Risk Factors for Cardiovascular Disease in Children With Type I Diabetes: Part 1

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Diabetes is a major risk factor for premature morbidity and mortality caused by cardiovascular disease (CVD). Although an increased prevalence of lipid abnormalities in many populations with diabetes has been observed, minimal data exist regarding the distribution, correlates, and determinants of lipid levels of children with diabetes. Early identification of hyperlipidemia and other CVD risk factors is requisite to timely and specific nursing interventions. Part I of this two part series will discuss the lipid profile, the link between cardiovascular disease and diabetes, and physiological risk factors for CVD in children with diabetes.

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Type I diabetes is one of the most common chronic diseases of childhood. Children with diabetes are at increased risk for developing cardiovascular disease (CVD) as adults. The purpose of this article is to present an integrative review of research on cardiovascular risk factors and how they impact children with type I diabetes. Results from selected epidemiologic and clinical studies of adults are incorporated throughout the article because these findings provided both the impetus and rationale for subsequent research with children. The ultimate goal of this article is to inform clinical practice. Toward that goal, implications for assessment and management of CVD risk factors, derived from a synthesis of the empirical evidence, are emphasized as part of the plan of care for children with type I diabetes.

Cardiovascular disease caused by atherosclerosis is a leading cause of morbidity and premature mortality in the United States. During the past 2 decades, population-based research efforts have focused on the emergence of risk for CVD in both black and white pediatric populations. These data describe the distribution and prevalence of traditional physiological risk factors (i.e., the lipid profile, blood pressure, adiposity); (Berenson, 1986; Lauer, Clarke & Beaglehole, 1984; Tamir et al., 1981) confirm the relationship between adverse levels of risk factors and anatomic changes in the aorta and coronary arteries (Newman et al., 1986; PDAY Research Group, 1990); document the fact that risk factors track from childhood to adulthood (Lauer, Lee & Clarke, 1988; Webber, Srinivasan, Wattigney & Berenson, 1991) and provide evidence of age-related increases in the clustering of risk factors (Aristimuno, Foster, Voors, Srinivasan, & Berenson, 1984). Epidemiologic and clinical studies indicate that plasma levels of lipids and lipoproteins, systolic and diastolic blood pressure and obesity (adiposity) aggregate in families (Nambodiril et al., 1989; Friedlander et al., 1987) and are influenced over time by environmental (lifestyle) factors, including patterns of nutrient intake, physical activity and tobacco use. Collectively, the results of these studies provide convincing evidence that primary prevention of CVD must begin early in childhood.

THE LIPID PROFILE AND CVD RISK

Components of the Lipid Profile

Cholesterol and triglycerides are water insoluble lipids transported in the blood in macromolecular complexes, termed lipoproteins. The protein com...
ponents are called apolipoproteins. Three main classes of lipoproteins can be measured in the blood: very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). LDL and HDL are mainly responsible for transporting cholesterol; VLDL is the major carrier of triglyceride. In nonfasting individuals, chylomicrons carry triglycerides of dietary origin (Cortner, Coates & Tershakovec, 1992). Triglycerides are the storage or carrier form of fatty acids in tissue and plasma. Cholesterol and triglycerides are solubilized by phospholipid and apolipoproteins in the different lipoproteins. Genetic abnormalities in any of the lipoprotein metabolic pathways may result in an adverse lipid profile. Excluding these monogenic disorders of lipid metabolism, most dyslipidemias are attributable to an interaction of genetic and environmental factors. The major environmental determinant of lipid levels is dietary intake.

Considerable research attention has focused on the structure and functions of lipoprotein fractions and their respective apolipoproteins. Clinical decision-making, however, emphasizes total and LDL cholesterol, triglycerides (atherogenic lipids) and HDL cholesterol (the protective lipoprotein involved in reverse cholesterol transport).

Lipids and CVD Risk

Epidemiologic, clinical, and metabolic studies, primarily of adult populations, have provided a great deal of data that is relevant to these components of the lipid profile and CVD risk. Results from the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT) (1984) and the Helsinki Heart Study (Frick et al., 1987) provided the major rationale for the “cholesterol hypothesis.” Simply stated, the higher the plasma level of total cholesterol, the greater the incidence of CVD; when the plasma cholesterol is reduced, the incidence of CVD decreases.

Although no long-term longitudinal studies of pediatric populations have been conducted, substantial evidence points to the importance of monitoring lipid levels and identifying children at risk for CVD early in life. Results from the Bogalusa Heart Study (Newman et al., 1986) combined with recent results from the PDAY study (PDAY Research Group, 1990) link antemortem levels of atherogenic lipids with lesions in the aorta and coronary arteries. In both studies, HDL was inversely associated with the extent of atherosclerotic involvement of these vessels. These data, combined with information on tracking, clustering, and interrelation-
TC, LDL, and HDL cholesterol levels are 70, 30, and 35 mg/dL respectively at birth. Because of the interaction of both genetic and environmental factors, these lipids approach young adult levels by age 2. Most children maintain their relative percentile rank (track) from 2 years of age until the onset of sexual maturation. During this time, dynamic sex, and race-related changes occur in the total lipid profile in nondiabetic children. Similar data generated from a cohort of children with type I diabetes are not available.

For clinical purposes, the most important shift observed during sexual maturation is that the ratio of total cholesterol to HDL increases progressively in white men but not in women or black men. The mechanisms for these race and sex specific changes are not entirely clear. Further, whereas HDL is strongly (inversely) related to sexual maturation in white men, the relationship is more pronounced in individuals with truncal obesity and hyperinsulinemia (Freedman, Srinivasan, Webber, Burke, & Berenson, 1987).

Recent attention in children and adolescents has focused on Lp(a) (Freedman et al., 1987; Utermann, 1989, Srinivasan, Dahlen, Jarpa, Webber & Berenson, 1991). This complex lipoprotein consists of lipid, carbohydrate, and two large apoproteins, B and a (Utermann, 1989). Although levels are higher in blacks than whites in the United States, a corresponding black excess in coronary atherosclerosis has not been observed. A recent study of nondiabetic children used parental myocardial infarction as a surrogate measure of future risk (Srinivasan et al., 1991). Children of white parents who had myocardial infarction had significantly increased levels of Lp(a) compared with those without disease. Among the white children, the prevalence of parental myocardial infarction was higher in those with Lp(a) levels above 25 mg/dL. This relationship was not observed in black children (Srinivasan et al., 1991). More research is needed before Lp(a) can be used in decisions regarding clinical management (CVD risk reduction) in children.

<table>
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<th>50</th>
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*All values have been converted from plasma to serum. Plasma value x 1.03 = serum value.
From the LRC Prevalence Study (North America).
**Table 4. Normal Plasma Lipoprotein Concentrations in the First Two Decades of Life**

<table>
<thead>
<tr>
<th>Age (y) and Sex</th>
<th>HDL-C (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>VLDL-C (mg/dL)</th>
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<td>Mean</td>
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<tr>
<td>15-19 F</td>
<td>297</td>
<td>35</td>
<td>52</td>
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</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol.


**LINK BETWEEN IDDM AND CVD**

The primary cause of morbidity and mortality in individuals with type I insulin-dependent diabetes mellitus (IDDM) is premature and extensive atherosclerotic-cardiovascular (CVD) disease (Betteridge, 1989). A two- to four-fold increase in the prevalence of CVD has been observed in this diabetic population.

Recent attention has focused on risk factors for CVD in children with IDDM. Currently available evidence suggests that lipid and lipoprotein abnormalities are more prevalent in children with IDDM compared with their nondiabetic counterparts. Although most of the available data suggest that children with IDDM have elevated levels of the atherogenic lipids and lipoproteins (including total cholesterol, LDL-cholesterol and total triglycerides) (Betteridge, 1989; Iwai et al., 1990; Ruderman & Haudenschild, 1984; Strobl et al., 1985), levels of HDL cholesterol, the protective lipoprotein, and the influence of metabolic control (as measured by \( \text{HbA}_{1c} \)) on both the atherogenic and protective components of the lipid profile remains controversial (Betteridge, 1989; Wilson, Fesmire, Endres & Blackett, 1985). In addition, minimal data exist regarding the interrelationship of known risk factors for CVD (i.e., lipids and lipoproteins, systolic, diastolic, and mean arterial blood pressure, relative weight and patterns of physical activity and smoking behavior) in children with IDDM.

Collectively these data point to the importance of comprehensive CVD risk factor assessment of children with IDDM. These data are requisite to the long-term objective of planning effective, timely nursing interventions focused on both primary and secondary prevention of CVD in this diabetic population.

Based on data from several large randomized intervention trials with non-diabetic subjects showing that the risk for CVD can be reduced by reducing plasma lipid and lipoprotein levels, the American Diabetes Association (1989) released the following consensus statement:

No randomized clinical trial has tested the hypothesis that lowering lipid levels will reduce the risk of CVD in people with diabetes. However, in view of the lack of any evidence showing the differences between nondiabetic and diabetic subjects in the role of plasma lipids as risk factors, it seems reasonable to assume that beneficial effects on cardiovascular events would result from lowering lipids (p. 575).

The lipid profile is only one small piece of the puzzle when attempting to prevent CVD in children. There are multiple risk factors that must be thoroughly assessed before attempting interventions to decrease the incidence of CVD in persons with IDDM. Diabetes control is an essential factor to be assessed. In addition, data on the physiologic CVD risk factors (family history, obesity and blood pressure) and lifestyle risk factors (diet, smoking, activity) will be discussed in terms of children in general and children with diabetes.

**PHYSIOLOGICAL RISK FACTORS**

**Diabetes Control**

The effect of diabetes control on lipid and lipoprotein levels is controversial. There are several mechanisms responsible for the alteration of lipoprotein levels in IDDM. Lipoprotein lipase is a lipoprotein that enhances the clearance of LDL and VLDL from the blood through accelerated formation of HDL. Insulin is another factor that regulates the way the body uses lipids and lipoproteins. In the insulin deficient state of IDDM, lipoprotein lipase activity is decreased and VLDL is increased, although a causal relationship between insulin secretion of VLDL has not been proven (Ginsburg,
CVD RISK FACTORS IN CHILDREN WITH DIABETES

In addition, with high glucose levels, sugar tends to bind to proteins in the blood. This “glycosylation” can accelerate the destruction of HDL and impair its ability to clear cholesterol from blood vessel walls. Glycosylation has the opposite effect on LDL and VLDL. Their elimination from the blood is prevented. Because many of the abnormalities of lipoproteins are believed to result from glycosylation, it seems logical that improvement of diabetes control would be beneficial in correcting the atherogenic profile. However, studies are inconclusive as to whether improved diabetes control improves levels of lipids and lipoproteins, which lipid and lipoprotein levels are improved, and by what degree. Studies have shown that intensive insulin therapy results in normalization of lipid and lipoprotein levels (Lopes-Virella, Wohltman, Mayfield, Loadholt & Colwell, 1983), that improved diabetes control does not correlate with cholesterol levels in black children with diabetes and correlates weakly with white children (Levitsky, Scanu & Gould, 1991) and that glycemic control did not effect lipids or lipoproteins (Cruckshanks, Orchard, & Becker, 1985; Haffner, Tuttle & Rainwater, 1991). The reasons for this controversial data may be that the designs and methods of the studies were different or that HbA1c is an inadequate measure of diabetes control, and therefore it is difficult to obtain clear data related to metabolic control when using an imprecise measure. It is also possible that reasons for abnormal lipid profiles in persons with diabetes may be additional environmental or genetic factors and not merely diabetes control (Levitsky et al., 1991). Although the data regarding the effect of diabetes control on lipid levels remain controversial, good diabetes control has been shown to decrease the risk of other diabetes complications (DCCT, 1995) and continues to be the goal of diabetes management.

Family History

In adult populations, heredity is an important factor in predicting atherosclerotic disease. Risk factors including hypercholesterolemia, hypertension, and diabetes mellitus are influenced by one’s genetic predisposition. Consequently, obtaining an accurate family medical history is essential for nurses evaluating a child’s risk of developing atherosclerotic disease. Although the NCEP recommends selective screening of children based on family history of CVD or hyperlipidemia, studies have shown that this method may fail to identify 40% to 60% of children with elevated TC (Garcia & Moodie, 1989). Recent studies point to the challenges in implementing this criterion in clinical practice (Dennison, Jenkins & Pearson, 1994). The NCEP selection process would fail to identify children with adverse lipid profiles who are from single-parent families, who have incomplete family histories, and whose parents have not had their cholesterol levels measured. Nevertheless, every attempt should be made to ascertain a comprehensive, multigenerational, reliable family history in both diabetic and nondiabetic children.

Blood lipid levels should be examined in children with a family history of cardiovascular disease or hyperlipidemia as part of the total risk profile. The risk factor analysis should include evaluation for hypertension, obesity, physical inactivity, and tobacco use (Hayman & Ryan, 1994).

No studies were found on the relationship between family history of cardiovascular disease and children with IDDM. However, a few studies exist on the relationship between family history and adult onset diabetes. A correlation has been found between hypertension and lipid abnormalities in those with adult onset diabetes (Colwell et al., 1990).

Caucasian children between the ages of 11 and 17 who have a parental history of myocardial infarction or diabetes were at least twice as likely to have high levels of serum total cholesterol and LDL than other children (Dennison et al., 1989). In this study, no correlation was noted in total and LDL cholesterol with black children. However, low HDL levels were observed in children with a positive parental history of myocardial infarction, hypertension, or diabetes.

A family history of cardiovascular disease is associated with, but not totally predictive of, high levels of cholesterol in childhood. Because coronary heart disease and hypertension begin in childhood, children in this high risk population should be screened and evaluated for hypercholesterolemia and other CVD risk factors.

Hypertension

The roots of essential hypertension seem to extend into childhood, although the prevalence of clinical hypertension is of a lesser magnitude in children (Horan et al., 1987). Studies suggest that children with hypertension have an increased rate of atherosclerotic plaque formation (Newman et al., 1986). Hypertension and levels of LDL cholesterol may be the most important factors in the early development of atherosclerotic lesions (Newman et al., 1986; PDAY Research Group, 1990). Adult
hypertension and obesity seem to correlate with childhood hypertension and obesity (Berenson, 1987). Hypertension in a first degree relative may be a risk factor for children (Nora, 1980).

Children with type I diabetes have an increased incidence of hypertension which increases the risk and progression of nephropathy and atherosclerosis (Newkumet, Goble, Young, Kaplowitz & Schieken, 1994). Blood pressure in children with type I diabetes may be normal before the onset of microalbuminuria. A rise in the diastolic blood pressure may accompany the development or progression of microalbuminuria in children with IDDM (Raal et al., 1992). Adolescent patients with diabetes seem to have a higher diastolic blood pressure at rest and a more marked blood pressure increase during exercise (Newkumet et al., 1994; Nordgren, Freuschuss & Persson, 1994). Diabetes control may correlate with the resting diastolic pressure and diabetes duration may correlate with the exercise diastolic blood pressure (Newkumet et al., 1994). Blood pressure reportedly increases during the pubertal growth spurt in diabetic and nondiabetic children. In one study, diabetic women had significantly higher diastolic blood pressures during this growth spurt than healthy control women (Mortensen, Hougaard, Ibsen & Parving, 1994).

Blood pressure measurements of children with IDDM may be influenced by age, sex, height, weight, ponderal excess, insulin dose, and some metabolic parameters such as HbA1c and creatinine (Virdis et al., 1992).

Hypertension causes macrovascular disease in individuals with diabetes mellitus. No reported clinical trial has tested the hypothesis that lowering blood pressure will reduce the risk of cardiovascular disease in diabetic patients. However, it is prudent to control hypertension in children with IDDM as well as assess their family history to minimize the risk of atherosclerosis in the future. Children with blood pressures greater than the 95th percentile on three separate occasions over a 1 year interval should be referred for further evaluation and possible treatment (Horan et al., 1987).

**Obesity**

Obesity in childhood and adolescence is a common health problem that has dramatically increased in the United States since the 1960s. National health studies estimate that 25% of adolescents are obese, which increases their risk of becoming obese adults (NHANES III, 1994). In addition to genetic and familial factors, overfeeding, bottle feeding, and early introduction of solid foods have been suggested as causes of obesity in children (Dubois, Hill & Beaton, 1979; Lauer, Connor, Leaverton, Reiter & Clarke, 1975).

Obesity is known to effect lipoprotein profiles adversely in adults and children. Lipoprotein profiles in children show a positive relationship between obesity and total cholesterol, VLDL and LDL-cholesterol whereas HDL cholesterol is inversely related to obesity (Freedman et al., 1987). Results from a recent longitudinal study of identical co-twins suggest that environmental influences on obesity affect the lipid profile adversely in the school-age years, adolescence, and in the transition between these two developmental phases (Hayman, Meininger, Coates & Gallagher, 1995). Obese children also tend to have higher blood pressure measurements (Srinivasan, Bao & Berenson, 1993).

Obese adolescents and young adults, especially those with abdominal fat preponderance (increased waist to hip ratio) carry a physiologic profile that places them at a greater risk of cardiovascular disease. Upper body/abdominal obesity is highly associated with hypertension, diabetes, and a low HDL. Lower body or femoral gluteal obesity has less impact on cardiovascular risk factors (Folsom et al., 1989). Obesity has a strong association with hypertension, hyperlipidemia and diabetes mellitus. Obesity may potentially be the most important modifiable risk factor for cardiovascular disease. Evidence strongly suggests that insulin plays a crucial role in pathophysiologic mechanisms linking upper body obesity, hypertension, and hypertriglyceridemia (Kaplan, 1989). Increased insulin and/or systolic blood pressure readings were associated with increased adiposity more frequently among individuals with elevated VLDL and LDL-cholesterol (Srinivasan et al., 1993). Adolescent women with IDDM show a tendency toward excess weight (Souissi et al., 1993). Obese children with IDDM are at a greater risk for a number of health problems including insulin resistance, and hypertension (Becue et al., 1988).

Obesity is much more common in adults who were overweight as children. However, several studies have shown that weight reduction was accompanied by increased HDL cholesterol and decrease triglycerides in obese children (Nuuinen & Knip, 1992; Bellu et al., 1993). Consequently, preventing obesity in children may decrease the risk of atherosclerosis and macrovascular disease in the diabetic and nondiabetic adult population. No randomized trials have been conducted to
determine the effects of weight reduction or increased physical activity on the incidence of macrovascular disease (Colwell et al., 1990).

Controversy exists regarding restriction of dietary fats in children. Low cholesterol and fat intake may interfere with normal growth and development and hormone production (Newman, Browner & Hulley, 1990). Adjustment of the child’s total caloric intake with proteins, complex carbohydrates, essential fatty acids, vitamins, and minerals is essential in preventing deficiencies when decreasing the total fat intake in the diet.

Children and their families need to receive consistent and ongoing education regarding the importance of nutrition in the management of hyperlipidemia. Involvement of the child in food choices, meal planning, and preparation encourages compliance in the gradual development of improved eating habits. Expanded nutritional education in the school systems and participation of the food industry in healthier eating also play major leadership roles in the management of hyperlipidemia in children.

CONCLUSIONS

When attempting to decrease CVD risk factors in children with diabetes, it is essential to optimize diabetes control. Children with a family history of cardiovascular disease are most at risk for developing CVD. Identification of children who are hypertensive or obese and referring them for intervention may also decrease CVD in children and adults with diabetes. Part II of this series will address lifestyle CVD risk factors and appropriate interventions.

REFERENCES


