

THE AMERICAN HEART ASSOCIATION (AHA) SCIENTIFIC SESSIONS 2005

The meeting was held from November 13 to 16, 2005, in Dallas.

Metabolic Syndrome in Kids Predicts Adult Diabetes, CVD

Children with pediatric metabolic syndrome are more likely to have cardiovascular disease (CVD) or diabetes as adults than children without the condition. John A. Morrison, MD, from the Cincinnati Children's Hospital Medical Center, and colleagues said that evaluating pediatric metabolic syndrome in childhood could identify patients at increased risk of CVD and diabetes, making targeted interventions possible.

To assess the association of pediatric metabolic syndrome with adult diabetes and CVD, the investigators used 30-year follow-up data on 917 former students from 573 families who participated in the National Heart, Lung, and Blood Institute Lipid Research Clinics Princeton School Study (LRC, 1973 to 1976) and the Princeton Follow-up Study (PFS 2000 to 2004). Both adult ATP III cutoffs and age-adjusted cutoffs were used to define pediatric metabolic syndrome.

Adult CVD status at PFS was obtained by self-report, and included myocardial infarction (MI), coronary artery bypass graft, angioplasty or stroke. Diabetes was based on self-report or fasting glucose ≥ 126 mg/dL. At LRC there were 12 cases of pediatric metabolic syndrome using ATP III criteria and 41 using the age-adjusted cutoffs. On PFS follow-up there were 21 cases of CVD and 52 cases of diabetes.

Pediatric metabolic syndrome is a strong, significant predictor of adult CVD (OR 11.2; $P < .0001$) and adult diabetes (OR 3.7; $P = .009$).

ACE, ARBs Reduce the Risk for Type 2 Diabetes

Inhibition of the renin-angiotensin system (RAS) may prevent the development of type 2 diabetes, although the exact mechanism is unclear. Richard Andraws, MD, and colleagues said that several large randomized trials have reported a reduction in the development of type 2 diabetes among patients treated with angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARBs).

Type 2 diabetes development has been a secondary endpoint in these clinical trials. Dr. Andraws and colleagues performed a meta-analysis to determine the magnitude of the effect of RAS inhibition on the prevention of type 2 diabetes.

The investigators looked at 12 trials that randomized 79,339 patients; 35,708 were treated with regimens containing ACE inhibitors or ARBs. The mean age of patients enrolled was 52 to 76 years and men made up from 32%

to 94% of the studies. Follow-up duration ranged from 1 to 6 years.

Treatment with an ACE inhibitor or ARB reduced the risk of the developing type 2 diabetes by 26% compared with other treatments (OR 0.735; $P < .001$).

These agents should be preferentially prescribed for the treatment of hypertension in patients at increased risk for developing type 2 diabetes. The use of these agents exclusively for primary prevention of type 2 diabetes is worthy of further investigation, Dr. Andraws said.

Fruit Intake Associated With Reduced Diabetes

While higher intake of fruits and vegetables is associated with lower risk of CVD and cancer, previous studies on its relation to diabetes were sparse and reported inconsistent findings, according to Lijing L. Yan, MD, from Peking University.

He and colleagues presented a study that evaluated the long-term correlation of fruit and vegetable intake in middle-aged adults with diabetes in older age. Investigators used data from the Chicago Western Electric Study.

Fruit and vegetable (including potato) intake determined from detailed dietary history were categorized into three strata: <14 cups per month (low), 14 to 42 cups per month (medium) and >42 cups per month (high). Data from the Western Electric Study are considered the best in its era, Dr. Yan wrote.

The percentage of patients with diabetes diagnosis in older age were 20.9%, 19% and 12.7% for low, medium and high fruit intake, respectively. The odds ratio for having diabetes was 0.85 for medium fruit intake and 0.50 for high intake compared with low intake (P for linear trend .023).

Findings were different for vegetable intake, the investigators reported: 13.1%, 19.1% and 21.3% of the participants developed diabetes in the low-, medium- and high-vegetable-intake groups, consecutively.

Higher fruit intake in middle age is associated with a lower risk of having diabetes in older age. Higher vegetable intake is associated with a nonsignificant higher risk of diabetes. Potential explanation for findings, wrote Dr. Yan is that in the late 1950s many people with generally unhealthy dietary habits had high vegetable intake. Further study is needed to examine diet in a holistic manner and to explore mechanisms for the associations observed.

Metabolic Syndrome Prevalent Among Blacks

The Jackson Heart Study (JHS), with comprehensive data on obesity, hypertension and dyslipidemia, provides a golden opportunity to study the prevalence of metabolic syndrome among the black population. This is according to lead investigator Jun Pan, MD, from the University of Mississippi Medical Center, and colleagues.

The all-black cohort included 5,302 participants. Metabolic syndrome was defined by the NCEP ATP III guidelines. Overall prevalence of the condition was 37.2%; it increased from 15.9% in those aged 20 to 34 years, to 39.4% in those aged 45 to 64 years, and 47.2% in those aged 65 and older. The prevalence was lower in men (30.1%) than in women. The three most prevalent abnormalities were central obesity (65.3%), hypertension (63.7%) and low HDL cholesterol (44%).

Metabolic syndrome was highly prevalent among JHS participants, the researchers said. Central obesity and hypertension contributed largely to metabolic syndrome in this black cohort.

Elevated HbA1c May Be Risk Factor for Stroke

While people with diabetes are at increased risk for stroke, it is unknown whether chronic hyperglycemia contributes to the development of cerebrovascular disease.

A prospective case-cohort study conducted by investigator Elizabeth Selvin, MD, and colleagues from Johns Hopkins University looked at 168 ischemic stroke cases, a subcohort of 705 nondiabetic adults and a cohort of 1,635 diabetic adults with 110 ischemic stroke cases from the ARIC study. Using Cox models, they assessed the relationship between HbA1c – in tertiles – and incident ischemic stroke during 8 to 12 years of follow-up. Dr. Selvin and colleagues controlled for stroke risk factors.

In patients without diabetes, the adjusted relative risk for stroke was 1.15 and 1.67 for the second and third tertiles of HbA1c compared with the lowest ($P=.049$). The tertiles of HbA1c for nondiabetic patients were 4.4%, 4.8% and 5.4%. In diabetic patients, the adjusted relative risk for stroke was 1.47 and 2.62 compared to the lowest tertile ($P<.001$) the HbA1c tertiles in these patients were 5.0%, 6.0% and 8.7%.

Elevated HbA1c may be an independent risk factor for stroke in people with and without diabetes. Dr. Selvin said that these results are similar in direction and magnitude to those previously observed for coronary heart disease. These results have implications for ongoing clinical trials investigating the effect of glucose-lowering treatments on combined cardiovascular outcomes.

38TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY

The meeting was held in Philadelphia from November 10 to 13, 2005.

SPP301 Has Strong Efficacy, Good Safety Profile

Positive phase 2b results of SPP301 (Speedel, Basel, Switzerland) in diabetic nephropathy were presented by Professor Rene Wenzel, principal investigator and head of

internal medicine at Zell am See Hospital, Austria.

According to the company, results showed that SPP301, a once-a-day oral endothelin-A receptor antagonist (ERA), decreased urinary albumin excretion (UAE) rate and total cholesterol in patients with diabetic kidney disease when administered in addition to standard treatment.

Professor Wenzel commented: "The compelling results of this trial offer hope for the treatment of diabetic nephropathy, the leading cause of end-stage renal disease [ESRD], for which treatment options are limited and the mortality rate unacceptably high. SPP301 may provide physicians with a novel approach to treating diabetic patients with nephropathy effectively and safely."

SPP301 is the only ERA being developed for this indication, said Jessica Mann, medical director, in a news release. A phase 3 clinical trial is underway. In the phase 2b trial, patients were randomized, and the trial was placebo-controlled, double-blind and parallel designed. It investigated the effects on UAE rate of 12-week therapy with SPP301 (5 mg, 10 mg, 25 mg or 50 mg) or placebo, administered in addition to standard treatment (ACE inhibitors or ARBs). Compared with placebo, all doses of SPP301 decreased UAE rate significantly ($P<0.001$), with the highest two doses demonstrating the greatest reduction in UAE rate. There was also a significant reduction in total cholesterol at all doses ($P<0.001$) compared with placebo.

SPP301 reduced proteinuria by >30% when added to standard treatment for 55% of all patients across all dose groups. SPP301 also has a good safety profile. Whereas other ERAs have previously been associated with liver toxicity, SPP301 has not thus far. In this trial, no significant increases in liver enzymes, aspartate aminotransferase or alanine aminotransferase were observed with SPP301 compared with placebo.

Fosrenol Demonstrated Long-Term Safety, Efficacy

According to data presented here, lanthanum carbonate (noncalcium Fosrenol, Shire Pharmaceuticals Group, Hampshire, UK) effectively maintained reductions in mean serum phosphorus levels while demonstrating safety and tolerability in ESRD patients for up to 6 years.

"These study results provide strong evidence of the safety and efficacy of [lanthanum carbonate]," said Alastair Hutchison, MD, colead investigator, from the Manchester Institute of Nephrology & Transplantation, Manchester, UK. "With a robust long-term safety profile, ESRD patients and physicians can rely on [lanthanum carbonate] to help manage hyperphosphatemia and meet Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines."

The open-label extension study enrolled 93 patients. Thirty-two were treated with lanthanum carbonate for

up to 6 years. The study revealed that as patients continued on therapy, the number of drug-related adverse events did not increase with drug exposure. The most common treatment-related adverse events were gastrointestinal in nature and no new or unexpected adverse events occurred during long-term treatment.

Importantly, patients treated with the drug also maintained reduced serum phosphorus and calcium phosphorus product levels, demonstrating the long-term effectiveness of lanthanum carbonate. The patients successfully controlled their serum phosphorus and calcium phosphorus product levels to within the K/DOQI guidelines effective at the time the study was conducted.

Data revealed that the phosphate-binding affinity of the drug was >200 times higher than sevelamer HCl at pH 3. When assessed at pH 5 to 7, the affinity of lanthanum carbonate was fourfold higher versus sevelamer HCl, demonstrating the pH binding affinity and independence of lanthanum carbonate in vitro. The presence of bile acids did not affect the stability of the agent, whereas bile acids led to a more than 13-fold reduction in phosphate-binding affinity of sevelamer HCl with the consequent release of its phosphate. The clinical relevance of the effect of pH on in vivo phosphate binding of lanthanum carbonate has not been established.

CERA Showed Sustained and Stable Control of Anemia

Roche's (Nutley, NJ) innovative antianemia agent CERA (Continuous Erythropoietin Receptor Activator) was able to control anemia in patients with chronic kidney disease (CKD). Patients were not on dialysis within a narrow target range set out in expert guidelines for >1 year. The phase 2 extension data mirror those presented in 2005 in dialysis patients, suggesting that CERA provides consistent antianemia activity in a broad spectrum of patients with CKD. Phase 2 results with CERA are being confirmed in an extensive phase 3 clinical program.

"CERA provided consistent and reliable hemoglobin levels in a controlled manner that resembles how the body naturally regulates itself," said lead investigator Robert Provenzano, MD, St. John Hospital and Medical Center, Detroit. "The current guidelines for anemia management, including those in the United States, recommend that CKD patients be kept in an optimal range between 11 g/dL to 12 g/dL and CERA achieved this at extended-dosing intervals. This is important news, as maintaining a patient in this range is difficult. Recent reports have pointed out that many patients' hemoglobin levels fluctuate with excursions outside of this target range. CERA would be the first agent with

demonstrated effectiveness at dosing intervals as long as 3 to 4 weeks. This is expected to substantially facilitate anemia management for physicians and patients, while allowing hemoglobin levels to remain on target with fewer interventions."

Link Between Higher Nighttime Blood Pressure, Lower Cognitive Function

Higher levels of blood pressure at night – especially loss of the normal nighttime dip in blood pressure – are linked to lower scores on tests of cognitive functioning, according to a paper presented here.

Results add to previous studies suggesting that information from 24-hour blood pressure monitoring is a better indicator of the risks of organ damage caused by hypertension than blood pressure readings taken in the doctor's office. Led by Gary L. Schwartz, MD, of Mayo Clinic College of Medicine, the researchers compared 24-hour blood pressure recordings with the results of standard cognitive tests in 389 patients, most of whom had hypertension.

Patients wore an ambulatory blood pressure monitor. Past research has shown that one-time measurements of blood pressure in the doctor's office do not fully capture the health risks associated with disturbances of blood pressure. Scores on the cognitive tests were significantly lower for patients with higher nighttime blood pressure levels. This included tests of specific cognitive function such as attention and processing speed.

Normally, blood pressure drops about 10% to 20% of daytime levels when a person lies down at night. In the new study, patients who did not have a normal nighttime dip in blood pressure also scored lower on the cognitive tests. Cognitive scores were unrelated to the patient's daytime blood pressure levels on 24-hour monitoring, or to their blood pressure levels measured in the doctor's office.

Through the sustained effects of high blood pressure over time, hypertension can damage virtually every organ in the body. High blood pressure has been linked to reduced cognitive function, even in young adults. The average age of the patients in this study was 63 years. Previous studies have shown a higher risk of damaging complications from hypertension in patients with higher blood pressure levels. The new results show that higher nighttime blood pressure is also related to reductions in specific areas of cognitive functioning. "These studies suggest that we may have to pay more attention to blood pressure levels and patterns throughout the day and night in order to protect our patients from the harmful effects of high blood pressure," Dr. Schwartz

said in a news release.

Statin Treatment After Kidney Transplant

Treatment with cholesterol-lowering statin medications can lower the high risk of MI and other cardiovascular events in kidney transplant recipients.

Led by Hallvard Holdaas, MD, of National Hospital in Oslo, Norway, the researchers analyzed the effects of treatment with fluvastatin (Lescol, Novartis, Cambridge, Mass) in 2,102 kidney transplant patients. One group of patients received fluvastatin for up to 8 years versus a placebo group. All patients had good long-term function of the transplanted kidney.

Fluvastatin was highly effective in reducing the patients' level of LDL cholesterol; average LDL decreased from 159 mg/dL to 98 mg/dL. Reductions were associated with a decreased risk of MI and other major cardiovascular events. The overall rate of such events was reduced by 21% in patients taking fluvastatin compared with placebo.

The overall risk of death from all causes was no different for patients treated with fluvastatin versus placebo. Both groups also had similar rates of long-term survival of the transplanted kidney.

"As patients continue to live longer after kidney transplantation, there is an increased need to prevent some of the long-term complications that can develop," Dr. Holdaas said in a news release. "One major risk is premature CVD, related to high cholesterol levels developing after transplantation."

The new study finds statins effective in lowering cholesterol and cardiovascular risks in kidney transplant patients. The magnitude of the protective effect – over a 20% reduction in the overall risk of major cardiovascular events – is similar to that noted in other groups of patients taking statins. Fluvastatin is a safe and effective treatment for kidney transplant recipients, Dr. Holdaas and colleagues concluded.

THE AMERICAN SOCIETY OF HUMAN GENETICS

The meeting was held in Salt Lake City from October 25 to 29, 2005.

Genetic Link Between Diabetes, CVD and Metabolic Syndrome

Researchers at Wake Forest University School of Medicine reported a genetic link between diabetes, CVD and metabolic syndrome.

"We reported evidence that type 2 diabetes, metabolic syndrome and the tendency to have CVD and resulting heart-related events are inherited together on specific parts of the human chromosomes," said

Donald W. Bowden, PhD, professor of biochemistry and internal medicine and associate director of the Wake Forest University Center for Human Genomics.

The findings are from the Diabetes Heart Study, a project to understand how genes and lifestyle influence the development of heart disease in diabetes families.

The study involved 1,180 people in 443 families from Forsyth County and the surrounding region. Each family includes at least two siblings who have diabetes. Researchers analyzed blood samples and DNA to locate regions of the human chromosomes that are connected with diabetes, metabolic syndrome and CVD.

"The results suggest that genes associated with the tendency for diabetes, [CVD] and metabolic syndrome, are inherited as a single trait," said Dr. Bowden. "The genes are at different locations on the chromosomes, which suggests that someone who has more than one of the genes may be more likely to have these diseases."

Although specific genes have not yet been identified, two of the genes are found on chromosome 3 and the others are found on chromosomes 4 and 14.

"Our findings suggest that individual genes could be contributing to these important clinical conditions and that the conditions are being inherited together," said Dr. Bowden. "This means these traits may be much more closely related than previously thought."

Indeed, 463 of the 1,180 participants in the diabetes study reported already being told they had CVD when the study began. "About half of the people with diabetes seem to have everything: diabetes, metabolic syndrome and CVD," said Dr. Bowden.

Diabetes is rapidly increasing in Americans and particularly among North Carolinians, where the frequency of diabetes may reach one in every 10 people by 2010.

CVD, as used in the study, refers to atherosclerosis. Metabolic syndrome is characterized by high triglycerides, low HDL and high LDL, elevated blood pressure, insulin resistance or glucose intolerance, a greater tendency for blood to clot, and elevated levels of C-reactive protein in the blood. According to the AHA, metabolic syndrome has become increasingly common in the United States, affecting more than 50 million Americans. It triples the risk of atherosclerotic heart disease and increases the risk for type 2 diabetes nearly fivefold.

Exactly how the individual genes are linked and inherited together is not clear and, Dr. Bowden said, is