Low High Density Lipoprotein Level Is Associated With Increased Restenosis Rate After Coronary Angioplasty

Prediman K. Shah, MD; and Jatin Amin, MD

Background. To determine the relation of post-–percutaneous transluminal coronary angioplasty (PTCA) restenosis to serum lipid fractions and to circulating levels of endogenous tissue plasminogen activator (t-PA) and its rapid inhibitor (PAI-1), 68 patients with coronary artery disease who underwent a successful PTCA were studied.

Methods and Results. During a mean follow-up of 9 months (range, 7–11 months), 28 (41%) patients developed restenosis. A low high density lipoprotein (HDL) cholesterol level was independently and strongly related to both the risk of restenosis (p < 0.001) and to the time of restenosis (p = 0.03). The mean HDL cholesterol level was 33±12 mg% in the restenosis group compared with 45±12 mg% in the nonrestenosis group (p < 0.001). Restenosis developed in 22 of 34 (64%) patients with an HDL cholesterol ≤40 mg% compared with six of 34 (17%) patients with an HDL cholesterol >40 mg% (p < 0.002). The only other variable that was significantly related to restenosis was a low PAI-1 level (p = 0.04).

Conclusions. The strong relation between a low HDL cholesterol level and the risk of restenosis suggests that lipid fractions could be important in the pathogenesis and prevention of restenosis. (Circulation 1992;85:1279–1285)

KEY WORDS • restenosis • high density lipoproteins • percutaneous transluminal coronary angioplasty

Serial angiographic studies after percutaneous transluminal coronary angioplasty (PTCA) have shown a 6-month restenosis rate of 25–52%.1–7 Although the mechanism(s) of restenosis remain incompletely understood, the histological examination of restenotic tissue reveals intimal hyperplasia with a variable lipid component.8–19 This histological appearance suggests that similar cellular processes may be involved in atherogenesis and restenosis. Because abnormal serum lipid fractions and biochemical abnormalities reflecting a prothrombotic state are positively related to coronary atherosclerosis,20–24 we hypothesized that a similar relation to restenosis might be found in patients undergoing PTCA.

Methods

Consecutive patients undergoing elective PTCA were considered for inclusion. Patients undergoing emergency PTCA and those in whom PTCA was deemed unsuccessful (after PTCA residual stenosis >50% or abrupt occlusion within 48 hours of the procedure) were excluded. Of 96 patients considered for inclusion, 28 patients met the exclusion criteria, leaving 68 patients for the study. These 68 patients, 40 men and 28 women with a mean age of 64 years, had PTCA with a successful outcome defined as a residual diameter stenosis of <50%. The indications for PTCA were stable angina in 27 patients, unstable angina in 35 patients, and postinfarction angina in six patients. Before PTCA, fasting levels of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, lipoprotein (a) (LPa), fibrinogen, circulating levels of endogenous tissue plasminogen activator (t-PA antigen), and the plasminogen activator inhibitor (PAI-1 antigen and PAI-1 activity) were measured. Total cholesterol was measured by an enzymatic method. The HDL level was measured in the supernatant after precipitation of LDL and VLDL cholesterol. LDL and VLDL levels were calculated using Friedwald formula. LPa level was measured in the Genentech Laboratories in San Francisco (courtesy of Richard Lawn, PhD). Fibrinogen levels were measured by a Fibrometer using the General Diagnostics Reagents. The levels of t-PA antigen and free PAI-1 antigen were measured in citrated plasma using a commercially avail-

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TABLE 1. Distribution of Selected Clinical, Angiographic, and Biochemical Variables

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Restenosis group n=28</th>
<th>Nonrestenosis group n=40</th>
<th>p (univariate)</th>
<th>p (multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65±9</td>
<td>63±9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>71</td>
<td>62</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with diabetes (%)</td>
<td>21</td>
<td>37</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>0</td>
<td>10</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with hypertension (%)</td>
<td>36</td>
<td>55</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with stable angina (%)</td>
<td>32</td>
<td>45</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with unstable angina/AMI (%)</td>
<td>68</td>
<td>55</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients on lipid-lowering drugs (%)</td>
<td>7</td>
<td>11</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients on β-blockers (%)</td>
<td>18</td>
<td>6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Angiographic variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with LAD–PTCA (%)</td>
<td>53</td>
<td>40</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis before PTCA (%)</td>
<td>90±10</td>
<td>87±8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis after PTCA (%)</td>
<td>30±10</td>
<td>29±10</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Inflation time (seconds)</td>
<td>354±178</td>
<td>294±146</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with dissection after PTCA (%)</td>
<td>11</td>
<td>22</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with thrombus after PTCA (%)</td>
<td>0</td>
<td>3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Biochemical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg%)</td>
<td>207±26</td>
<td>223±36</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mg%)</td>
<td>148±22</td>
<td>151±35</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL cholesterol (mg%)</td>
<td>25±11</td>
<td>28±13</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg%)</td>
<td>33±11</td>
<td>45±12</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tryglycerides (mg%)</td>
<td>236±67</td>
<td>213±143</td>
<td>0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Liprotein (a) (mg/ml)</td>
<td>6±7.9</td>
<td>7±6.7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (mg%)</td>
<td>375±124</td>
<td>380±133</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>t-PA antigen (ng/ml)</td>
<td>18±11.8</td>
<td>18±12</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PAI-1 antigen (ng/ml)</td>
<td>8.8±5.9</td>
<td>11.7±7.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PAI-1 activity (units/ml)</td>
<td>8±7.1</td>
<td>12±8</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; LAD, left anterior descending coronary artery; PTCA, percutaneous transluminal coronary angioplasty; LDL, low density lipoprotein; VLDL, very low density lipoprotein; HDL, high density lipoprotein; t-PA, tissue plasminogen activator; PAI-1, rapid inhibitor of t-PA.

Available ELISA kit (Immubind t-PA and PAI-1 ELISA Kit, American Diagnostica Inc., New York). The PAI-1 activity was measured in citrated plasma using a commercially available two-step indirect enzymatic assay (Spectrolyse tm/pL [1–1], American Diagnostica, Inc.) based on the principle first presented by Chiemelewska et al.25 The coefficients of variation between and intra-assay for the fibrinolytic markers is <8%. Clinical data including history of diabetes, hypertension, cigarette smoking, and use of various medications were also prospectively recorded. The angiographic variables included the location of stenosis, percentage intraluminal thrombus, and intimal dissection stenosis before and after PTCA, the cumulative duration of balloon inflation, presence of angiographic signs and 6–12 weeks and 12–26 weeks after the procedure and at last follow-up.

**Statistical Methods**

Data are presented as mean±SD. For each variable, histograms were printed separately for cases with restenosis and those without restenosis. For variables with a very skewed distribution (cholesterol, HDL, LDL, VLDL, triglycerides, fibrinogen, t-PA antigen, PAI-1 activity, LPa, and balloon inflation time), a log transformation was taken. Univariate analysis using unpaired t test for continuous variables and χ² test for categorial variables was used to compare patients with and without restenosis.

A multivariate analysis was performed to determine the variables predictive of restenosis and time to restenosis using Cox proportional hazards model run in a stepwise procedure (BMDP2L).
Results

Twenty-eight patients developed clinical manifestations of recurrent myocardial ischemia during a mean follow-up period of 9±1 months (range, 7–11 months). Coronary angiography was performed in 25 of these 28 patients and restenosis involving the previous site of PTCA was confirmed in all. The percentage of diameter stenosis at the previous PTCA site was >70% in all 25 patients. In two patients, reappearance of an exercise-induced reversible thallium perfusion defect in the distribution of the previously dilated coronary artery was considered an indication of restenosis. In one patient, development of an acute myocardial infarction in the distribution of the previously dilated coronary artery was considered an indication of restenosis. The remaining 40 patients were considered to be free of clinically significant restenosis on the basis of absence of clinical symptoms of ischemia and a negative thallium stress test for ischemia in the distribution of the previously dilated coronary artery at last follow-up, which ranged from 7 to 10 months after PTCA.

Clinical, Biochemical, and Angiographic Determinants of Restenosis

Tables 1 and 2 summarize the results of univariate and multivariate analysis of the distribution of variables in the patients with and without restenosis. On univariate analysis, only three variables, i.e., total cholesterol, HDL cholesterol, and PAI-1 activity, differed significantly between the patients with and those without restenosis. In comparison with patients without restenosis, the patients with restenosis had significantly lower levels of total cholesterol, HDL cholesterol and PAI-1 activity. Even after exclusion of patients on β-blockers, the HDL cholesterol level was significantly lower in the restenosis group compared with those without restenosis (32±9 versus 44±11 mg%; p<0.001).

On multivariate analysis, HDL cholesterol and PAI-1 activity were the only two variables significant for predicting the probability of restenosis (Table 2).

HDL Cholesterol and Restenosis

Figures 1 and 2 shows the relation between HDL cholesterol level and restenosis. Of the 28 patients with restenosis, 22 (78%) had an HDL cholesterol level ≤40 mg%, whereas an HDL cholesterol ≤40 mg% was present in only 12 of 40 (30%) patients without restenosis (p<0.001). Restenosis developed in 22 of 34 (64%) patients with an HDL cholesterol ≤40 mg% compared with only six of 34 (17%) patients with an HDL cholesterol >40 mg% (p<0.002). The mean HDL cholesterol level was 33±11 mg% in patients with restenosis compared with 45±12 mg% in those without restenosis (p<0.001). Of the 28 patients with restenosis, the mean time from PTCA to restenosis was 3.6±1.9 months for the 22 patients with an HDL cholesterol ≤40 mg% compared with 6.3±3.2 months for the six patients with an HDL cholesterol >40 mg% (p=0.03). A multivariate analysis model confirmed that HDL cholesterol and PAI-1 levels were also significant for predicting the time to restenosis (Table 2).

Discussion

This study demonstrates a highly significant relation between a low HDL cholesterol level and restenosis rate after PTCA. An HDL cholesterol level ≤40 mg% was associated with a nearly fourfold higher restenosis rate compared with HDL cholesterol levels >40 mg% (64% versus 17%; p<0.002). In addition, among patients with restenosis, the time to restenosis was also significantly shorter in patients with an HDL cholesterol level below 40 mg% compared with those with an HDL cholesterol level above 40 mg% (3.6±1.9 versus 6.3±3.2 months, p=0.03). The levels of LDL cholesterol, VLDL cholesterol, and LPa, all known atherogenic risk factors,20,21,26 were not significantly related to restenosis. A multivariate analysis confirmed the strong and independent relation between HDL cholesterol level and restenosis rate.

Restenosis within 6 months after successful PTCA occurs in 25–52% of patients, and the restenosis rate has remained unchanged despite improvements in operator experience and instrumentation.2,27,28 The restenosis rate of 41% observed in this study is in keeping with the restenosis rates observed in patients with unstable acute ischemic syndromes.5,29 The pre-

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**TABLE 2.** Results of Multivariate Analysis of Variables Predictive of Restenosis and Time to Restenosis

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable entered</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High density lipoprotein</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>PAI-1 (rapid inhibitor of tissue plasminogen activator)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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**Figure 1.** Bar graph shows restenosis rate after percutaneous transluminal coronary angioplasty in 68 patients. Note the nearly fourfold higher restenosis rate in patients with a high density lipoprotein (HDL) cholesterol level ≤40 mg% compared with those whose level is >40 mg%.
the mechanism(s) of restenosis remain incompletely understood, although most investigators attribute restenosis to a reparative reaction of the arterial wall to the injury produced by PTCA. Early case reports emphasized the importance of the fibrocellular response in the media of dissected coronary arteries with histological evidence of an extensive proliferation of smooth muscle cells. Biopsy of restenotic tissue, obtained during the course of transluminal atherectomy, has shown a variable histological picture with the majority of lesions demonstrating intimal hyperplasia as the dominant finding. A similar intimal proliferative reaction has also been observed in the animal models of angioplasty. The exact mediators of the proliferative response to arterial injury are not known but may include mitogens derived from platelets, smooth muscle cells, endothelial cells, or macrophages. Clinical trials have, however, failed to demonstrate a reduced restenosis rate with antiplatelet agents, although a protective effect of antiplatelet therapy against acute thrombotic complications has been noted.

Organized thrombus and granulation tissue have been seen at the site of medial tear months after PTCA of the femoral artery and have been implicated in restenosis. In view of this hypothesis, we investigated the possibility that an impaired endogenous fibrinolytic state and elevated fibrinogen levels, known to be positively associated with coronary artery disease and its acute manifestations, may be associated with a higher restenosis rate. Regulation of the endogenous fibrinolytic system is achieved primarily at the level of synthesis and activity of endothelial derived t-PA and its rapid circulating inhibitor, PAI-1. Decreased levels of t-PA activity are predominantly caused by increased levels of PAI-1 and thus elevated PAI-1 levels are associated with an increased risk of arterial thrombosis. In our study, contrary to expectation, the circulating PAI-1 activity tended to be lower in the restenosis group compared with the nonrestenosis group, although the relation was weaker than that of HDL and restenosis. The reason for this seemingly paradoxical and unexpected finding is not clear at this time and requires further study. To our knowledge, the relation between circulating markers of the fibrinolytic state and restenosis has not been previously reported. Fibrinogen levels were also not significantly different in the restenosis group compared with the nonrestenosis group. Clinical trials involving long-term anticoagulation with warfarin and short-term anticoagulation with intravenous heparin have not shown benefits in terms of a reduced restenosis rate.

Yet another mechanism of restenosis may be an accelerated form of atherosclerosis, the rate of which is influenced by the known atherosclerotic risk factors. A number of factors have been reported as being associated with an increased risk of restenosis, and these include patient-specific factors, anatomical and lesion-specific factors, as well as procedure-related factors. Clinical characteristics such as unstable angina, diabetes mellitus, male sex, and cigarette smoking have been reported to increase the risk of restenosis in some but not in other studies. Hyperlipidemia, an important risk factor for coronary atherosclerosis, has not been systematically evaluated as a risk factor for restenosis after PTCA. Myler et al in a report involving 494 patients, described a history of hypercholesterolemia (total cholesterol level >300 mg%) in the preceding 6 months as a significant risk factor for restenosis after PTCA. However, no details about lipid fractions were provided in their report. In a brief report, Hamm et al described a significantly higher restenosis rate in patients with hyperlipidemia; however no details of lipid fractions were reported.

Our findings of an inverse relation between HDL levels and the restenosis rate are supportive of this concept because a low HDL cholesterol is known to be a strong risk factor for coronary artery disease. In a recent study in which atherectomy was performed on native as well as restenotic arterial segments, histological examination of the specimens retrieved showed that 25% of the restenotic segments consisted entirely of atherosclerotic plaque, whereas the remaining 75% showed intimal hyperplasia often superimposed as a discrete layer over an underlying atherosclerotic plaque. Recent preliminary reports have also described a strong independent relation between plasma lipoproteins, specifically low HDL cholesterol, and the restenosis rate in patients undergoing PTCA. In an earlier report, Austin et al failed to find a relation between total cholesterol and restenosis except when the total cholesterol level exceeded 350 mg%; however, no lipid fractions were determined. In a subsequent report, Austin et al failed to find a relation between serum lipid fractions and restenosis at 4 years of follow-up after PTCA. The reasons for the discrepancy between the results of our study and those of Austin et al are not clear. Because the presence or absence of restenosis was ascertained within the first 7–10 months of PTCA in our study compared with 4 years after PTCA in the study of Austin et al, it is possible that any short-term influence of lipid fractions on the restenosis
rate may have been eliminated over a longer follow-up period.

Thus, it is conceivable that at least in a subset of patients, restenosis may reflect accelerated atherosclerosis and a low HDL cholesterol at the time of arterial injury may thus contribute to restenosis. The inverse relation between HDL cholesterol level and coronary artery disease has been attributed to the scavenger function of HDL cholesterol but could also be related to the inhibitory effects of HDL on platelet function and intimal proliferation.62–65 Favorable effect of lovastatin, a hypolipidemic drug, on the restenosis rate lends further credence to the potential role of lipid abnormalities in restenosis.66

Study Limitations

There are several limitations to this study that must be pointed out. First, coronary angiography was not performed in all patients; therefore, asymptomatic restenosis may have been missed in some patients. However, this possibility was minimized by considering restenosis to be absent only when in addition to lack of symptoms objective evidence of exercise-induced ischemia was also absent at last follow-up.67 Second, a single measurement of biochemical variables before angioplasty was used without serial measurements after angioplasty, which may have shed additional light on the relation between lipid subfractions and restenosis.

Despite these limitations, the strong statistical relation between pre–PTCA HDL levels and subsequent restenosis suggest the possibility of a causal relation.

Clinical Implications

If the results of this study are confirmed, the findings would justify evaluation of interventions that modify serum lipid fractions for reduction of restenosis after coronary angioplasty.

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