CLINICAL STUDY

Elevated Levels of Low-Density Lipoprotein Cholesterol, Homocysteine, and Lipoprotein(a) Are Associated With the Occurrence of Symptomatic Bypass Graft Disease 1 Year Following Coronary Artery Bypass Graft Surgery

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Severe coronary artery bypass graft disease occurs at a rate of approximately 16%–31% within the first year of surgery. Clinical variables, including postoperative lipid profiles closest to the 1-year follow-up, lipoprotein(a) levels, and homocysteine levels were assessed as predictors of early (≤1 year) symptomatic coronary artery bypass graft disease [AU: OK AS EDITED?]. *Of 77 living consecutive patients (from the practice of one cardiologist) who underwent bypass surgery, 60 were asymptomatic at 1 year and 17 had developed recurrent symptoms and had an angiogram that confirmed >50% lesion in at least one saphenous bypass graft. Using multivariate analysis, the strongest predictors of early symptomatic coronary artery bypass graft disease within 1 year of bypass surgery were elevated levels of low-density lipoprotein cholesterol (>100 mg/dL) (odds ratio [OR], 8:1; p=0.034), homocysteine (>10 μmol/L) (OR, 8:1; p=0.019), and lipoprotein(a) (>30 mg/dL) (OR, 4:1; p=0.011). Male gender was associated with a reduced risk (OR, 1:9; p=0.01) of symptomatic graft disease within 1 year of surgery. The authors conclude that low-density lipoprotein, homocysteine, and lipoprotein(a) levels are associated with symptomatic coronary artery bypass graft disease at 1 year after surgery. (Prev Cardiol. 2004;7:XXX–XXX)* ©2004 CHF, Inc.

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There are more than 900,000 coronary artery bypass graft (CABG) surgeries performed in the United States each year. Earlier studies indicate that 10%–15% and 16%–31% of all saphenous bypass grafts (SVG) are severely diseased at 6-month and 1-year follow-up, respectively, following CABG.[1–3] It is recognized that SVG closure within 1 month of surgery is due to thrombosis, whereas SVG disease up to 1 year is due to intimal hyperplasia with thrombotic events that can be reduced with the use of aspirin.[3] Following the first year of surgery, atherosclerosis becomes the main mechanism for disease progression in SVG.[4,5]

Several studies indicate that graft handling, surgical techniques, hematologic abnormalities, the use of antiplatelet drugs, and poor bypass targets can influence SVG patency.[1,3,6–8] Recently, prebypass use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, also known as statins, appears to reduce cardiovascular events after bypass surgery.[9] It is unclear whether statins' protective role is achieved through lipid lowering or via their pleiotropic properties, or both.

It is uncertain at this time whether elevated levels of lipoprotein(a) (Lp[a]) and homocysteine play

Table. Baseline Characteristics of Symptomatic vs. Asymptomatic Patients Following Coronary Artery Bypass Surgery. Categorical Variables Are Presented as Percentages and Continuous Variables as Mean ± Standard Deviation

Variable	Asymptomatic Group	Symptomatic Group	*p* Value
Categorical variables (%)			
Men	72	47	<0.082
History of diabetes	28	47	<0.157
History of hypertension	59	76	<0.259
History of myocardial infarction	27	29	<1.000
Current smokers	15	18	<1.000
History of smoking	67	82	<0.364
Use of left internal mammary artery	82	87	<1.000
Use of statins after bypass	35	24	<0.558
Use of aspirin after bypass	90	76	<0.200
Prior history of angioplasty	17	6	<0.438
Continuous variables (mean ± SD)			
Age (years)	65.27±10.07	64.47±9.84	<0.773
Ejection fraction before bypass (%)	50.37±12.26	55.75±13.05	<0.227
Total number of bypass grafts used	3.63±1.34	4.00±1.00	<0.227
Total cholesterol after bypass (mg/dL)*	172.33±37.30	194.35±42.48	<0.041
Low-density lipoprotein level after bypass (mg/dL)*	97.92±28.88	114.53±43.74	<0.372
High-density lipoprotein level after bypass (mg/dL)*	43.15±12.67	40.18±9.40	<0.155
Triglyceride level after bypass (mg/dL)*	145.43±64.80	189.12±79.85	<0.023
Homocysteine (μmol/L)**	10.36±3.35	11.61±3.05	<0.172
Lipoprotein(a) level after bypass (mg/dL)**	32.42±39.11	44.24±41.18	<0.280
Creatinine	1.02±0.23	0.96±0.20	<0.415

*Collected at a range of 2–26 months after bypass surgery; **collected at a range of 2–31 months after bypass surgery

a role in early SVG disease. In this study, clinical parameters, lipid measurements, and homocysteine levels were evaluated as predictors of severe symptomatic SVG disease at 1-year follow-up after CABG.

METHODS

The medical records of 94 consecutive living patients who underwent CABG between 1999 and 2001 from the practice of one cardiologist were reviewed. Patients who died (n=7), were lost to follow-up (n=8), had an abnormal technetium 99 sestamibi scan results [AU: BRAND NAME DELETED PER JOURNAL STYLE] but refused angiography (n=1), or were symptomatic with positive technetium 99 sestamibi test but had patent grafts on angiography (n=1) were excluded. The remainder of patients (n=77) were divided into two categories: asymptomatic (n=60) at 1 year after CABG and had no further diagnostic cardiac testing, and developed recurrent symptoms (n=17) and had angiographically confirmed >50% lesion in at least one SVG.

Data was collected for independent variables through telephone interviews or detailed medical record review and included age, gender, history of diabetes, hypertension, stroke, history of smoking, family history of heart disease, history of myocardial infarction, history of percutaneous revascularization before bypass, aspirin and statin therapy after bypass, height, weight, body mass index, and complete fasting lipid panel before and after surgery at an average of 10.8 months from the date of bypass (range 2–26 months). Lp(a) and homocysteine levels were obtained as a part of routine follow-up after surgery (range 2–31 months). Low-density lipoprotein (LDL) cholesterol level was calculated according to the Friedewald formula: LDL=total cholesterol – (high-density lipoprotein cholesterol + triglyceride/5) when triglycerides were ≤400 mg/dL. All symptomatic patients had a coronary angiogram to define their coronary and bypass graft anatomy. A diseased graft for symptomatic patients was defined by angiography as a lesion ≥50%.

STATISTICAL ANALYSIS

Bivariate and multivariate analyses of the data were performed. Baseline characteristics were analyzed with the Fisher exact test for dichotomous variables and *t* test for continuous variables. A logistic regression model was performed for predictors of severe SVG disease controlling for age, diabetes, and number of grafts. We used a listwise deletion method in the logistic analysis. Symptomatic patients with pat-

ent grafts were excluded from this analysis (n=1).

RESULTS

Of the total number of patients included in this retrospective study (N=77), a comparison was made between two groups: asymptomatic patients (n=60) who did not require revascularization within 1 year of CABG surgery and symptomatic patients (n=17) who underwent angiography demonstrating at least one severe lesion (>50%) in at least one SVG.

Baseline clinical characteristics are displayed in the Table. Significant differences were found only for total cholesterol and triglyceride levels. Furthermore, the logistic regression model (adjusting for history of diabetes, age, and number of bypass grafts) showed that LDL cholesterol >100 mg/dL (odds ratio [OR], 8:1; $p=0.034$), homocysteine >10 µmol/L (OR, 8:1; $p=0.019$) and Lp(a) >30 mg/dL (OR, 4:1; $p=0.011$) were associated with symptomatic graft closure at 1 year after surgery. Male gender was associated with a reduced risk (OR, 1:9; $p=0.01$). Cox and Snell R^2 indicated that these factors explain 26% of the variation. The model correctly predicts 96.7% of asymptomatic patients and 47.1% of symptomatic patients. Overall, the model predicts 85.7% of all cases.

DISCUSSION

In this study we have shown that LDL, Lp(a), and homocysteine levels are associated with symptomatic bypass graft disease at 1 year after surgery. It is well established that elevated lipoprotein levels are associated with an increased risk of atherosclerosis and plaque formation and trigger an inflammatory response in the blood vessels.[10,11] In addition, recent studies have shown a significant correlation between Lp(a)[12] **[AU: REFERENCES 11 AND 12 HAVE BEEN SWAPPED IN TEXT AND REFERENCE LIST TO APPEAR IN NUMERICAL ORDER]** and homocysteine[13–16] levels and the development of cardiovascular events. Lp(a) is thrombogenic, reducing plasmin generation and enhancing fibrin accumulation at sites of endothelial injury. However, an increase in Lp(a) levels was not always a consistent predictor of increased cardiovascular events.[17] Furthermore, studies evaluating the role of Lp(a) on bypass graft stenosis after CABG were also conflicting, showing either no influence[18] or an increase in SVG disease.[19]

Elevated homocysteine levels are also associated with thrombosis. Several studies have linked elevated homocysteine levels to an increase in cardiovascular events[13–16] and SVG disease after CABG.[20,21] However, the association between homocysteine and SVG disease has not been consistent in all studies.[18]

Our data support a role of LDL, Lp(a), and homocysteine in bypass graft disease at 1 year. The mechanisms by which Lp(a) and homocysteine promote SVG disease are unknown but might be the result of inflammation and/or thrombosis or possibly an early accelerated atherosclerotic process in SVG. Whether the aggressive treatment of elevated LDL, homocysteine, and Lp(a) levels reduces early graft disease is unclear and warrants further evaluation in future prospective studies.

STUDY LIMITATIONS

The study is limited by its retrospective nature. Asymptomatic patients did not undergo routine angiography at 1 year and therefore it is unclear how asymptomatic graft disease would have affected our findings. Also, patients who died were not included in this analysis because their Lp(a) and homocysteine levels could not be obtained. However, the results of this study are compelling and warrant further investigation by a larger, prospective trial currently ongoing at our institution.

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