LITERATURE REVIEW

Risk of Coronary Heart Disease in Type 2 Diabetes Mellitus With Elevated Homocysteine

John E. Kirkpatrick, MA, MD


Address: Thrivent Financial for Lutherans, 4321 North Ballard Road, Appleton, WI 54919-0001.

Correspondent: John E. Kirkpatrick, MA, MD.

Key words: Coronary heart disease, type 2 diabetes mellitus, homocysteine.

Received: February 17, 2004
Accepted: February 17, 2004

There is no doubt about the increase in Type 2 Diabetes in the developed world. With this increase has come the devastating effects of cardiovascular disease. Type 2 diabetics continue to experience 2- to 4-fold increases in cardiovascular mortality. Since the Framingham Heart Study some 50 years ago, researchers have continued to evaluate risk factors for coronary heart disease. Many emerging risk factors have been entertained in the last few years, and new ones are being introduced in the literature frequently.

Elevated homocysteine has gained notoriety although few prospective studies have focused on a diabetic population. This long-term prospective study examines moderately elevated plasma homocysteine and the ability to predict CHD events in type 2 diabetics over a 7-year period.

The study was begun in 1982 and followed 830 Type 2 diabetics between the ages of 45–64. The group consisted of patients on oral agents (72%), insulin (14%), and diet therapy (14%). Plasma homocysteine levels were measured at entry. Other variables were previous history of myocardial infarction, glycosolated hemoglobin A1C, high blood pressure (cutoff of 160/95), BMI, smoking, duration of DM, lipid levels, creatinine and creatinine clearance. A plasma homocysteine level of 15 μmol/L was used as a cutoff corresponding to the 90th percentile distribution for those who are considered to be ‘mildly’ elevated.

RESULTS

Observationally, women with plasma homocysteine levels >15 μmol/L were older (P<0.001), had a longer duration of DM (P<0.017), and had lower creatinine clearance (P<0.001) than those with plasma homocysteine <15 μmol/L. Levels of fasting glucose, hemoglobin A1C, and creatinine clearance...
were lower and serum creatinine was higher in men with homocysteine levels >15 μmol/L. Type 2 diabetics with plasma homocysteine levels >15 μmol/L had a higher CHD mortality rate and higher rate of fatal or nonfatal MI when adjusted for age, sex, and creatinine clearance. Further adjustment for lipid levels, glycosolated hemoglobin, hypertension, smoking, BMI, antihypertensive medication, and aspirin did not alter the association. There was further subgroup analysis of those who had no MI at baseline, and the results were similar to the whole cohort.

DISCUSSION

The authors surmise a strong and independent association between elevated plasma homocysteine and the risk for CHD. In nondiabetic individuals, literature has shown a stronger correlation of CHD in those with previous cardiac history than those without. The authors attempt to justify that this is not the case in type 2 diabetics. The unadjusted relative risk of CHD mortality in all patients was 2.71 (P<0.001). The adjusted relative risk for age, sex and creatinine clearance was 2.30 (P=0.002). The adjusted relative risk for multiple factors was 2.94 (P<0.001). For men, 26% of those with an elevated homocysteine died during the study; for women, 24% experienced CHD mortality. The mean age of the males with elevated homocysteine was 58.7, and the mean age for women was 61.4 years.

There certainly is value in examining the implications of this emerging cardiac risk factor in the diabetic population. Unfortunately, the study began in the early 80s; diabetic management and standard of care has evolved since then. For example, the cutoff for hypertension used was 160/95, certainly not in line with current JNC 7 guidelines. Similar discrepancies exist when the lipid measures were evaluated. Adequate blood pressure values, lipid management, and better diabetic control will be variables the next study must evaluate.