UT SOUTHWESTERN MEDICAL CENTER NEWS

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Lowering cholesterol early in life protects against heart disease later

DALLAS – March 22, 2006 – New research from UT Southwestern Medical Center indicates that lowering "bad" blood cholesterol earlier in life, even by a modest amount, confers substantial protection from coronary heart disease.

The findings, appearing in the March 23 issue of *The New England Journal of Medicine*, found that people with genetic variations affording them lower low-density lipoprotein (LDL) cholesterol in their blood from birth were significantly less likely to develop coronary heart disease later in life than those without the variations. These variations exist in a recently discovered gene called *PCSK9*.

Based on 15 years of data tracking more than 12,000 multiethnic subjects ranging in age from 45 to 64, the researchers found that people who had cholesterol-lowering genetic variations that lowered their LDL level by about 40 milligrams per deciliter were eight times less likely to develop coronary heart disease than those without the mutations. Those with genetic profiles lowering their LDL by about 20 mg/dl from average had a twofold reduction in heart disease.

"These data indicate that a moderate, life-long reduction in LDL cholesterol is associated with substantial reduction in the incidence of coronary events, even in populations with a high prevalence of other cardiovascular risk factors," said Dr. Helen Hobbs, the study's senior author, director of the Eugene McDermott Center for Human Growth and Development and an investigator in the Howard Hughes Medical Institute at UT Southwestern. She also directs the Donald W. Reynolds Cardiovascular Clinical Research Center at UT Southwestern. Dr. Hobbs coauthored the study with Dr. Jonathan Cohen, professor of internal medicine and researchers from the UT Health Science Center in Houston and the University of Mississippi Medical Center in Jackson.

Dr. Scott Grundy, director of the Center for Human Nutrition at UT Southwestern, served as chairman of the National Cholesterol Education Program's Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, which in 2001 set guidelines for the clinical use of cholesterol-lowering medications to reduce the risk of cardiovascular disease. "This study demonstrates the great importance of high blood cholesterol in causing coronary heart disease," said Dr. Grundy.

"It also shows the benefit of maintaining a low cholesterol level throughout life. The foundation for keeping low blood cholesterol is a reduced intake of saturated fats and cholesterol and maintaining a desirable body weight. But in some people it may be necessary to add drugs to reduce cholesterol levels.

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Fortunately, newer cholesterol-lowering drugs have been developed that are both effective and safe for most people."

Previous research has established that people with a high level of LDL cholesterol in their blood are at greater risk of developing coronary heart disease. The present study further documents that life-long reductions in LDL cholesterol can actually help prevent heart disease.

Previous findings by Dr. Hobbs and colleagues at UT Southwestern had identified specific mutations in the gene called *PCSK9* that are associated with lower LDL cholesterol levels in people who have the mutations. Those genetic studies were based on data gathered from the UT Southwestern-directed Dallas Heart Study, a groundbreaking multiyear investigation of cardiovascular disease involving 6,000 Dallas County residents.

The new findings are based on data obtained from subjects drawn from the Atherosclerosis Risk in Communities Study (ARIC), which tracked the health of participants from four communities in Mississippi, Minnesota, North Carolina and Maryland for 15 years, beginning in 1987. UT Southwestern's collaborators at the UT Health Science Center in Houston analyzed blood samples from those participants to determine who carried the cholesterol-lowering genetic variations. The researchers then tracked the subjects'15-year health history and found the association between lower long-term LDL levels and lower risk of heart disease.

The *PCSK9* gene produces an enzyme that normally controls the number of LDL receptors lining the surface of liver cells. These LDL receptors latch on to LDL and remove it from the blood. Dr. Hobbs and co-workers previously found that genetic mutations that inactivate *PCSK9* result in lower levels of the PCSK9 enzyme, leading to higher levels of LDL receptors. By increasing the amount of "bad" cholesterol the liver cells can remove from the blood, LDL levels are lower in the blood of people with the mutations.

High levels of PCSK9 tend to raise the blood concentrations of LDL. Currently statins are the standard class of drugs prescribed to lower LDL in patients. However, statin treatment may increase the production of the PCSK9 enzyme, Dr. Hobbs said, which in turn may limit the effectiveness of these drugs. Developing new therapies that inhibit PCSK9 activity not only should lower LDL levels, but in addition, might enhance the effectiveness of statins, she said.

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