Editorial Comment

Lipids and Vascular Restenosis

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This issue of Circulation presents two interesting reports addressing the possible importance of plasma lipid and lipoprotein levels in vascular restenosis, which occur in a minority of the patients who undergo coronary angioplasty or carotid endarterectomy.1,2 Both articles present evidence suggesting that lipids may play a role in these processes.

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Coronary artery restenosis after angioplasty continues to affect about 30% of patients undergoing this procedure despite extensive efforts to reduce its incidence.3 Recurrent carotid artery stenosis after endarterectomy occurs in about 20% of these arteries, but functional impairment necessitating surgery develops in only a fraction of the cases.4,5 Whereas angioplasty and carotid endarterectomy produce different types of damage to the vessel wall, the reparative response to both kinds of insults is thought to involve an initial proliferation of smooth muscle cells within the intima and, in the case of angioplasty, within gaps in the old atherosclerotic plaques.6,7 This is followed later by deposition of collagen and in some cases lipids within the intima. In most cases, this intimal proliferative response is self-limited, but in a minority of instances the proliferation is more exuberant, resulting in a localized stenosis at that site. Because of the morphological resemblance of these restenoses to early atheromas and because hyperlipidemia is known to stimulate the development of intimal hyperplasia in rabbits,8 it has long been suspected that elevated plasma lipid levels may be involved in vascular restenoses associated with excessive intimal smooth muscle proliferation.

The case control study of Colyvas et al9 in this issue of Circulation presents strong evidence that those patients undergoing carotid endarterectomy who develop restenosis of sufficient severity to require reoperative endarterectomy exhibit widespread abnormalities of serum lipids. Elevations of total cholesterol, total triglycerides, and apolipoprotein (apo) B were observed in the 20 patients with restenosis as compared with controls, whereas high density lipoprotein cholesterol (HDL-C) was reduced in patients with restenosis. Multivariant analysis indicated that low density lipoprotein (LDL) apo B and HDL-C were independent predictors of restenosis. Interestingly, a high prevalence of the E4 allele of apo E was observed in restenosis patients. This allele has been reported to be associated with elevated levels of total cholesterol, LDL cholesterol (LDL-C), and apo B in the Finnish population.9 These findings are supported by the work of Sälenius et al10 who found that carotid endarterectomy patients with low cholesterol, low triglycerides, and high HDL-C had significantly less high-grade stenosis. Therefore, the limited evidence available to date suggests that lipid abnormalities may play a role in the development of hemodynamically significant restenosis after carotid endarterectomy.

The article in this issue by Shah and Amin1 presents evidence that lipids may also be involved in restenosis after coronary angioplasty. These authors studied 68 angioplasty patients, 28 (41%) of whom developed restenosis. A battery of serum lipids and lipoproteins—including total cholesterol, LDL-C, HDL-C, very low density lipoprotein cholesterol, and lipoprotein (a)—were examined as well as fibrinogen and circulating levels of endogenous tissue-type plasminogen activator (t-PA antigen) and plasminogen activator inhibitor (PAI-1 antigen and activity). Low HDL-C and PAI-1 levels were found to be independently and significantly related to restenosis. The finding of low PAI-1 levels in restenosis patients is seemingly paradoxical, as the authors acknowledge, because elevated levels of PAI-1 would be expected in a prothrombotic state. However, the association of low HDL-C with restenosis is in keeping with the findings of Colyvas et al2 in endarterectomized patients and supports the role of lipids in restenosis after angioplasty.

Nonetheless, the findings of Shah and Amin1 must be considered in the context of several other published studies on the subject of lipids and recurrent coronary stenosis. In an early study11 that examined results of a number of routinely obtained laboratory tests in 443 patients who underwent angioplasty, the only statistically significant difference in test results that we found between patients who developed restenosis and those who did not was a higher level of cholesterol in a subgroup of women who developed restenosis, than in the corresponding no-restenosis group. Myler et al12 described a history of hypercholesterolemia in the preceding 6 months as a risk factor for restenosis but provided no details about lipid fractions. More recently, in a study of lipids and lipoproteins and recurrent stenosis we found no association among total cholesterol, total triglycerides, LDL-C or HDL-C, apo A-1 or B, and restenosis.13 Arora et al14 in a study involving 723 angioplasty patients found that cholesterol levels at the time of angioplasty did not predict recurrent stenosis, whereas follow-up cholesterol levels showed an
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was significantly associated with restenosis. A recent Japanese study16 also reported higher levels of Lp(a) in patients undergoing restenosis than in those not suffering restenosis.

Several other studies addressing this question have so far appeared only in abstract form. Hirshfeld et al17 found no association between atherogenic risk factors and restenosis after angioplasty. Reis et a18 reported that, whereas lipid levels measured at the time of angioplasty were not significantly associated with restenosis, the total cholesterol/HDL-C ratio obtained 3–6 months after angioplasty was strongly associated with restenosis. Harlan et a19 found no association of lipids with restenosis except that HDL-C levels above 40 mg/dl were associated with a reduced restenosis rate. On the other hand, Bergelson et a20 reported small but statistically significant differences in a number of lipid and lipoprotein parameters between success and restenosis groups. Thus, whereas the report of Shah and Amin1 adds further evidence to the question of the role of lipids (lipoproteins) in restenosis after angioplasty, it seems clear that no consensus on this issue has yet emerged. Based on available evidence, it appears that except perhaps for patients with extremely high or low values, lipid levels at the time of angioplasty are not the principal determinants of whether restenosis will occur. This, of course, does not exclude the possibility that substantial manipulations of lipid metabolism may bring about a reduction in restenosis rates.

Two approaches have been used to try to accomplish this, both giving mixed results. The first approach has involved the administration of fish oil supplements containing ω-3 fatty acids to patients, starting at the time of angioplasty and continuing for 6 months thereafter. Studies by Dehmer et al21 and Milner et a22 reported significant reductions in restenosis rate in patients receiving ω-3 fatty acids compared with controls. However, Grigg et a23 and Reis et a24 in double-blinded, placebo-controlled studies failed to observe any reduction in the incidence of restenosis in the treated group. The divergent results do not appear to be easily accounted for by differences in the studies. The second approach, which has been employed to lower cholesterol levels, is to use lovastatin, a drug that inhibits the rate-limiting enzyme in cholesterol biosynthesis. Sahni et a25 in a study involving 157 patients found that lovastatin produced a significant reduction in restenosis rate (14%) compared with the control group (38%). However, Hollman et a26 in a preliminary report found that an aggressive lipid-lowering regimen consisting of diet, lovastatin, and colestipol applied in 55 consecutive angioplasty patients resulted in no reduction in restenosis rate compared with historical controls, despite lowering total cholesterol levels to an average of 130 mg/dl.

Why should the role of lipids in restenosis after coronary angioplasty appear less clear than their role in restenosis after carotid endarterectomy? To begin with, the processes differ in significant respects. For example, dissection and other damage to the media are much more prominent in angioplasty than in endarterectomy and may affect lumen diameter. Also, recurrent stenosis after coronary angioplasty, if it develops, usually occurs within 6 months, whereas restenosis after carotid endarterectomy may take several years to develop to the point where functional impairment results, allowing time for lipid accumulation in the lesions to take place. Another possibility is that, because of the larger caliber of the carotid arteries than the coronaries, only the most severe carotid restenoses come to reoperation, and these may be the ones associated with the greatest lipid abnormalities.

In summary, the studies of Colyvas et a2 and Shah and Amin1 add significant new information about the relation between serum lipids and arterial restenosis after carotid endarterectomy and coronary angioplasty. However, much additional work is needed to resolve the numerous discrepancies in the literature and to extend our understanding of the ways in which lipids may stimulate smooth muscle cell proliferation before a clear understanding of the role of lipids and lipoproteins in the development of vascular restenosis will emerge.

References
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