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Lipids and Cardiovascular Disease

Cholesterol and Glucose Metabolism and Recurrent Cardiovascular Events Among the Elderly

A Prospective Study

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OBJECTIVES The aim of this research was to evaluate the prognostic value of cholesterol absorption assessed with the serum cholestanol-to-cholesterol concentration ratio (lower level reflects decreased cholesterol absorption) among elderly cardiovascular patients (DEBATE [Drugs and Evidence-Based Medicine in the Elderly] study).

BACKGROUND The components of the metabolic syndrome have been unexpectedly associated with better prognosis among elderly cardiovascular patients. On the other hand, a metabolic syndrome-type state is characterized by high synthesis and decreased absorption of cholesterol.

METHODS This was a prospective cohort study of home-dwelling individuals age 75 years and older with cardiovascular diseases (247 women, 129 men) recruited from the community. Main outcome measure was multivariate-adjusted time to 3.4-year mortality and recurrent major cardiovascular events.

RESULTS Serum total and low-density lipoprotein cholesterol levels did not predict outcome. Instead, the mortality risk (64 deaths) increased with increasing levels of cholestanol-to-cholesterol ratio. Patients in the 2nd, 3rd, and 4th quartiles had a relative hazard ratio (HR) for death of 2.54 (95% confidence interval [CI] 1.05 to 6.12), 2.48 (95% CI 1.03 to 6.00), and 3.53 (95% CI 1.52 to 8.19) compared with the lowest quartile, even though 50% of individuals in the lowest cholestanol quartile had metabolic syndrome or diabetes. In multivariate models, the lowest cholestanol ratio quartile was independently associated with lower mortality (relative HR, 0.37, 95% CI 0.17 to 0.81), and with fewer major cardiovascular events (115 events, relative HR, 0.59, 95% CI 0.35 to 0.98).

CONCLUSIONS Low cholesterol absorption was associated with fewer recurrent cardiovascular events, and with better survival in elderly patients despite frequent abnormalities of glucose metabolism. (J Am Coll Cardiol 2006;48:708–14) © 2006 by the American College of Cardiology Foundation

The aging of the population and postponement of cardiovascular diseases to older ages lead to an increasing number of cardiovascular patients age 75 years and older. Prevention would be important also in old age (1), but a number of studies have suggested that established cardiovascular risk factors of mid-life—such as cholesterol, blood pressure, and overweight—may paradoxically indicate better or neutral prognosis, especially in the oldest patients (2–5). Underlying mechanisms are complex, and because predictors of vascular events in the elderly are poorly understood, new approaches are needed. The metabolic syndrome is the object of intensive research as a "combined" risk factor. It is characterized by a constellation of risk factors, including abdominal obesity, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, small dense low-density lipoprotein (LDL) particles, elevated blood pressure, proinflammatory and prothrombotic states, as well as high plasma insulin (insulin resistance). Metabolic syndrome has been shown to increase cardiovascular and mortality risk in middle-aged populations (6,7). However, data on the metabolic syndrome are controversial in the elderly. In our previous population-based study of individuals age 75 years or older, the components of the metabolic syndrome, including plasma insulin, were unexpectedly associated with better prognosis especially in those with cardiovascular diseases (3,8). Interestingly, we have earlier shown that glucose metabolism and the insulin resistance syndrome are also connected to cholesterol metabolism (9–13). Specifically, a metabolic syndrome-type state is characterized by high synthesis and decreased absorption of cholesterol (9,10,13). In these studies we have used the serum measurement of some noncholesterol sterols to reflect cholesterol synthesis and absorption (14–16). Of these sterols, plant sterols (campesterol and sitosterol) as well as cholestanol are sensitively connected to cholesterol absorption (higher serum levels reflect higher absorption), and lathosterol to cholesterol synthesis (higher serum levels reflect higher synthesis).

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Abbreviations and Acronyms

APOE = apolipoprotein E
CI = confidence interval
DEBATE = Drugs and Evidence-Based Medicine in the Elderly study
HDL = high-density lipoprotein
HR = hazard ratio
HsCRP = high-sensitivity C-reactive protein
LDL = low-density lipoprotein
MMSE = Mini-Mental State Examination

We hypothesized that closer analysis of the relationship between cholesterol and glucose metabolism could shed light on the controversial survival data in the elderly cardiovascular patients. Therefore we investigated—using levels of serum noncholesterol at baseline—whether the details of cholesterol metabolism would be related to mortality and cardiovascular diseases during a 3.4-year follow-up in home-dwelling elderly individuals.

METHODS

The subjects of the present study were the participants of the DEBATE (Drugs and Evidence-Based Medicine in the Elderly) study, the design of which has been described in detail previously (17–19). Briefly, in a population-based setting, we recruited 400 home-dwelling individuals (mean age 80 years, 260 of them women) age 75 to 90 years into a "real life" prevention trial. They were retrieved from a random sample of 4,821 subjects age 75 to 95 years and living in Helsinki, Finland. All subjects had a diagnosis of an atherosclerotic disease (prior myocardial infarction, coronary artery disease, previous stroke or transient ischemic attack, peripheral artery disease). During the first visit in the clinic, the participants underwent a brief clinical examination performed by the study nurse including the measurements of blood pressure, waist circumference, weight and height, peak expiratory flow, and laboratory tests. Cognitive function was assessed with a Mini-Mental State Examination (MMSE) where a score of <24 points suggests possible dementia. The history of an atherosclerotic disease and possible diabetes and hypertension was reviewed and confirmed (from hospital records where appropriate) by the investigators. The patients signed an informed consent, whereafter they were randomized to the intervention (n = 199) and control groups (n = 201) of the multifactorial prevention study. The research protocol of the DEBATE study had been approved by the Ethics Committee of the Department of Medicine, University of Helsinki. No specific exclusion criteria were set because of the real-life nature of the study.

During the mean follow-up of 3.4 years, the treatment in the intervention group was tailored according to current European guidelines (20) by a geriatrician-internist with consultations as appropriate. The procedures were every-day clinical practice; no experimental treatments were used. The control group received the usual care by primary care physicians, and only visited the study nurse (not the study geriatrician) yearly. Because the present analyses relate baseline characteristics (signs of metabolic syndrome) to study end points, we initially planned to restrict the analyses to the control group only. Preliminary analyses (including analyses of clinical end points) showed, however, that the relationships were similar in both control and intervention groups, and, therefore, the results are presented for the total study population. Moreover, the 1-year feasibility analysis showed that while the intervention procedures improved cardiovascular medications and decreased LDL cholesterol, they failed to change significantly factors related to the metabolic syndrome (body mass index, waist circumference, blood pressure, glucose, HDL cholesterol, or triglycerides) (18).

All routine laboratory measurements (including serum lipids, glucose, and high-sensitivity C-reactive protein [hsCRP]) were performed in the fully qualified central laboratory of the Helsinki University Central Hospital. To convert glucose from mmol/l to mg/dl, multiply by 18.0; to convert cholesterol from mmol/l to mg/dl, multiply by 38.6; to convert triglycerides from mmol/l to mg/dl, multiply by 88.6.

The metabolic syndrome was defined according to the clinical criteria of the Adult Treatment Panel III of the National Cholesterol Education Program (21). A patient had metabolic syndrome if they had 3 or more of the following risk factors: waist circumference of more than 102 cm in men and 88 cm in women, a triglyceride level of 1.7 mmol/l or more, a level of HDL cholesterol of <1.04 mmol/l in men and <1.30 mmol/l in women, a blood pressure of 130/85 mm Hg or more, and a fasting glucose level of 6.1 mmol/l or more. Apolipoprotein E (APOE) alleles were determined as described earlier (22).

Noncholesterol sterols were measured as described previously (9–13), and they are expressed as a ratio to serum cholesterol to standardize for variations in cholesterol concentrations. These noncholesterol sterols include lathosterol (which reflects cholesterol synthesis) and plant sterols (campesterol and sitosterol) and cholestanol (which reflects cholesterol absorption). The level of baseline serum cholestanol-to-cholesterol ratio was used to divide the participants into quartiles of cholesterol absorption efficiency. Cholestanol was used in the analyses because it is not influenced by dietary plant sterols. However, end point data were similar whether any of the absorption markers (absolute or ratios) were used.

At the yearly evaluations, all participants (intervention and control) visited the study nurse, and baseline clinical evaluation and laboratory examinations were repeated (17). Possible study end points and hospital admissions were reviewed, and hospital records retrieved as needed (19).

The study period ended December 31, 2003, whereafter all surviving participants, not residing in institutions, of both groups were contacted by telephone during January 2004. The aim of the interview was to check current