# Metabolic Syndrome Has Lifelong Consequences

## *Children with the disorder are significantly more likely to develop CVD and diabetes before age 50.*

BY BRUCE JANCIN
*Denver Bureau*

DALLAS — Children who meet criteria for metabolic syndrome are nearly ninefold more likely to develop cardiovascular disease before age 50, John A. Morrison, Ph.D., said at the annual scientific sessions of the American Heart Association.

They are also greater than threefold more likely to develop diabetes mellitus prior to age 50 than individuals who did not meet criteria for metabolic syndrome as children, added Dr. Morrison, professor of pediatrics at the University of Cincinnati and a researcher at Cincinnati Children's Hospital Medical Center.

Although metabolic syndrome in adults is known to at least double the risk of cardiovascular disease and diabetes, little is known about the adult consequences of pediatric metabolic syndrome.

This major hole in the knowledge base provided the impetus for Dr. Morrison to gather longitudinal data using the Princeton follow-up study, a 30-year follow-up of participants in the National Heart, Lung, and Blood Institute–sponsored Lipid Research Clinics Study.

He presented 30-year follow-up data on 917 subjects from 573 families who were 5-19 years old when they participated in the Lipid Research Clinics in the mid-1970s. As children, only 12 of them met National Cholesterol Education Program Adult Treatment Panel-III criteria for metabolic syndrome.

However, those criteria work poorly in children, who seldom exhibit the full adult expression of abnormalities in waist circumference, blood pressure, and lipids. For that reason, pediatric researchers often use the more appropriate age-adjusted Cook criteria; by this standard, 41 subjects had pediatric metabolic syndrome.

At 30-year follow-up, 21 participants had developed known cardiovascular disease and 52 had diabetes. The risk of cardiovascular disease in young adulthood was 8.5-fold greater in subjects who had metabolic syndrome as a youth than in those who didn't. The risk of diabetes was increased 3.2-fold—and among those participants who had pediatric metabolic syndrome as well as a parental history of diabetes, the risk climbed to 5.3-fold.

"Evaluating pediatric metabolic syndrome in childhood could identify patients at increased risk of cardiovascular disease and diabetes, making targeted interventions possible," Dr. Morrison concluded.

In another study, he found that preteen central adiposity emerged as the key precursor to subsequent development of metabolic syndrome during adolescence.

The study involved 1,175 girls, about half of whom were black and the rest white, who participated in the NHLBI-sponsored Growth and Health Study.

**Metabolic syndrome did not develop if waist circumference was no longer increased at age 18-19.**

**DR. MORRISON**

Those who had central adiposity as evidenced by an elevated waist circumference at age 11 years and who still had an increased waist circumference at age 18-19 had a 12.1% prevalence of metabolic syndrome at the latter age, a rate roughly sixfold greater than typical in young adulthood. In contrast, not a single participant who had an increased waist circumference at age 11 but not at age 18-19 developed metabolic syndrome (Pediatrics 2005;116:1178-82).

"The take-home message here is identify who's at risk and act on it," Dr. Morrison said.

In a separate presentation, Aaron S. Kelly, Ph.D., said several biochemical markers of cardiovascular risk show promise for identifying at-risk children even before they develop metabolic syndrome. These fall under the headings of adipocytokines, markers of systemic oxidative stress, and inflammatory markers.

He reported on 34 children. One-third were of normal weight and healthy. Another third were overweight but otherwise healthy. The rest were overweight and met at least three of the Cook modified criteria for metabolic syndrome.

Levels of the adipocytokine leptin—known to be related to insulin resistance—increased stepwise from the normal to the overweight to the metabolic syndrome subjects. So did levels of C-reactive protein and interleukin-6 as well as 8-isoprostane, a marker of systemic oxidative stress thought to be involved in the early stages of the atherosclerotic process.

In contrast, levels of adiponectin—which is associated with insulin sensitivity—were highest in the normal children and lowest in the overweight kids with metabolic syndrome, according to Dr. Kelly of the St. Paul (Minn.) Heart Clinic and the University of Minnesota, Minneapolis. ■

# Hybrid Type 1 & 2 Diabetes Emerging in Pediatric Patients

BY ROBERT FINN
*San Francisco Bureau*

SAN FRANCISCO — The rise in the diagnosis of type 2 diabetes among children is calling attention to certain differences in disease characteristics between children and adults, Dr. Francine Ratner Kaufman reported at the Third World Congress on Insulin Resistance Syndrome.

In fact, some children seem to have a form of diabetes that's a hybrid between type 1 and type 2, said Dr. Kaufman of the University of Southern California, Los Angeles.

The typical child with type 1 diabetes will have a positive antibody test and low fasting C-peptide values. The situation is reversed in the typical child with type 2–negative antibodies and high fasting C-peptide. But some children have a positive antibody test along with high fasting C-peptide levels. It's those children who have the hybrid form.

Before the advent of insulin pumps and refined methods of glucose control, children with type 1 diabetes were typically underweight. Better control means that more of these children are of normal weight, and about 20% may even be obese. That means that obesity alone cannot be used to distinguish type 1 from type 2 disease, even though at least 85% of children with type 2 diabetes are overweight or obese.

Type 2 diabetes seems to take a somewhat different course in children than in adults. In adults the disease is often indolent, preceded by a long asymptomatic period. Screening reveals many adults who have undiagnosed type 2 diabetes.

In contrast, at least five studies of overweight children, who would be expected to be at high risk of type 2 diabetes, have found very low rates—6% or less—of undiagnosed type 2 diabetes. This may indicate that children progress more rapidly than do adults through progressive B-cell failure to type 2 diabetes, narrowing the window when prevention and early treatment may have benefit.

A recent study found few parameters that can help distinguish children who have impaired glucose tolerance and will go on to develop type 2 diabetes from those who will revert to normal glucose tolerance (Diabetes Care 2005;28:902-9). The two groups were similar in fasting and postprandial glucose, insulin, and C-peptide levels, for example. The best predictor turned out to be rapid increases in weight and body mass index.

Other studies have shown that the presence or absence of diabetic ketoacidosis fail to distinguish type 1 from type 2 diabetes in children.

These similarities between the two types, along with the presence of a hybrid form, argue for the "accelerator hypothesis," which views type 1 and type 2 diabetes as the same disorder of insulin resistance, set against different genetic backgrounds, Dr. Kaufman said. ■

# *Early Evidence of Atherosclerosis Seen In Adolescents With Type 1 Diabetes*

BY MIRIAM E. TUCKER
*Senior Writer*

ATLANTA — Adolescents with type 1 diabetes may have early evidence of atherosclerosis, Dr. Maria V. Karantza reported at the annual scientific sessions of the American Diabetes Association.

The increased risk appears to be related to conventional cardiovascular disease risk factors such as dyslipidemia, hemoglobin $A_{1c}$, and tobacco exposure rather than nontraditional risk factors related to endothelial function, suggesting that strategies targeting modifiable risk factors could benefit these patients, said Dr. Karantza of the University of California, Los Angeles.

Carotid artery intima-medial thickening (IMT), considered an indirect measure of cardiovascular disease (CVD), was evaluated by B-mode ultrasound in 90 adolescents with type 1 diabetes (mean age 16.6 years) with 16 of their healthy siblings (mean age 16.7 years). Overall, IMT was significantly greater among the diabetic group than the controls (0.564 mm vs. 0.54 mm), she reported.

There were no differences between the two groups in body mass index, blood pressure, gender, or family history of diabetes/CVD. None of the controls smoked, while six of the diabetics (all male) were smokers; the difference was not statistically significant.

The two groups also did not differ by conventional risk factors such as cholesterol, triglycerides, or microalbumin/creatinine ratio, or by nontraditional risk factors such as fibrinogen, von Willebrand factor antigen, plasminogen activator inhibitor-1, or IL-6.

When broken down by gender, significant differences in IMT between diabetic and control subjects were only seen among the males (0.582 mm vs. 0.524 mm), and not the females (0.548 mm vs. 0.556 mm).

Among the males with diabetes, IMT was significantly correlated with $HbA_{1c}$ and tobacco exposure, as well as with total cholesterol and apolipoprotein B. Among the female diabetics, IMT was correlated positively with a family history of CVD and negatively correlated with HDL cholesterol.

The findings suggest that conventional CVD risk factors result in increased IMT, and probably cause the initial endothelial dysfunction in these young people. The subsequent loss of normal endothelial homeostatic properties would eventually lead to a "proinflammatory, proadhesive, and procoagulant endothelial surface that is not yet present in our cohort. Early treatment of modifiable risk factors could avert the chronic inflammatory process which, if unabated, will result in the advanced chronic plaque formation," she said. ■