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### **Cardiovascular Disease Risk Factors Part VII: Combined Factors which Begin in Childhood: Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children**

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The study of cardiovascular risk factors is almost always discussed in relationship to adults and particularly to those who are in middle age or beyond. And, while it is possible to examine the contribution of one factor or another to cardiovascular disease risk, the reality is that people rarely have one factor without having other risk factors. In 2003, the American Heart Association issued a “Scientific Statement” on obesity, insulin resistance, diabetes and cardiovascular risk in children. The information in this discussion is drawn from that statement.

Atherosclerotic cardiovascular disease is the number one killer in the adult population of Western societies, but the disease processes and risk factors associated with its development begin during childhood. Insulin resistance refers to the process whereby your body does not respond to insulin properly. Among many others, there are two principle actions of insulin:

1. To tell the liver to stop making sugar. Often a patient will say, but how can my sugar be elevated, I haven't eaten anything. It is because the liver is making sugar out of fat, protein and carbohydrates in a process called, gluconeogenesis. (“**Gluc-**”, sugar; “**-neo**”, new; and “**-genesis**”, “to make”)
2. To tell the muscles and other parts of the body to clear sugar from the blood by taking it into the cells for energy.

When the liver ceases to respond to the signal from insulin to stop making sugar and when the muscles cease to respond to insulin by absorbing sugar, a person is said to be “insulin resistant.”

Obesity plays a central role in the insulin resistance syndrome, which includes:

- elevated insulin levels,
- hypertension,
- abnormal cholesterol
- abnormal triglycerides,
- type 2 diabetes mellitus, and
- an increased risk of atherosclerotic cardiovascular disease.

The incidence of type 2 diabetes reported in children has increased alarmingly.

Resistance of the body to the actions of insulin results in increased production of this hormone by the pancreas which results in elevated insulin levels in the blood (hyperinsulinemia).. Obesity beginning in childhood often precedes the hyperinsulinemic state. Other components of the insulin resistance syndrome are also present in children and adolescents. An association between obesity and insulin resistance has been reported in the young, as has the link between insulin resistance, hypertension, and abnormal lipid profile.

There is increasing evidence that being overweight during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia (abnormal cholesterol and/or triglycerides), and elevated blood pressure in young adulthood. Weight loss by obese youngsters results in a decrease in insulin concentration and improvement in insulin sensitivity. Moreover, it has been determined that an increased size of the heart, called “left ventricular mass,” which is an independent risk factor for cardiovascular disease in adults, is present in childhood.

The specifics of the transition from risk factors in childhood to diabetes and cardiovascular disease are not clear, but evidence points to their association with disease in adults. On the basis of current knowledge and from studies in adults, it is reasonable to suggest that lifestyle modification and weight control in childhood could reduce the risk of developing the insulin resistance syndrome, type 2 diabetes mellitus, and cardiovascular disease.

Obesity increases the risk of cardiovascular disease in adults and has been strongly associated with insulin resistance in persons with normal blood sugar and in individuals with type 2 diabetes. The association of obesity with the insulin resistance syndrome and cardiovascular risk is not only related to the degree of obesity but also seems to be critically dependent on body fat distribution. Thus, individuals with greater degrees of central obesity – fat around the abdomen -- develop this syndrome more frequently than do those with a peripheral body fat distribution.

Studies in obese adults have shown sustained improvement in cardiovascular risk in association with a 10% to 15% weight loss maintained over time. One other report, however, suggested that a weight loss of 16% resulted in a differential risk factor response, including a dramatic reduction in the incidence of type 2 diabetes but not in the 8-year incidence of hypertension.

### **Hypertension and the Insulin Resistance Syndrome**

There is a relationship between insulin metabolism/resistance and essential hypertension.

- Insulin increases salt retention by the kidney.
- Insulin resistance is also associated with increased activity of the part of the nervous system which makes us anxious, jittery and increases the blood pressure.

- Insulin also stimulates muscle growth in the walls of the arteries which contributes to elevation in the blood pressure.
- Insulin levels have been found to be significantly higher in adult patients with essential hypertension and borderline hypertension than in adults with normal blood pressure.

These differences have been reported to be independent of age, sex, and ethnic group

Although the prevalence of essential hypertension in children is low, the beginnings of the disease are present long before clinically accepted levels of hypertension are recognized. Substantial evidence from genetic and epidemiological studies confirms that blood pressure tracks over time and that the roots of essential hypertension extend into the first and second decades of life.

### **Lipid Abnormalities (Cholesterol and Triglycerides) and the Insulin Resistance Syndrome**

Insulin resistance plays a major role in abnormal cholesterol in individuals with normal glucose tolerance, as well as in those with impaired glucose tolerance and type 2 diabetes. Lipid abnormalities have also been reported in obese adults, who have elevated triglycerides and LDL cholesterol and low levels of HDL cholesterol. Similar lipid profiles have been reported in obese and nonobese adults with type 2 diabetes, in obese normoglycemic adults, and in nonobese adults with impaired glucose tolerance.

The association between obesity and dyslipidemia observed in adults also has been documented in children and adolescents. In the Lipid Research Clinics Population Studies Data Book, obese adolescents had an abnormal "atherogenic" – a lipid profile which promotes cardiovascular disease -- lipid profile consisting of:

- elevated LDL cholesterol and
- elevated triglycerides and
- low HDL cholesterol.

Investigators from the Bogalusa Heart Study reported that overweight schoolchildren, in comparison with their lean counterparts, were 2.4 to 7.1 times more likely to have elevated total cholesterol, LDL cholesterol, and triglycerides, and 12.6 times more likely to have hyperinsulinemia.

### **Assessment by the American Heart Association**

Although the end points for cardiovascular risk are not seen in childhood, the components of the insulin resistance syndrome:

- obesity,
- hypertension,
- dyslipidemia, and

- hyperinsulinemia

track from childhood into adulthood, which supports the conclusion that the precursors of cardiovascular disease are present early in life. Because insulin resistance often is associated with type 2 diabetes, the first step in assessment is to identify children who would benefit from intervention. Testing has been recommended for children at significant risk for the presence or development of type 2 diabetes. These are children who in general are:

1. overweight;
2. have a family history of type 2 diabetes;
3. have a predisposition based on race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander); and
4. have signs of insulin resistance or conditions associated with insulin resistance (eg, acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome).

The diagnosis of diabetes can be made by using either the fasting glucose or the 2-hour value on an oral glucose tolerance test.

### **Type 2 Diabetes Mellitus in Children and Adolescents**

Type 2 diabetes mellitus has long been considered a disease of adults, in whom it is the most prevalent form of diabetes (90%) and is associated with increased risk of cardiovascular disease morbidity and mortality. During the past 10 years, however, an increasing frequency in the occurrence of type 2 diabetes mellitus has been reported in adolescents.

There are now reports of type 2 diabetes in Native American, Hispanic, African-American, South Asian, and white youth. This increase in frequency of type 2 diabetes seems to parallel the increase in prevalence and severity of obesity in children and adolescents.

The pathophysiology of the development of type 2 diabetes mellitus is complex. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time. It seems that at some point a loss of control of blood glucose begins to emerge, resulting in dietary glucose intolerance. This ultimately results in type 2 diabetes.

It is known that obese individuals may develop different degrees of insulin resistance, and not all individuals develop glucose intolerance. The factors that make some individuals more likely to progress to type 2 diabetes mellitus are not well understood at the present time. A strong family predisposition is known to exist; therefore, parental history is important in risk assessment.

Type 2 diabetes mellitus is emerging as a major public health problem for adolescents. The early onset of type 2 diabetes suggests that these patients will be at risk for the development of cardiovascular disease at a young age. If the secular trend seen with increasing prevalence and severity of obesity in childhood and adolescence continues, it is likely that the problem of type 2 diabetes also will increase in the pediatric age group.

### **Significance**

As more research evidence is accumulated, it is also important to deal with the problems of insulin resistance and type 2 diabetes in children and adolescents from a clinical standpoint.

- The first approach should focus on prevention of obesity in childhood.
- More attention should be paid to increasing physical activity and decreasing calorie consumption in this age group.
- Once obesity is established in a child or adolescent, vigorous clinical efforts should be directed at treating it.
- At present, this involves therapy directed at behavior change, but in the future it may include pharmacological and surgical approaches in the appropriate patients.
- Clinicians should watch vigilantly for the subtle signs that indicate the development of insulin resistance, glucose intolerance, and type 2 diabetes.
- Early recognition of these problems can lead to better treatment.

The best approach to prevention of future cardiovascular disease in these young patients is early recognition and aggressive therapy. Without this, it is likely that this patient population is destined to develop cardiovascular complications and require substantial resources for future management.

Remember, it is your life and it is your health.