Association of Cholesterol Levels and Occurrence of Angiographically Detectable Endothelial Disruption during Coronary Angioplasty

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Summary

Background: Disruption of the atherosclerotic plaque is a common feature of both acute coronary syndromes and balloon dilatation of coronary artery stenoses.

Hypothesis: The study was undertaken to evaluate whether the known association of cholesterol levels and acute coronary syndromes also exists for the occurrence of angiographically detectable endothelial disruption (ED) following coronary angioplasty.

Methods: For this purpose, we examined 79 consecutive patients (men/women 58/21; mean age: 62 ± 11 years), with a noncalcified, de novo, significant stenosis in a single native coronary artery, undergoing elective coronary intervention because of stable effort angina. Coronary angioplasty was performed using regular balloon catheters, aiming for a balloon/artery ratio of 1, with stent implantation allowed only provisionally. Following balloon dilatation, patients were divided into two groups according to the presence or absence of angiographically detectable ED.

Results: Endothelial disruption occurred in 28 patients (35%). The two groups with and without ED were comparable with respect to clinical, angiographic, and procedural parameters. A history of hypercholesterolemia was significantly more frequent in patients with ED (93 vs. 2%; $p < 0.001$). Total and low-density lipoprotein (LDL) cholesterol levels were significantly higher in the group with ED (230.1 ± 46.5 vs. 204.4 ± 30.2 mg/dl, $p < 0.05$; and 150.6 ± 39.2 vs. $125.8 \pm$

26 mg/dl, $p < 0.03$, respectively). A cut-off value of LDL cholesterol ≥ 135 mg/dl identified patients at higher risk of developing ED.

Conclusion: High cholesterol levels appear to favor the occurrence of ED during coronary angioplasty. Aggressive lipid-lowering therapy and a more careful procedural approach may be warranted in patients with hypercholesterolemia undergoing coronary interventions in order to decrease the occurrence of ED and the associated clinical (acute ischemia) and procedural (stent implantation) consequences.

Key words: percutaneous coronary interventions, dissection, stent, hypercholesterolemia

Introduction

Spontaneous loss of integrity of the atherosclerotic plaque, with subsequent thrombus formation and impairment of coronary blood flow, is the basis for the clinical manifestations of acute coronary syndromes. While inflammatory and/or infectious injuries can act in weakening the atherosclerotic plaque, it is mechanical trauma that plays a fundamental role in promoting plaque rupture, since it commonly occurs at the site of greatest mechanical stress (represented by the junction between the fibrous cap and the adjacent normal intima).^{1–3} A correlation between cholesterol levels and the occurrence of acute coronary events has long been recognized. Also, reduction of cholesterol levels has been demonstrated to decrease the incidence of acute coronary events, most probably by means of a change in plaque composition and vulnerability rather than volume.^{4–6}

Disruption of the atherosclerotic plaque, with development of endothelial dissection, is also a consistent feature of balloon dilatation of coronary artery stenoses, representing one of the mechanisms along with stretching or tearing of the media and adventitia, leading to an increased luminal size.⁷ The occurrence of plaque fracture/endothelial dissection after balloon dilatation can lead to acute ischemic complications, since it may either extensively involve the arterial wall or promote the activation of the coagulation cascade, with subsequent thrombus formation and impairment of coronary blood flow. Furthermore, even when flow is not compromised, the devel-

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opment of an angiographically detectable plaque fracture/endothelial dissection commonly warrants stent implantation for the purpose of reducing restenosis.⁸ While clinical (absence of unstable angina), angiographic (long, eccentric, calcified, and irregular lesions) and procedural (balloon/artery ratio > 1.1) variables have been identified as predictors of plaque fracture/endothelial dissection during percutaneous coronary interventions,⁹ no relationship with cholesterol levels has been previously reported.

The aim of our study was, therefore, to determine whether there is a relationship between cholesterol levels and occurrence of plaque fracture/endothelial dissection during coronary balloon angioplasty.

Methods

All the patients consecutively undergoing elective percutaneous coronary intervention at the catheterization laboratory of Maggiore Hospital in Bologna, Italy, were considered for enrollment. Written informed consent was obtained before inclusion in the study. Inclusion criteria were stable effort angina and the presence in a single native coronary artery of a *de novo* (i.e., nonrestenotic), noncalcified, significant ($\geq 50\%$ diameter narrowing) stenosis. Exclusion criteria were (1) acute coronary syndrome (i.e., unstable angina or myocardial infarction), which is associated with a high prevalence of spontaneously ruptured coronary lesions; (2) restenotic or venous grafts lesions that do not have a pure atherosclerotic composition; (3) chronic total occlusion requiring a more aggressive dilatation technique that might be in itself responsible for the occurrence of endothelial dissection; (4) planned elective stent implantation, which is commonly associated with the use of undersized balloons and/or low inflation pressures.

The procedure of coronary angioplasty was carried out as standardized in our laboratory. In addition to the ongoing anti-ischemic drugs, pretreatment of patients included aspirin 100–165 mg/day and ticlopidine 250 mg twice daily, the latter started at least 48 h prior to the procedure. Upon introduction of coronary angioplasty hardware, an intravenous bolus of heparin 70 U/kg was given, while adjunctive boluses were subsequently administered, if necessary, to maintain an activated clotting time (ACT) of 200–250 s. Regular balloon catheters were used. The balloon size was chosen to achieve a balloon/artery ratio of 1 during inflation, as determined by quantitative coronary angiography (QCA) performed prior to the procedure (Philips Integris 5000 system, Philips Medical Systems/Agilent Technologies, Andover, Mass., USA). One or more inflations lasting 30 to 90 s were performed with the goal of achieving a residual stenosis < 30%. In the enrolled patients, stent implantation was allowed only provisionally to treat acute complications and/or suboptimal results following balloon dilatation.

Upon completion of the procedure, the presence/absence on angiography of plaque fracture/endothelial dissection was noted by each operator and then reviewed by a second investigator. It was defined as an angiographically visible intraluminal

filling defect, extraluminal opacity, or flap at the dilatation site. The plaque fracture/endothelial dissection was classified according to the National Heart, Lung and Blood Institute criteria¹⁰ as type A (radiolucent area within the lumen with minimal or no persistence of contrast), type B (parallel double lumen separated by a radiolucent area with minimal or no persistence of contrast), type C (persistent presence of contrast outside the coronary lumen), type D (spiral luminal filling defect), type E (new persistent filling defects), or type F (non A–E types leading to impaired flow or total coronary occlusion). Quantitative coronary angiography was then performed with respect to both angiographic (reference vessel diameter, stenosis length, percent stenosis, and minimal lumen diameter [MLD] before and after the procedure) and procedural (maximal inflation pressure, balloon/artery ratio) variables. For cases in which procedures had finished with stent implantation, the parameters considered were those after the last balloon inflation before stenting.

According to the presence/absence of angiographically detectable plaque fracture/endothelial dissection, the patients were subdivided into two groups. These groups were then compared with respect to age, presence of cardiovascular risk factors (current cigarette smoking, history of hypertension, hypercholesterolemia, and diabetes), treated vessel, lesion type (according to the American Heart Association/American College of Cardiology classification),¹¹ and measured angiographic and procedural parameters. Further comparison was also performed with respect to total, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglyceride levels as soon as these data were made available. To blind the operators to these values, blood sampling for lipid determination was performed only on the morning of the procedure. For the purposes of our study, hypercholesterolemia was defined as the presence of total cholesterol levels ≥ 190 mg/dl and/or LDL cholesterol levels ≥ 130 mg/dl.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation (SD) for continuous variables and as frequencies for categorical variables. Comparison between groups was performed using a Student's unpaired *t*-test or a chi-square statistics. A *p* value of < 0.05 was considered statistically significant.

Results

Between October 1999 and January 2001, 79 consecutive patients (58 men, 21 women, mean age 62 ± 11 years) were enrolled. Percutaneous coronary intervention was performed on the left anterior descending in 34 (43%) cases, the left circumflex in 25 (32%), and the right coronary artery in 20 (25%) (*p* = NS). In 60 (76%) cases, the coronary lesion was type A, in 18 (23%) type B₁ and in 1 (1%) type B₂ (*p* = NS). A history of hypercholesterolemia was present in 48 (61%) patients, and only 28 (58%) were treated with statins. Total cholesterol levels ≥ 190 mg/dl and LDL cholesterol levels ≥ 130 mg/dl were found in 56 (71%) and 42 (53%) patients, respectively.

TABLE I Epidemiologic characteristics and drug treatment of the two groups

	No endothelial disruption	Endothelial disruption	p Value
Patients (n)	51	28	
Age (years)	63 ± 12	61 ± 8	NS
Male (n) (%)	38 (75)	20 (71)	NS
Current smoker (n) (%)	18 (35)	12 (43)	NS
History of hypertension (n) (%)	30 (59)	10 (36)	NS
Diabetes (n) (%)	2 (4)	2 (7)	NS
History of hypercholesterolemia (n) (%)	2 (4)	26 (93)	<0.001
Beta blockers (n) (%)	44 (86)	28 (100)	NS
Calcium antagonists (n) (%)	22 (43)	10 (36)	NS
Nitrates (n) (%)	26 (51)	22 (79)	<0.05
ACE inhibitors (n) (%)	10 (20)	10 (36)	NS
Aspirin (n) (%)	51 (100)	28 (100)	NS
Ticlopidine (n) (%)	47 (92)	28 (100)	NS
Statins (n) (%)	16 (31)	12 (43)	NS

Abbreviations: ACE = angiotensin-converting enzyme, NS = not significant.

Overall, angiographically detectable plaque fracture/endothelial dissection occurred in 28 (35%) patients, 26 (93%) of whom had a history of hypercholesterolemia. Of the 48 patients with a history of hypercholesterolemia, 26 (54%) had plaque fracture/endothelial dissection, compared with only 2 (6%) of the 31 with no such a risk factor ($p < 0.005$). Plaque fracture/endothelial dissection was observed in 38 (68%) of the 56 patients with total cholesterol levels ≥ 190 mg/dl and in 4 (17%) of the 23 with values < 190 mg/dl ($p = \text{NS}$). Similarly, the occurrence of plaque fracture/endothelial dissection was observed in 22 (52%) of the 42 patients with LDL cholesterol ≥ 130 mg/dl, compared with 6 (16%) of the 37 patients with values < 130 mg/dl ($p < 0.05$). The lesion type was A in 20 (71%) patients, B₁ in 7 (25%) patients, and B₂ in 1 patient (4%). Stent implantation following balloon dilatation was per-

formed in 58 (73%) patients: 22 (79%) of the 28 with plaque fracture/endothelial dissection due to suboptimal result and/or presence of plaque fracture/endothelial dissection, and 36 (71%) of the 51 without plaque fracture/endothelial dissection due to suboptimal result ($p = \text{NS}$).

Comparison of the epidemiologic characteristics of the two groups with and without plaque fracture/endothelial dissection is reported in Table I. The two groups were comparable, except for a significantly higher rate of nitrate use (79 vs. 51%; $p < 0.05$) and a significantly higher prevalence of a history of hypercholesterolemia (93 vs. 4%; $p < 0.001$) in the patients with plaque fracture/endothelial dissection. No differences between the two groups were found with respect to the angiographic and procedural variables, as reported in Table II.

TABLE II Angiographic and procedural parameters in the two groups

	No endothelial disruption	Endothelial disruption	p Value
Treated vessel (n)			
LAD (%)	24 (48)	10 (36)	NS
LCx (%)	13 (25)	12 (43)	NS
RCA (%)	14 (27)	6 (21)	NS
Lesion type (n)			
A (%)	42 (82)	20 (71)	NS
B ₁ (%)	9 (18)	7 (25)	NS
B ₂ (%)	0 (0)	1 (4)	NS
Stenosis length (mm)	8.34 ± 2.06	8.09 ± 2.41	NS
Stenosis pre (%)	80.31 ± 10.21	81.39 ± 8.73	NS
Stenosis post (%)	22.94 ± 12.96	18.19 ± 12.18	NS
MLD pre (mm)	0.63 ± 0.32	0.53 ± 0.22	NS
MLD post (mm)	2.39 ± 0.61	2.55 ± 0.25	NS
Reference diameter (mm)	3.10 ± 0.60	2.97 ± 0.40	NS
Max. inflation pressure (atm)	10.23 ± 2.44	9.50 ± 2.44	NS
Balloon/artery ratio	0.99 ± 0.07	1.01 ± 0.05	NS
Stent implantation (n) (%)	36 (71)	22 (79)	NS

Abbreviations: LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery, MLD = minimal lumen diameter, NS = not significant.

FIG. 1 Mean ($\pm$ SD) values of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol and triglycerides in the two groups with and without plaque fracture/endothelial dissection.

In patients with plaque fracture/endothelial dissection, both total and LDL cholesterol levels were significantly higher than in those without (230.1 ± 46.5 vs. 204.4 ± 30.2 mg/dl, $p < 0.05$, and 150.6 ± 39.2 vs. 125.8 ± 26 mg/dl, $p < 0.03$, respectively) (Fig. 1). No differences were observed with respect to HDL cholesterol (46.3 ± 11.2 vs. 48.9 ± 13.1 mg/dl, $p = \text{NS}$) or triglycerides (156.2 ± 51.1 vs. 145.9 ± 61.1 mg/dl, $p = \text{NS}$) (Fig. 1).

By plotting the individual values of total cholesterol in all patients, a wide dispersion was observed, with no clear cut-off value that separated patients with from those without plaque fracture/endothelial dissection (Fig. 2). In contrast, when the individual values of LDL cholesterol were similarly plotted, it appeared that levels ≥ 135 mg/dl were associated with a significantly higher incidence of plaque fracture/endothelial dissection. It developed in 19 (56%) of the 34 patients with LDL

≥ 135 mg/dl, compared with only 9 (20%) of the 45 patients with LDL < 135 mg/dl ($p < 0.05$) (Fig. 3).

Discussion

The incidence of acute coronary syndromes, known to be sustained by spontaneous disruption of the atherosclerotic plaque, is higher in the presence of high cholesterol levels and is reduced by lowering cholesterol.⁴⁻⁶ Lipid-lowering therapy with statins has been shown to achieve a significant clinical benefit. The benefit of statin therapy appears mainly to be related to a change in plaque composition rather than volume, since coronary angiography has shown a minimal decrease in the severity of stenosis and increase in luminal diameter.⁴⁻⁶ More direct studies of plaque morphology using intracoronary ultrasound have confirmed the effects of statin therapy on plaque composition. In addition to a retardation of plaque growth, there was an increase in plaque hyperechogenicity (reflecting a decrease in the lipid or necrotic tissue) after prolonged treatment with atorvastatin.¹² Lipid-lowering treatment, therefore, appears capable of stabilizing atherosclerotic plaques by reducing the size of the atheromatous core. The size of the atheromatous core along with the thickness of the fibrous cap is known to play a major role in plaque vulnerability.¹⁻⁶ Additional evidence for a relationship between hypercholesterolemia and plaque composition comes from experimental animal studies in which sustained high cholesterol levels induced by cholesterol feeding resulted in plaques with a larger lipid core (and thinner fibrous cap).^{1, 4, 13}

While lipid-rich plaques are known to be vulnerable to spontaneous mechanical forces (inducing tension, compression or flexion, and therefore triggering the rupture),¹ there is no information on the response of those plaques to the jatrogenic trauma induced by balloon angioplasty. Our data sug-

FIG. 2 Distribution of the individual values of total cholesterol in patients with and without plaque fracture/endothelial dissection after balloon coronary dilatation. No cut-off value that discriminates between patients with and without endothelial disruption could be identified.

FIG. 3 Distribution of the individual values of low-density lipoprotein (LDL) cholesterol in patients with and without plaque fracture/endothelial dissection after balloon coronary dilatation. A cut-off value of 135 mg/dl appeared to discriminate between patients with and without endothelial disruption. Plaque fracture/endothelial dissection occurred in 56% of the patients above this value compared with only 20% of those below ($p < 0.05$).

gest the existence of a relationship between cholesterol levels and incidence of plaque fracture/endothelial dissection during coronary angioplasty. Under comparable angiographic and procedural conditions, in fact, significantly higher total and LDL cholesterol levels were found in patients who developed plaque fracture/endothelial dissection.

Even though the average total and LDL cholesterol were lower in patients without endothelial disruption, the individual values of both total and LDL cholesterol resulted to be highly variable in both groups of patients. By plotting the individual values of LDL cholesterol, which is the fraction actually depositing within the vessel wall, a cut-off value of about 135 mg/dl could be identified. However, considering all study patients with plaque fracture/endothelial dissection, an LDL ≥ 135 mg/dl had a positive predictive accuracy of only 44%. Thus, it appears not appropriate to rely on LDL cholesterol for the prediction of the occurrence of plaque fracture/endothelial dissection after balloon coronary angioplasty. Of greater importance is the observation that a history of hypercholesterolemia was present in almost all patients with endothelial disruption compared with less than half of those without such a history. This suggests that it may be the chronic exposure to high cholesterol levels that favors plaque vulnerability, presumably by increasing the lipid component of the atherosclerotic plaque. High cholesterol levels per se, found on a single measurement with no previous history, could just reflect the recent onset of hypercholesterolemia. Cholesterol levels probably need to be elevated for a sufficient time period to alter the lipid component of the plaque.

Lack of differentiation between chronic and recent onset hypercholesterolemia should be considered as one of the limitations of our study. This might explain why cholesterol levels were in general poorly predictive of plaque fracture/endothelial dissection in our patient cohort. The most important limitation, however, is the lack of use of more accurate intracoronary imaging techniques, such as ultrasonography or angioscopy, for plaque characterization and optimal detection of endothelial disruption. The suboptimal accuracy of angiography is, in fact, well known since it shows an incidence of plaque fracture/endothelial dissection ranging from 9 to 45%, compared with 50 to 80% observed in autoptic and intravascular imaging studies.¹⁴⁻¹⁸ Underestimation of the real incidence of plaque fracture/endothelial dissection, which was angiographically detectable in 35% of our population (and therefore comparable with previous studies),^{14, 15} could possibly weaken our conclusions. However, in routine clinical practice, angiography represents the reference technique for balloon angioplasty, and thus our findings maintain relevance.

Conclusion

We believe that our retrospective results should be regarded as hypothesis generating and, therefore, require prospective confirmation in a larger population. Confirmation of our findings has important clinical implications, such as the need for a more careful approach when performing coronary inter-

ventions on patients with elevated LDL cholesterol (especially when a history of hypercholesterolemia is present) or the widespread use of aggressive and prolonged lipid-lowering treatment before coronary intervention whenever possible. These strategies may allow for a reduction in the incidence of plaque fracture/endothelial dissection and associated clinical and procedural consequences, such as ischemic complications and need for stent implantation.

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