The purpose of the behaviour change component is to help the obese child learn to eat like a non-obese person, to become aware of current habits, to normalize and accept responsibility for their eating behaviour. Finally, all children are encouraged to exercise for 30–60 min/day for at least 3 days/week. In addition to the child-structured portion of the program, family support is critical. The family needs to be taught how to give the child positive support without nagging or taking over the child's weight-loss program. Using this type of program, we have been able to achieve adequate weight loss in adolescents who are motivated to lose weight. When dealing with childhood obesity, one must always remember that if the child or adolescent does not want to lose weight then no weight loss program, regardless of its approach, organization or cost, will be successful.

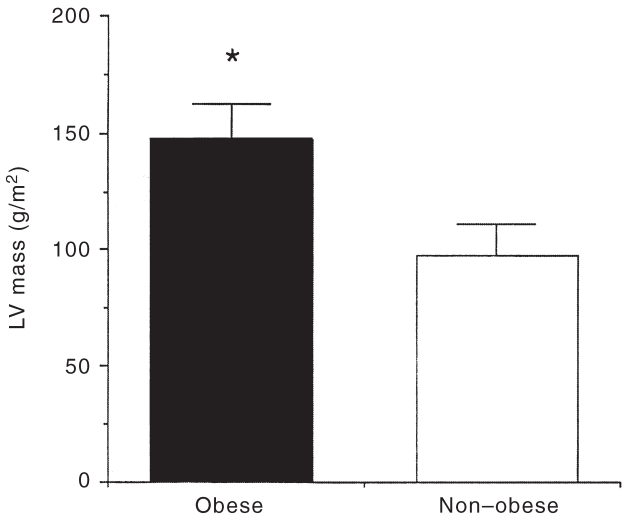

Fig. 1 Comparison of left ventricular (LV) mass determined by echocardiogram from 55 obese and 45 non-obese adolescents. The obese adolescents have a significantly increased LV mass (*$P < 0.001$).

Hypertension

During the past 20 years, it has become increasingly clear that hypertension constitutes a major disease process in adolescents as well as adults. The incidence of hypertension in the pediatric population varies from 0.5 to 11%, depending upon the age group investigated and the criteria used to define hypertension. Using the standard blood pressure tables for age, gender and weight, normal blood

pressure is defined as a systolic and diastolic blood pressure that is less than the 90th percentile, whereas elevated blood pressure is a blood pressure that is above the 90th percentile rank for age and sex.[6] The definition of hypertension is reserved for those individuals that have a blood pressure that is abnormal, greater than the 90th percentile for age and sex, on at least three separate examinations over 6–12 months intervals, if not associated at the time of the initial examination with signs and symptoms found with hypertensive cardiovascular disease (myocardial hypertrophy, papilledema, persistent headaches, blurred vision, coma, convulsion etc.). As with adult hypertension, the majority of children with high blood pressure have essential hypertension. We have evaluated 120 consecutive children referred for evaluation of hypertension. In this group of children, 59% had essential and 41% had secondary causes for the hypertension. The types of secondary hypertension in our children were: (i) renal causes in 70%; (ii) cardiac causes in 20%; (iii) endocrine causes in 8%; and (iv) other causes in the remaining 2%. Of the patients with essential hypertension, over 75% of them were overweight.

The management of high normal or high blood pressure without an identifiable cause includes: (i) weight reduction if the child is obese; (ii) exercise; (iii) moderate salt restrictions; (iv) avoiding the use of tobacco; and (v) avoiding cigarette smoking. For patients with severe elevations of blood pressure, pharmacologic therapy may often be required. Pharmacologic therapy is indicated in children with severe hypertension (that is, blood pressures greater than the 95th percentile for age and sex), children with significant hypertension (greater than the 90th percentile) who are unresponsive to non-pharmacological therapy and children with significant hypertension associated with end-organ damage. In the past, diuretics and beta blockers were the initial steps of therapy for the hypertensive child; however, we believe that the first-line therapy of a child with hypertension should be angiotensin I converting enzyme (ACE) inhibitors or calcium channel blockers. Because of side-effects (alterations in glucose, lipid metabolism and depression), diuretics and beta blockers should be used as second-line therapy. The other new agents in the management of hypertension are alpha blockers and the combined alpha beta adrenergic receptor blocker, Labetalol.

Hyperlipidemia

Hyperlipidemia is known to be an important risk factor for the development of adult-onset heart disease. In order to understand abnormalities of lipid metabolism and their treatment, it is important to understand the process by which the body handles cholesterol. The three major sources of cholesterol are intracellular production, dietary fat and recycling of cholesterol through the gastrointestinal pathway. Dietary fat that is digested and absorbed is reprocessed in the liver. The liver then secretes the reprocessed fats either into the intestine, as bile acids, or into the blood stream in combination with triglycerides as VLDL particles. The VLDL particles are converted in the plasma to LDL, which can then be taken up by the cells and reconverted into cholesterol. The LDL particles are guided by apoproteins (lipoproteins surface proteins) to the LDL receptor sites on the cell. The number of LDL receptors and their affinity for apoproteins determines the level of cholesterol in the body. The cell prefers to use exogenous cholesterol rather than to manufacture its own cholesterol. This preferential usage depends on a biochemical feedback system, whereby raising intracellular cholesterol levels reduces cholesterol production by inhibiting the rate limiting enzyme 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA) reductase and by activation of the enzyme acylcoenzyme A transferase (ACAT), which esterifies cholesterol for storage. Increased intracellular cholesterol also reduces cellular LDL cholesterol uptake by blocking formation of LDL receptors and by inhibiting LDL receptor gene expression. Intracellular cholesterol that is not used or stored by the cell is passed out of the cell. Some of the excess cholesterol combines with recycled LDL particles to form HDL particles. These HDL particles eventually are removed from the circulation by the liver. The formation of HDL cholesterol is the major means by which excess cholesterol is removed from the cells. Abnormalities in the method by which the cell handles LDL receptor formation is the cause of one of the most common genetic forms of hyperlipidemia, familial hypercholesterolemia. In this disease there is an alteration in either the number or the function of the LDL receptors leading to a reduced binding of LDL cholesterol to the receptors, a higher serum LDL cholesterol concentration, a higher plasma cholesterol level and atherogenesis.

Most individuals with hyperlipidemia are asymptomatic. The only pertinent physical findings or symptoms associated with hyperlipidemia include: (i) a history of abnormal glucose tolerance or hyperuricemia (seen with all types of hypertriglyceridemia); (ii) a history of xanthoma (seen with familial hypercholesterolemia); and (iii) a history of recurrent unexplained pancreatitis or abdominal pain (seen with exogenous hyperchylomicronemia, familial hypercholesterolemia or combined familial hyperlipidemia). The major method for diagnosing hyperlipidemia is to measure the concentration of the blood lipoproteins. Lipid screening is currently recommended only if a child has a history compatible with hyperlipidemia, consisting of the above described physical findings and symptoms or a family history of premature atherosclerotic disease (defined

as appearance of clinical manifestations of atherosclerosis prior to 50 years of age for men and 60 years in women). Blood evaluation of lipids needs to be interpreted, as with blood pressure, based on population norms.[7] Traditional values greater than the 90th percentile cut-offs have been used for defining abnormal cholesterol and triglyceride levels. For cholesterol, the 95th percentile for all ages and sex is greater than 200 mg/dL and for triglyceride it is greater than 115 mg/dL.

The cornerstone of lipid management, regardless of cause, is diet. Both the saturated fat content and cholesterol content of the diet must be reduced in order to obtain maximum dietary benefit. Saturated fats appear to increase the synthesis of LDL cholesterol and to decrease LDL cholesterol disposal. Polyunsaturated fats decrease VLD triglyceride, cholesterol and apoprotein B synthesis. Mono-unsaturated fats (such as canola oil, olive oil, and peanut oil) are especially beneficial, because they not only reduce LDL cholesterol, but also reduce the LDL to HDL cholesterol ratio. Other ways in which changes in diet can lower cholesterol are to increase the intake of high fiber foods and other water soluble fibers. Marine or omega-3 fatty acids also can help reduce VLDL triglyceride levels, primarily by decreasing VLDL synthesis. Dietary therapy, at best, will only cause a 5–20% decrease in cholesterol. However, it has been our experience that classic dietary therapy, where the index child is placed on a low cholesterol diet without treating other family members, is doomed to failure.[8] Because most lipid abnormalities are inherited, frequently in an autosomal dominant fashion, if a child has an elevated cholesterol one or both parents will also be found to have a high cholesterol. We have recently compared the use of a family focused therapy to standard dietary counselling. We have found that compared to standard therapy, family intensive therapy results in a significantly greater reduction in total cholesterol and LDL cholesterol, not only in the index case but also in other family members.[8]

The goal of therapy should be to reduce total cholesterol below 200 mg/dL and LDL cholesterol below 120 mg/dL, while maintaining HDL cholesterol levels greater than 40 mg/dL. If these goals cannot be reached by non-pharmacological therapy alone, pharmacological agents need to be considered. Because pharmacological agents are not without side-effects, most pediatric lipid specialists do not recommend adding lipid-lowering drugs unless dietary means are unable to reduce total cholesterol below 250 mg/dL and LDL cholesterol below 175 mg/dL. The current lipid-lowering drugs that are used in the pediatric population include the bile acid resins, nicotinic acid, HMG CoA reductase inhibitors (such as lovastatin, pravastatin, and simvastatin) and gemfibrozil.

It is important to remember that, although there is now increasing evidence in the adult, treatment of hyperlipidemia can result in reduction of coronary mortality and even regression of atherosclerotic lesions. Little to no data on the efficacy of long-term treatment of mild to moderate elevated cholesterol to prevent atherosclerosis later in life is available in the pediatric population.

Smoking

Cigarette smoking is the major avoidable cardiovascular risk factor.[9] One of the most disturbing features about smoking is that since 1964 more than 30 000 Americans have stopped cigarette smoking, yet cigarette smoking has not decreased in its prevalence among adolescent populations. In fact, over the past 2–3 years, adolescent cigarette smoking has actually increased. Adolescents represent the largest group of individuals at risk to start cigarette smoking. Smoking is known to increase cardiovascular risk directly by altering blood pressure, increasing total serum cholesterol levels and decreasing HDL cholesterol levels. In addition, maternal smoking is known to affect the fetus by interfering with fetal growth, causing increased perinatal deaths and producing premature delivery. The most effective way of treating smoking is through its prevention. Because the incidence of smoking is highest among adolescents, it is critical to prevent smoking in this age group. Most studies suggest that a school-based prevention program beginning in the 6th grade with booster sessions throughout the remaining 6 years of secondary education can result in a significant reduction in the incidence of adolescents smoking.

Physical activity

A reduced amount of physical activity has been documented to be an important cardiovascular risk factor. The amount of exercise an individual regularly performs inversely correlates with cholesterol and triglyceride levels and with obesity. In a recent study of 200 boys and girls between the ages of 12 and 17, the exercise time on the treadmill indirectly related to their level of resting blood pressure and their body mass index. That is, individuals whose exercise endurance was less than the 5th percentile for their age and sex almost uniformly had mild to moderate elevations in blood pressure and had a body mass index that was greater than 28 kg/m^2 (Figs 2,3). Although it is clear in the adult that physical activity can reduce coronary risk, there is little to no information concerning the long-term effects of childhood exercise programs in reducing the risks for development of cardiovascular disease.

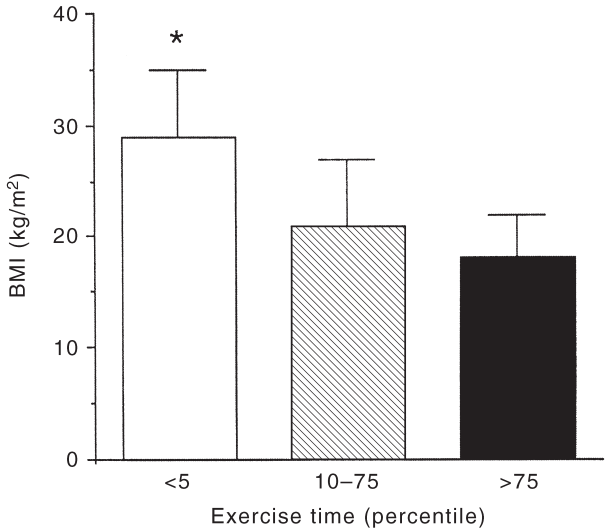

Fig. 2 Relationship between exercise endurance (exercise time) and body mass index (BMI) in 200 children who have undergone a treadmill exercise test. The children whose exercise endurance is less than the fifth percentile have a significantly increased BMI. *P < 0.01 compared with the 10–75 and > 75 percentiles.

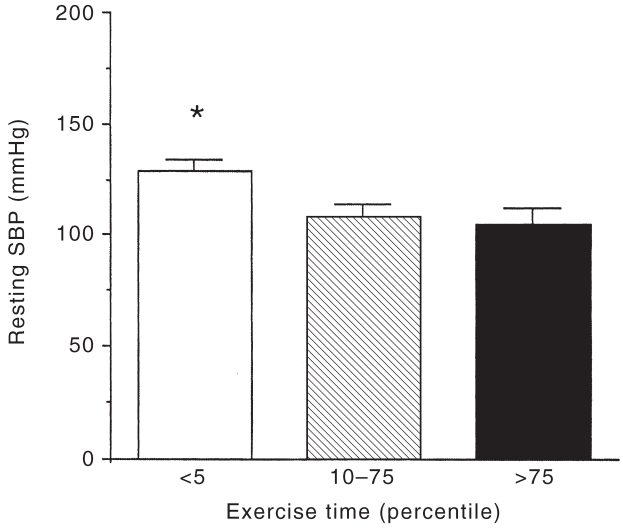

Fig. 3 Relationship between exercise endurance (exercise time) and resting systolic blood pressure (SBP) in 200 children who have undergone a treadmill exercise test. The children whose exercise endurance is less than the fifth percentile have a significantly increased resting SBP. *P < 0.01 compared with the 10–75 and > 75 percentiles.

Table 1 Recommended cardiovascular health schedule

Birth
1. Obtain family history for early coronary artery disease and hyperlipidemia. If positive, introduce risk factors and parental referral.
2. Start growth chart.
3. Obtain parental smoking history and try to refer parents who are smoking for smoking cessation classes.

Age 0–2 years
1. Update family history and growth chart.
2. With introduction of solids, begin teaching regarding a healthy diet that is nutritionally adequate and low in salt and in saturated fats.
3. Recommend healthy snacks as 'finger foods'.

Age 2–6 years
1. Update family history and growth chart. Review growth chart with family. Concept of weight for height should be introduced, trying to identify children who are showing signs of obesity.
2. Change to a low-fat milk.
3. Start blood pressure chart at 3 years of age. Review the concept of lowering salt intake.
4. Encourage parent/child play that develops coordination and may produce a more permanent increase in lifestyle activity.
5. Obtain lipid determination in children with positive family history or with parental cholesterol exceeding 200 mg/dL (obtain parental lipids if necessary and if lipid screening is abnormal initiate nutritional counselling).

Age 6–10 years
1. Update family history, blood pressure and growth charts.
2. Complete cardiovascular health profile with child. Obtain family history, smoking history, blood pressure percentile, weight for height, measure cholesterol if indicated and determine level of cardiovascular fitness.
3. Reinforce a prudent diet that is low in fat and cholesterol. Begin antismoking counselling.
4. Introduce fitness for health, life sport activities for child and family.
5. Discuss role of TV watching and sedentary life style and obesity.

After 10 years of age
1. Update family history, blood pressure and growth charts annually. Review prudent diet, risks of smoking and fitness benefits whenever possible.
2 Consider lipid profile in indicated patients.
3. Fitness review of personal cardiovascular health status.

Prenatal environment

Barker and coworkers have popularized the idea that factors which disturb fetal development and/or growth can profoundly influence postnatal outcome.[10,11] In a study recently published, Barker *et al.* have demonstrated that in 156 men born between 1907 and 1925, the death rate from cardiovascular disease fell progressively with increasing birth weight, head size and ponderal index.[10] In another study, they have demonstrated that death rates from coronary artery disease are three-fold higher if weight was less than 8.2 kg at the age of 1 year, compared with those who weighed more than 12.3 kg at age 1.[11] Barker has suggested that increased cardiovascular risk is more dependent on being born small for gestational age rather than being born premature. The first person to suggest that maternal environment for the fetus may affect the long-term outcome for cardiovascular risk was Freinkel in 1980, who hypothesized the fuel-mediated teratogenesis theory.[12] Barker has suggested that growth during critical periods of early life may permanently affect the structure and physiology of a range of organs, including the pancreas, liver and blood vessels. For example, people who are thin at birth tend to develop the combination of insulin resistance, hypertension and non-insulin dependent diabetes, whereas those who are short in relation to head size tend to develop hypertension. Similarly, others have demonstrated that offspring of diabetic mothers have an increased risk of developing childhood obesity, impaired glucose tolerance and diabetes in adolescence.[13] Thus, many individuals have suggested that normalization of maternal metabolism during pregnancy may be a potent therapeutic and preventive approach to the long-term prevention of premature morbidity and mortality from atherosclerotic heart disease.

Summary

Because coronary artery disease has its origins in childhood, it is critical that pediatricians become involved in the identification and treatment of children at risk for early development of cardiovascular disease. An appropriate cardiovascular health schedule that all pediatricians should be following is outlined in Table 1.

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