Reversal of Atherosclerosis and Sclerosis

The Two Components of Atherosclerosis

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This review of atherosclerosis reversal considers two major features of the disease, atherosclerosis and sclerosis. In 1904, Marchand recognized the consistent association of fatty degeneration and vessel stiffening and introduced the term atherosclerosis to indicate this combination. Current research is focused principally on the lipid component (atherosclerosis), and the sclerotic component of the disease receives less attention because typical reversal experiments evaluate lesions by histopathology in animals or by serial angiography in humans. In either case, the standard methodology used is sensitive to the atheromatous component and does not adequately evaluate the sclerotic component. However, when measurements of arterial elasticity are made in atherosclerotic animal models and humans, the coexistence of atherosclerosis and sclerosis is confirmed.

Factors Influencing Atherosclerosis Reversal

Atheromatous aspects of the disease are prime targets for reversal because lipids add significantly to the volume of lesions and thus contribute to vascular obstruction and end-organ damage. Cholesterol, cholesterol esters, and phospholipids compose up to 60% of the dry weight of advanced lesions. The bulk of lesion cholesterol, except for crystalline cholesterol monohydrate and cholesterol trapped by altered connective tissue, exchanges with plasma cholesterol, and so reduction of plaque cholesterol should occur when plasma cholesterol levels are reduced. During the final stages of lesion progression, a major accumulation of free cholesterol occurs either as a supersaturated solution or in a variety of crystalline states. The exchange of plasma cholesterol with cholesterol monohydrate crystals in plaques is too slow to be measured, and so any local event that precipitates these crystals will reduce the potential for reversal. Also, cholesterol monohydrate crystal can induce necrosis and fibrosis in plaques that contribute additional risk of vascular obstruction.

The fatty acids esterified to cholesterol in plasma and plaques reflect the habitual fatty acid composition of diet. In typical advanced atherosclerotic lesions, cholesterol esters are predominantly oleic and linoleic, but there is much individual variation. When atherosclerosis is induced in animals the fatty acid composition of diet may alter the severity and reversibility of lesions independent of any effect on plasma cholesterol level. For example, peanut oil enhances the effect of cholesterol feeding increasing lesion severity and fibrosis.

Evidence for Reversal of Atherosclerosis in Animals

Reversal of atherosclerosis has been observed in all the major species used in atherosclerosis research: rabbits, swine, dogs, chicks, pigeons, and subhuman primates. Animal model reversal evidence is based on groups compared after sacrifice except in dogs where DePalma et al. followed progression and regression by repeated laparotomy to inspect abdominal lesions. Subhuman primates are preferred animal models for regression studies because they develop lesions that closely mimic the human disease. The atherosclerotic Macaque has been shown to develop xanthomata, myocardial infarction, and cerebral ischemia and stroke (if there is concurrent hypertension).

In the 1970s, unequivocal reduction of coronary lesion size in rhesus and cynomolgus monkeys accompanied by reduction in arterial lipid content was demonstrated. This occurred when hypercholesterolemic diets were withdrawn. However, removal of lesion collagen occurred slowly and only in carotid and femoral arteries, not in aorta, subclavian, or coronary arteries. Fibrolysis in regressing lesions appeared to affect only some new intimal collagen fibers, whereas others escaped and matured into thick heavily cross-linked scars resistant to lysis. In other experiments with advanced dietary atherosclerosis, arterial collagen content was increased even after prolonged regression periods.
In very early arterial lesions, regression is more readily achieved, and Stary\textsuperscript{30} observed normalization of cell kinetics after returning monkeys to a basal diet for 3–10 months. Reparative changes included a measurable decrease in intracellular lipid and a return to normal cellular proliferative patterns. Initial signs of disease reversibility were seen as soon as 4 weeks after serum cholesterol had returned to baseline levels. Foam cell production stopped, and normalization of smooth muscle cell morphology was observed.

In addition to drugs\textsuperscript{19,20} given during the period of hypercholesterolemic diets, exercise has been shown to reduce the severity of resulting lesions in monkeys through diminished overall lesion development, reduction of intimal thickening, reduction in lesion collagen, and widening of the coronary artery lumen.\textsuperscript{31} After lesions have been induced, there is pilot data in monkeys indicating that exercise can also produce beneficial effects.\textsuperscript{32}

**Controlled Trials of Reversal of Atherosclerosis in Humans**

Duffield and coworkers\textsuperscript{33} conducted an unblinded, but randomized, study of femoral atherosclerosis in patients with claudication. Patients with diabetes, diastolic hypertension, and rest pain in the legs were excluded. There were 12 drug-treated patients (eight Fredrickson Type II, three Type III, and one Type IV hyperlipoproteinemia) and 12 “usual care” patients whose lipids were untreated (eight Type II, one Type III, and three Type IV hyperlipoproteinemia). Type II patients were treated with 12–24 g/day of cholestyramine plus 3–6 g niacin. Type III patients were treated with clofibrate; Type IV patients were treated with niacin. Femoral angiograms were performed at entry and after 13 months. In the interval between angiograms, total blood cholesterol levels averaged 233 mg/dl in treated compared with 287 mg/dl in usual care patients, triglyceride 163 mg/dl in treated compared with 260 mg/dl in usual care, high-density lipoprotein (HDL)-cholesterol 59.6 mg/dl in treated compared with 42.3 mg/dl in usual care, and low-density lipoprotein (LDL)-cholesterol 150 mg/dl in treated compared with 197 mg/dl in usual care. In drug-treated patients, 10 among 144 1-cm femoral segments showed lesion progression, and in usual care patients, 27 among 156 such segments showed progression (p<0.01). The number of subjects was too small to analyze trial on the basis of response for each patient.

The National Heart, Lung, and Blood Institute Type II Study as reported by Brensike et al\textsuperscript{34} tested the effects of 24 g cholestyramine on coronary atherosclerosis in subjects with Type II hyperlipoproteinemia and overt coronary disease. It was randomized, placebo controlled, and double blind. Average entry levels were total cholesterol, 323 mg/dl; triglyceride, 164 mg/dl; HDL-cholesterol, 39 mg/dl; and LDL-cholesterol, 251 mg/dl. A low-fat diet reduced LDL-cholesterol levels 5% in each group. During the interval between angiograms, LDL-cholesterol levels in the placebo group were reduced an additional 5%, and LDL-cholesterol levels in the cholestyramine group were reduced 26%. Originally, 250 subjects were planned, but recruitment was stopped after 54 months when 143 patients had been randomized. Angiograms were first repeated after 2 years in 31 subjects, but when apparent change was found in only nine, the schedule for repeat angiograms was lengthened to 5 years. Coronary angiograms from 116 subjects (57 placebo-treated and 59 cholestyramine-treated) were eventually evaluated in pairs with the temporal sequence and treatment masked.

Definite progression occurred in 35% of placebo compared with 25% of drug-treated patients. Probable progression was found in 14% of placebo compared with 7% drug treated. Definite regression was found in 2% of placebo compared with 3% of drug treated. A mixed response with lesions changing in opposite directions in the same subject was found in 2% of placebo and 8% of drug-treated patients. The investigators concluded that there was suggestive evidence that cholestyramine retarded the progression of coronary atherosclerosis. An additional conclusion drawn after baseline demographic inequalities and lesion severity were taken into account was that a treatment effect could be demonstrated in lesions with 50% or more stenosis. In placebo patients, 33% of such lesions showed progression compared with 12% in cholestyramine-treated patients (p<0.05).

The Cholesterol Lowering Atherosclerosis Study (CLAS) evaluated angiographic endpoints in native coronary arteries, aortocoronary venous bypass grafts, and femoral and carotid arteries. It was placebo controlled but not double blind.\textsuperscript{35} One hundred eighty-eight nonsmoking men aged 40–59 years with previous coronary bypass surgery were randomized to drug plus diet or placebo plus diet. One hundred sixty-two completed two angiograms. At entry, total plasma cholesterol levels ranged from 185 to 350 mg/dl and averaged 245 mg/dl. Average LDL-cholesterol on entry was 170 mg/dl, and average HDL-cholesterol was 44 mg/dl. Combined colesterol plus niacin therapy produced 26% reduction in total plasma cholesterol levels (to 180 mg/dl), 43% reduction in LDL-cholesterol levels (to 97 mg/dl), and simultaneous 37% elevation of HDL-cholesterol levels (to 61 mg/dl).

Drug treatment reduced 2-year progression of atherosclerosis in native coronary arteries, both in average number of lesions that progressed per subject (p<0.03) and in the percentage of subjects with new atheroma formation (p<0.03). Among 80 drug-treated subjects, eight (10%) developed new native coronary lesions; among 82 placebo-treated subjects, 18 (22%) developed new native coronary lesions. Drug treatment also significantly reduced the percentage of subjects with any adverse change
(p < 0.03) and percentage of subjects with new lesions (p < 0.04) in bypass grafts. Fourteen (18%) among 80 drug-treated subjects developed new graft lesions; 25 (30%) among 82 placebo-treated subjects developed new graft lesions. Perceptible improvement in overall coronary status occurred in 16.2% of colestipol-niacin-treated subjects compared with 2.4% of placebo-treated subjects (p = 0.002). Evidence for benefit retained strong statistical significance after our results were divided to compare treatment effects separately when entry cholesterol levels were above or below 240 mg/dl.

CLAS evidence implicates the entire range of cholesterol levels between 185 and 350 mg/dl as coronary risk factors. It should be noted that all subjects in this trial were nonsmokers during the experimental period, and average blood pressure levels were within the range of normal. Also, drug-treated CLAS subjects had more changes in blood lipid levels for longer periods than in any previous trial.

Factors Influencing Sclerosis and Its Reversal

Clinical effects of sclerosis are more subtle than those of atherosclerosis, and there is little evidence that sclerosis alone leads to end-organ damage. To emphasize this difference between sclerosis and atheromatosis, Pickering reported the case of a physician runner with calcified lower leg vessels. Calcification of the dorsalis pedis artery was found by radiography when he injured his foot at age 40. Twenty-five years later, he was still asymptomatic while running but had radiographic evidence of calcification in all arteries below the knee. Biopsy of the dorsalis pedis at age 65 showed Monckeberg’s medial calcification, and at the time of Pickering’s report, he could run a mile without symptoms at age 79. However, it should be noted that atherosclerotic intimal lesions producing symptoms or end-organ damage invariably have a major fibrous component. Increased lesion collagen and destruction of medial elastin plus compositional changes in these fibrous proteins are important mechanisms underlying sclerosis in atherosclerosis. Pure sclerosis (lipid deposition alone) such as occurs in fatty streaks does not produce end-organ damage but may contribute to sclerosis by an effect on endothelium-derived relaxant factor (EDRF), as discussed later.

The majority of sclerotic vessels are not calcified (by radiographic examination) but have reduced systolic expansion and abnormally rapid pulse wave propagation. In both normal and sclerotic vessels, the increase in vessel volume is greater for equal increments of pressure at diastolic than systolic pressures, and so vessel sclerosis measurements must be corrected for ambient intra-arterial pressure. Elastin, plus smooth muscle, determine vessel volume responses at lower pressures, but collagen predominates at high pressure.

Pressure and velocity pulse wave propagation rates are predictable from pressure volume measurements. High-frequency intrarterial pressure pulse wave transmission rates differ at systolic and diastolic pressures and can be free of artifact from reflected waves. Noninvasive pulse wave propagation procedures are less sophisticated but adequate to detect sclerosis due to atherosclerosis and differentiate this from sclerosis of other origin. The propagation rate of the pressure pulse can be measured with surface transducers from carotid, brachial, femoral, popliteal, and dorsalis pedis arteries. Pulse wave arrival times from the heart (measured from the electrocardiograph R wave) are usually more reproducible than pulse wave transmittal times between two vessel sites because it is difficult to measure short vessel lengths from the body surface. Arrival times based on the electrocardiogram include a period of cardiac ejection that is typically considered to be constant and factored out when comparing arrival times at two peripheral sites. This assumption can introduce significant error when heart rates are not regular.

The propagation of a velocity pulse can be measured by ultrasound and has the advantage that deep vessels can be studied. Ultrasound imaging has been used to measure local vessel sclerosis by evaluating local vessel diameter change. The procedure most commonly used in population surveys uses Ep, a modulus of elasticity calculated from diameter change. Ep is determined with data that normalizes for pulse blood pressure and vessel size differences between subjects but assumes that pulse pressure in the imaged vessel is identical to brachial artery pressures and does not correct for average blood pressure levels.

Age alone causes loss of vascular elasticity; young vessels retract to significantly shorter lengths than do old vessels when removed at autopsy. Pressure volume and pulse wave velocity measurements in arterial segments free of visible atherosclerosis indicate an average loss of compliance with increasing age; there is also a redistribution of the relative stiffness among vessels. In young subjects (11–20 years old), the thoracic aorta and carotid arteries are the most compliant large vessels; iliac and femoral arteries are the least compliant with the abdominal aorta intermediate. In older subjects (36–52 years old), there is overall loss of vascular compliance, and the gradient of compliance from central to peripheral vessels is reduced by dilation of the aorta and carotid arteries plus increased wall thickness in iliac and femoral arteries. In rural China, where atherosclerosis is rare, increasing age is associated with increased pulse wave velocity. Recognition of atherosclerotic vessel stiffening relies on detection of vessels too stiff for the individual’s age.

Atherosclerosis rarely occurs in forearm vessels, so demonstration of reduced brachial artery compliance in young hypertensive subjects is persuasive evidence of an effect of hypertension independent of age and atherosclerosis. In vivo measurements of forearm arterial distensibility in asymptomatic hypertensive
subjects indicate reduced compliance compared with nonhypertensive subjects.\textsuperscript{41,57} In one of these studies, average transmural pressures were brought to a common level in hypertensive subjects and controls by placing the forearm in a pressure chamber.\textsuperscript{51} Intraarterial measurements of pulse wave velocity indicate loss of both systolic and diastolic compliance in borderline and established hypertension.\textsuperscript{57} In animal models, both increased collagen and elastin plus change in the composition of each may play a role in reducing arterial compliance.\textsuperscript{58,59} Reversal of fibrous plaques, along with reduction of calcium, collagen, and elastin, has been demonstrated with calcium antagonists but only in rabbits.\textsuperscript{60} It is of interest that some calcium antagonists, as well as calcium entry blockers in clinical use, have been found to reduce diet-induced atherosclerosis in rabbits\textsuperscript{60} and cynomolgus monkeys\textsuperscript{61} without reducing elevated plasma lipid levels and with greatest effect on arterial wall connective tissue. Atherosclerosis in hypertensive subjects causes additional loss of compliance. A nomogram plotting pulse wave velocity against the product of age times blood pressure in healthy volunteers has been published by Maarek and coworkers.\textsuperscript{62} With this approach, hypertensive subjects with more rapid pulse wave velocity measurement were shown to have increased prevalence of significant carotid artery stenosis.\textsuperscript{62}

Diabetes mellitus with chronic elevation of blood glucose levels produces vascular sclerosis as part of widespread connective tissue damage.\textsuperscript{8} Nonenzymatic glycosylation of many proteins occurs in vivo at rates that are proportional to ambient glucose level. The degree of glycosylation of short-lived proteins such as hemoglobin reflects recent blood glucose levels, but glycosylated products can accumulate for many years in long-lived proteins such as vascular, articular, and lens collagen. Glycosylation reduces the elasticity of connective tissue in skin, joints, eyes, and blood vessels.\textsuperscript{63} In blood vessels, glycosylation can also lead to LDL-cholesterol trapping and contribute to atherosclerosis as well as sclerosis.\textsuperscript{8} Pulse wave velocity is increased in diabetics compared with normal controls.\textsuperscript{49}

Sclerosis and atherosclerosis may interact to influence local events in the atherosclerotic lesion. In 1953, Crawford and Levene\textsuperscript{64} suggested that aortic plaques might be compressed into the media during systole causing focal atrophy. Although they made this suggestion as a result of vessels studied when removed at autopsy\textsuperscript{64} and what happens to aortic plaques in vivo remains unknown, significant differences in pulsation have recently been observed in vivo by ultrasound imaging that compared carotid plaques with adjacent normal carotid wall.\textsuperscript{51} It is also known that when prosthetic vascular grafts are placed at surgery, the compliance of graft and artery must match, or connective tissue overgrowth will occur at the site of anastomosis.\textsuperscript{65} If lesion hardening leads to compliance mismatch between plaques and adjacent arterial wall, this might also stimulate tissue growth reactions at plaque edges leading to enlargement of the plaque. Platelet-derived growth factor (PDGF) is known to stimulate smooth muscle proliferation and production of fibrous connective tissue by smooth muscle in plaques\textsuperscript{66} but has been considered a systemic factor delivered from circulating platelets. However, recent evidence indicates that smooth muscle cells within plaques can also synthesize PDGF.\textsuperscript{67} Further, functionally altered endothelial cells and macrophages exposed to atherogenic stimuli are also capable of producing similar growth factors.\textsuperscript{66} Because local controls for plaque growth factors exist, local events such as compliance mismatch could influence progression and regression.

Evidence for Reversal of Sclerosis

First evidence for reversal of the sclerotic component of atherosclerosis came from cholesterol feeding experiments by Farrar et al\textsuperscript{12,44} in normotensive non diabetic rhesus and cynomolgus monkeys. Aortic pressure pulse wave velocity was significantly increased after 18 months of lesion induction at a time when lesions were estimated to cover 80\% of the intimal surface. The increase in pulse wave velocity did not appear until after 12 months of cholesterol feeding when lesions covered 35\% of aortic surface, and changes in pulse wave velocity could not be explained by changes in either aortic wall collagen or elastin content. Twenty-four months after cholesterol feeding was withdrawn, aortic pressure pulse wave velocity returned to levels seen before cholesterol feeding, and aortic lesions were reduced to cover only 35\% of the intimal surface.\textsuperscript{64} Farrar et al concluded that change in pulse wave velocity reflected changes in aortic atherosclerosis after fibrous and fatty plaques covered 35\% of the aortic surface.

Similar cholesterol feeding experiments in cynomolgus monkeys as reported by Harrison et al\textsuperscript{68} have indicated that the sclerosis reversal may be mediated by EDRF. These studies indicate that intimal lesion formation reduces production or delivery of EDRF but leaves the medial muscle still sensitive to it. Similar conclusions were reached by Ludmer et al\textsuperscript{69} from coronary angiographic studies in humans. Armstrong et al\textsuperscript{3} have shown that medial architecture is altered with cholesterol feeding and does not return to normal with lesion regression. Resumption of EDRF production by the healing but still-thickened intima may account for reduction of sclerosis without reversion to normal architecture.\textsuperscript{3,70} Harrison et al\textsuperscript{68} suggests that increased production of EDRF in coronary arteries after reduction of plasma cholesterol could improve angina without reducing lesion size.

The question of sclerosis reversal in humans has not been examined with rigor; studies to date have typically been short-term investigations of vessel physiology or population surveys where each subject is studied once. Transient increases of arterial compliance without changes in blood pressure have been reported with calcium channel blockade in
brachial artery\textsuperscript{71} and in femoral artery with oral isosorbide dinitrate.\textsuperscript{50} Avolio et al\textsuperscript{72} suggest that a low-salt diet may improve arterial compliance. They found that pulse wave velocity in adults and children who had eaten a low-salt diet for an average of 25 months was significantly slower than in age-matched controls drawn from a previous group of volunteers. Unfortunately, the number of subjects studied by Avolio et al did not allow adequate age matching, and there were no observations in the same individual on and off a low-salt diet. Confirmation of this result would suggest that alterations of smooth muscle tone may also contribute to changes in arterial compliance and sclerosis. The ease with which serial studies of sclerosis can be done in humans has been known for more than 25 years,\textsuperscript{49} but observations for periods comparable to the primate studies of Bond and Armstrong have not been reported.

Conclusions

The sclerotic and atherotic components of atherosclerosis are closely linked, and both are adversely affected by elevated blood cholesterol, hypertension, and diabetes. Both components have been shown to be reversible in animal models. The balance between atherosclerosis and sclerosis measured at one time appears to vary from one individual to the next, and whether the two measures “track” each other with any degree of consistency during progression and regression remains unknown. Studies by Farrar et al\textsuperscript{44} suggest that tracking in the aorta may occur when atherosclerosis exceeds a threshold of 35\% lesion coverage. Reversal of atherosclerosis appears to be the key to reduction of end-organ damage, but reversal of sclerosis is desirable. Angiographic imaging is now used to track intra-luminal lesion volume in controlled human reversal trials but could usefully be augmented by imaging sensitive to other aspects of atherosclerosis. A long-range goal should be to link what can be learned by histopathology of animal studies of atherosclerosis reversal with clinical trials in humans.

Measurements of sclerosis are noninvasive and well suited to repeated evaluation of the same subject. So far, they have only been used for short-term studies or as one-time substitutes for imaging where sclerosis is considered a surrogate for atherosclerosis. Recent results of cholesterol feeding in primates suggest that it is more logical to measure both atherosclerosis and sclerosis in parallel and evaluate both aspects of reversal at the same time. Sclerosis measurements have potential advantage over imaging in epidemiologic research because they can be simple and robust under field conditions. Sclerosis measures could also add to imaging in controlled trials to evaluate long vessel segments.

The current outlook for atherosclerosis control is promising; we know that mortality from coronary heart disease can be reduced\textsuperscript{73,74} and that the underlying coronary lesions can be improved by treatment.\textsuperscript{35} For efficient control of atherosclerosis, lesion stabilization and reversal should begin as early as possible; the importance of early intervention is well established by animal studies. Although current trials of atherosclerosis regression are directed at raised symptomatic coronary lesions, an ideal approach would attempt reversion when asymptomatic raised lesions appear in adolescents or young adults. At present, noninvasive procedures for the coronary arteries lack sufficient precision, but other vessels could be studied. The abdominal aorta would be one promising target because fatty streaks progress to raised lesions here in parallel with similar events in the coronary arteries.\textsuperscript{75} The aorta is accessible to measures of sclerosis and could be imaged noninvasively to evaluate atherosclerosis. Another possible target vessel might be the carotid artery because sclerosis occurs here in adolescents and can be detected by elastic modulus measurements. Abnormal Ep values are more common in children of families with high risk factor levels.\textsuperscript{76} Also, a case of lesion reversal detected by ultrasound imaging in the carotid artery has been reported.\textsuperscript{77} The possibility of conducting clinical trials in young adults where both sclerosis and atherosclerosis is evaluated in parallel by noninvasive means should be given serious consideration.

Summary

In 1904, Marchand\textsuperscript{4} recognized the consistent association of fatty degeneration and vessel stiffening and introduced the term “atherosclerosis” to indicate this combination. Current research is focused principally on the lipid component, but there is evidence that both aspects are reversible. Atheromatous lipids add significantly to the volume of lesions and thus contribute to vascular obstruction and end-organ damage. Reversal of atherosclerosis has been observed in all the major species used in atherosclerosis research; rabbits, swine, dogs, chicks, pigeons, and subhuman primates. Direct evidence for reversal in humans is based on angiographic trials and is less extensive. One femoral artery and one coronary artery trial indicate that the lesions can be stabilized. CLAS, the largest angiographic trial to date, indicates that coronary lesion reversal is possible.

Clinical effects of sclerosis are more subtle, and there is little evidence that sclerosis alone leads to end-organ damage. However, it should be noted that atherosclerotic lesions producing end-organ damage invariably have a major fibrous component. Sclerotic vessels have reduced systolic expansion and abnormally rapid pulse wave propagation, which can be measured noninvasively. Primate studies indicate that sclerosis is induced by hypercholesterolemic diets and is reversible when these diets are withdrawn. Changes in sclerosis may be another useful indicator of the formation and reversal of lesions and may involve changes in EDRF. Future studies of atherosclero-
sis reversal should use a combination of measures to evaluate both atherosclerosis and sclerosis.

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