Intense Changes Cut Weight, Heart Risk in Type 2

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — One-year data from a large, federally funded clinical trial have shown that intensive lifestyle intervention can produce significant weight loss and reduce cardiovascular risk factors among patients with type 2 diabetes, Dr. F. Xavier Pi-Sunyer reported at the annual scientific sessions of the American Diabetes Association.

The Look AHEAD (Action for Health in Diabetes) study is an ongoing 16-center randomized clinical trial designed to determine whether intensive lifestyle modification—including both decreased caloric intake and increased physical activity—can reduce the rates of both fatal and nonfatal myocardial infarctions and strokes in overweight volunteers with type 2 diabetes over a planned follow-up of 11.5 years, compared with traditional medical care.

The trial was funded primarily by the National Institutes of Health; other major donors include Federal Express, Health Management Resources, Johnson & Johnson, Lifescan Inc., Optifast-Novartis Nutrition, Roche Pharmaceuticals, Ross Products Division of Abbot Laboratories, and SlimFast Foods Company.

The study includes 5,145 patients with type 2 diabetes with a mean age of 59 and mean body mass index of 36 kg/m^2; 37% are from ethnic/racial minority groups. Approximately 15% are insulin users, and the same proportion have a history of a previous cardiovascular event. They receive care from their own physicians in the community, while the study sites provide the intervention.

The intensive lifestyle intervention (ILI), to which 2,570 patients were randomized, consisted of an initial 6-month phase in which they attended three group sessions and one individual session per month, all conducted by trained diabetes educators and emphasizing nutrition and physical activity aiming at a personal weight loss goal of 10% from baseline.

During months 7 through 12, subjects attended two or three sessions per month, either individually or in a group. Those who had achieved the first goal were aiming to maintain their weights, while those who hadn't continued to aim for the 10% loss.

Calorie recommendations were calculated based on baseline and goal weights, initially set at 1,200-1,500 kcal/day for those weighing 250 pounds or less at baseline and 1,500-1,800 kcal/day for those weighing more than 250 pounds. Participants could choose a regimen that included liquid meal replacements. Exercise was gradually increased to at least 25 minutes/day. Most participants walked, aiming for 10,000 daily steps, said Dr. Pi-Sunyer, director of the Obesity Research Center, St. Luke's–Roosevelt Hospital Center, New York.

The 2,575 control patients received diabetes support and education (DSE) consisting of three to four group meetings per year in which diet, exercise, and social support were discussed but no intervention was actually delivered, he said.

Of the 97% of study subjects who attended the 1-year exam, the ILI group had lost a mean of 8.3% of their body weight, compared with 0.4% in the controls, a highly significant difference. The average weight loss was about 18 pounds. The ILI group continued to lose weight for about the first 8 months of the study, after which their weight tended to plateau but did not rebound.

Triglycerides dropped by 30.3 mg/dL with the intervention group, compared with 14.6 mg/dL for the control.

DR. PI-SUNYER

On average, the men lost about 3-4 pounds more than the women did. By race, whites lost a mean of 10% of their baseline body weight, compared with about 6.5% for Hispanics and African Americans and 6% among Native Americans. The 385 insulin users in the group lost a mean of 7% of their baseline body weight, and the 1,464 on oral antidiabetes medications lost 8%, whereas the 326 not taking any medications lost the most, with a mean of 9%.

Fitness, as measured by treadmill testing, improved by 16% in the ILI group and 11% in the controls, after adjustment for weight loss. Fitness improved significantly across all body mass indexes and in both genders and all the ethnic/minority groups. Changes in fitness were highly correlated with changes in activity level and in body weight, Dr. Pi-Sunyer noted.

Hemoglobin A_{1c} levels dropped from 7.25% at baseline to 6.6% at 1 year in the ILI group, a highly significant difference. In contrast, the drop from 7.3% to 7.15% in the DSE group was not significant.

Similarly, fasting glucose dropped by a mean of 21.5 mg/dL with ILI, compared with just 7.2 mg/dL in the DSE group. The improved hemoglobin A_{1c} occurred despite a greater reduction in glucose-lowering medications in the ILI group, he noted.

Systolic blood pressure dropped by 6.8 mm Hg in the ILI group vs. 2.8 mm Hg with DSE, and diastolic by 3.0 mm Hg vs. 1.8 mm Hg. Again, the reduction was significant only for ILI. Although LDL cholesterol levels didn't change significantly in either group, HDL cholesterol rose to a greater degree with ILI (3.4 vs. 1.4 mg/dL). Triglycerides dropped by 30.3 mg/dL with ILI, compared with just 14.6 mg/dL for DSE.

At 1 year, the ILI group was taking an average of 2.7 medications for glucose, blood pressure, and/or lipid lowering, compared with 3.2 for the DSE group, Dr. Pi-Sunyer reported.

"Continued intervention and follow-up will determine whether these changes will be maintained and lead to a reduction in cardiovascular events," he said. ■

Lipid Disorders in Type 1 March to a Different Drummer

BY BRUCE JANCIN
Denver Bureau

KEYSTONE, COLO. — The size and composition of lipids in type 1 diabetics—rather than classically abnormal lipid levels—may explain the dyslipidemia of many such patients and why they end up with cardiovascular disease, Dr. Robert H. Eckel said at a conference on the management of diabetes in youth.

Case in point: HDL cholesterol levels in persons with type 1 diabetes are typically normal or even elevated. Moreover, their HDL cholesterol is particularly rich in the large, buoyant subfraction believed to be particularly cardioprotective, according to Dr. Eckel, immediate past president of the American Heart Association and professor of medicine, physiology, and biophysics at the University of Colorado.

So why, then, do diabetic patients have cardiovascular disease rates so high that the National Cholesterol Education Program has deemed diabetes a coronary disease equivalent?

The answer isn't known, but Dr. Eckel believes the work of Dr. Alan M. Fogelman and colleagues at the University of California, Los Angeles, provides strong clues. They have shown the HDL cholesterol in patients with CAD and high HDL cholesterol levels is modified so as to be proinflammatory. In vitro studies have found that this HDL cholesterol stimulates production of cytokines that enhance lipid oxidation, vascular inflammation, and plaque growth.

"I'm wondering if the HDL present in type 1 diabetes is defective in its ability to act as an antioxidant, making it noncardioprotective. I think it's a hypothesis that has not been adequately addressed," Dr. Eckel said at the conference sponsored by the University of Colorado and the Children's Diabetes Foundation, Denver.

Danish investigators have demonstrated that type 1 diabetic patients have increased transcapillary escape rates of LDL cholesterol from the intravascular space into the arterial wall (Atherosclerosis 2003;170:163-8). Under such circumstances, a person could have a normal plasma LDL cholesterol value—as do many type 1 diabetic patients—and yet faster LDL cholesterol transit into the vessel wall would lead to accelerated atherosclerosis.

Although Dr. Eckel emphasized he is a strong proponent of aggressive lipid modification in patients with type 1 diabetes—"an LDL below 100 mg/dL should be considered the ceiling," he said, adding that surprisingly, there is "almost zero" evidence that favorably modifying lipids improves cardiovascular outcomes in these high-risk patients.

For example, the Heart Protection Study—widely hailed as a landmark clinical trial—included 615 type 1 diabetic subjects among its more than 20,000 participants. In striking contrast to the study's overall results, the 5-year cardiovascular event rate in type 1 diabetic patients was not significantly better with aggressive LDL cholesterol lowering with 40 mg/day of simvastatin than placebo, although a favorable trend was noted (Lancet 2003;361:2005-16).

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DR. ECKEL

On the other hand, intriguing preliminary evidence suggests lipid-modifying therapy may reduce the risk of various forms of diabetic microangiopathy. For example, Indian physicians have reported that simvastatin slowed progression of retinopathy in hypercholesterolemic diabetic patients (Diab. Res. Clin. Pract. 2002:56:1-11).

This result is lent credence, Dr. Eckel said, by a prospective study of 1,441 type 1 diabetic participants in the Diabetes Control and Complications Trial (DCCT) conducted by investigators at Harvard University. They found subjects in the highest quartile for LDL cholesterol had an adjusted 3.8-fold greater risk of developing clinically significant macular edema than those in the lowest quartile (Diabetes 2004;53:2,883-92).

In addition, University of Pittsburgh investigators have reported simvastatin therapy was associated with trends toward slower progression of both neuropathy and nephropathy, compared with placebo in a small study of 39 type 1 diabetic patients without overt nephropathy (J. Diabetes Complications 2001;15:113-9).

"That's an interesting observation that requires many more interventional trials," Dr. Eckel commented.

He added that despite the absence of firm proof of the efficacy of preventive strategies in type 1 diabetic patients, their extremely high cardiovascular risk warrants aggressive measures. In addition to an LDL cholesterol of less than 100 mg/dL—and a target of 55-70 mg/dL or less in those with CAD—he supports a target triglyceride level below 130 mg/dL and an HDL cholesterol greater than 40 mg/dL.

The triglyceride goal can be achieved by improved glycemic control, weight reduction, exercise, a high-fiber Step-II AHA diet, fibrates, and fish oil capsules sufficient to provide 2.7-7.7 g of omega-3 fatty acids per day, he added. ■