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Atherosclerosis: Making a U Turn

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Abstract

The development of potent cholesterol-reducing medications in the last decade of the twentieth century has altered the approach to prevention and treatment of cardiovascular disease (CVD). Initial experience with statins, and more recently with the addition of PCSK9 inhibitors, has proven that human CVD, like that in animal models, can be halted and regressed. Available clinical data show that the lower the achieved level of low-density lipoprotein cholesterol, the greater the regression of disease. Investigative studies are now aimed to understand those factors that both accelerate and impede this healing process. Some of these are likely to be modifiable, and the future of atherosclerotic CVD treatment is likely to be early screening, use of measures to repair atherosclerotic arteries, and prevention of most CVD events.

INTRODUCTION

Although the description of atherosclerosis as a disease associated with excess lipid, primarily cholesterol accumulation within the artery, traces back to the nineteenth century, our understanding that this disease can be cured dates to the mid-twentieth century. Studies in animals and in occasional patients described the reduction of atherosclerosis and the opening of partially occluded arteries with manipulations that markedly reduced circulating levels of cholesterol-containing lipoproteins (1).

More recently, potent cholesterol-reducing medications and the development of improved noninvasive methods to assess vascular disease have confirmed that it is possible to cure, or at least reduce, atherosclerosis. To determine the mechanisms for this, investigative studies first required an animal model that would develop high circulating levels of cholesterol and atherosclerotic lesions. Rats do not develop high levels of cholesterol when their dietary cholesterol is markedly increased; this is because the rat liver reduces its cholesterol biosynthesis (2). In contrast, cholesterol-fed rabbits develop atherosclerosis, in part due to a relative deficiency of hepatic lipase (3), the final enzyme in chylomicron and VLDL (very-low-density lipoprotein) metabolism. Regression was first illustrated in this model when investigators showed that a change back to a standard rabbit diet reduced cholesterol-rich arterial plaques (4). Subsequently, studies in monkeys and pigs (1) confirmed the bidirectional changes in atherosclerotic plaque size associated with changes in blood cholesterol (**Figure 1**). Studies in rabbits also illustrated that the size and/or the composition of lipoproteins was critical for atherosclerosis development. This was accidentally discovered

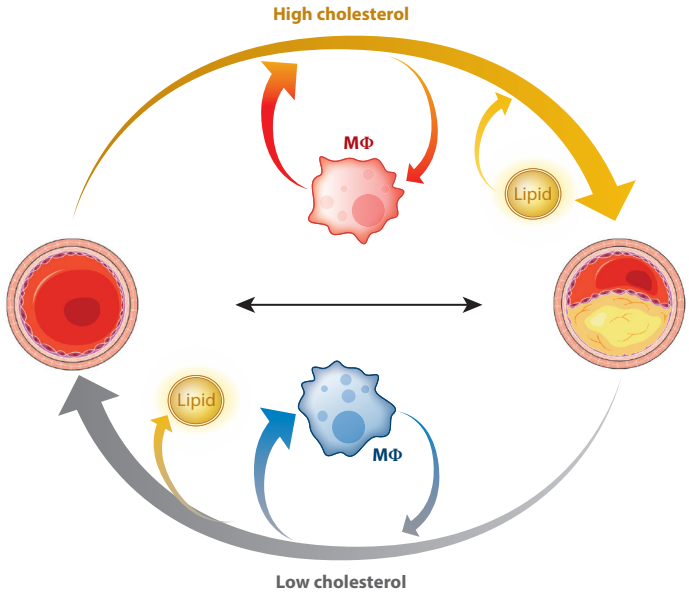

Figure 1

Cholesterol effects on atherosclerotic lesion biology. Hypercholesterolemia, found in the circulation of most adults in the western world, leads to lipid collection within the arterial wall (*yellow arrow*). This promotes or is accompanied by the influx of inflammatory macrophages (indicated in *red*). But atherosclerosis is reversible (*gray arrow*). Marked reductions in cholesterol reduce the lipid content of the atherosclerotic plaque. Repair also requires the influx of alternatively activated or reparative macrophages (shown in *blue*) and an increase in arterial collagen. A more stable lesion results, which in humans translates to a reduction in acute clinical events.

in an investigation of the relationship between atherosclerosis and diabetes; diabetic rabbits have reduced disease despite increased circulating cholesterol and triglyceride levels (5). The reason for this is that the circulating lipoproteins, primarily chylomicrons, are too large to enter the arterial wall (6).

Mice can be genetically altered to lack apolipoprotein (Apo)E, which is required for clearance of partially metabolized (remnant) lipoproteins; to lack the low-density lipoprotein receptor (LDLr); or to overexpress ApoB. Such mice become hypercholesterolemic and develop atherosclerosis, especially when fed a diet that contains large amounts of cholesterol and saturated fat. These single genetic variations are sufficient to create atherosclerosis in animals that are otherwise atherosclerosis resistant. Thus, the only ingredient required to produce atherosclerotic lesions is an elevated level of ApoB lipoproteins.

Within the past decade, a number of methods have been developed to explore the biology of atherosclerosis regression in mice (7). Switching from a high-cholesterol to a chow diet allows regression in some models, and usually requires blood cholesterol reductions to less than 200 mg/dl. Transplant of aortic segments with lesions that have developed in hypercholesterolemic mice into mice with low (i.e., normal) cholesterol levels leads to regression. Other regression methods entail genetically reversing hypercholesterolemia (8, 9). As noted below, these experiments have defined many of the biological processes involved in normal and defective regression.

EVIDENCE FOR REGRESSION IN HUMANS

That atheroma can regress in humans has been suggested by autopsy studies after famine and in the setting of chronic wasting disease, including cancer (10–13). Regression has been subsequently confirmed by coronary angiography. As early as the mid-1960s, the first prospective, interventional study of niacin therapy demonstrated improved femoral angiograms (14). Since then, lipid-lowering therapy and intensive lifestyle changes have shown significant angiographic regression of coronary atherosclerosis. The reductions in clinical events are greater than might be predicted from the relatively small changes in lesion size (15–22), with >50% reduction in events in subjects with metabolic syndrome and >80% reduction in others (23). This surprise may be explained by the stabilization of high-risk, lipid-rich, thin-cap atheroma (vulnerable plaques), rather than significant reduction in overall plaque area. This stabilization and reversal have been demonstrated by several invasive and noninvasive imaging modalities (below), highlighting that compositional changes in plaque independent of size changes may be worthwhile to achieve.

Some studies have evaluated only the most severe proximal lesions of the major vessels (24–27), whereas others have included all lesions (28–31), comparing each lesion and/or a global change score of all lesions. As can be expected, more dramatic regression has been noted when fewer, more severe lesions were followed over time (32), which overall has made comparison of these studies challenging. Regardless, regression has been visualized by coronary angiography and has since been confirmed by other invasive and noninvasive imaging modalities as well.

Beyond angiography, intravascular ultrasound (IVUS) offers direct imaging of the artery wall, including the intima, media, and external elastic lamina, with some ability to characterize plaque composition and volume. In several large prospective randomized clinical trials of lipid-lowering therapy in patients with stable coronary artery disease, IVUS has demonstrated plaque regression as measured by percent atheroma volume (PAV) and total atheroma volume (TAV). Higher-intensity statin therapy is associated with small but significant improvements in PAV and TAV paralleling significant reductions in LDL cholesterol, particularly in the lowest LDL cholesterol levels (below 88 mg/dl) (33–36). Addition of ezetimibe to statin therapy results in significantly more regression than high-intensity statin therapy alone (37). More recently, a large randomized

trial of the PCSK9 inhibitor evolocumab showed significant reductions in PAV and TAV with mean LDL cholesterol below 40 mg/dl, as compared with progression on statin therapy with mean LDL cholesterol of approximately 90 mg/dl (38). A meta-regression of 11 randomized trials including >7,000 patients showed that at a median of 18 months of follow-up, the rates of plaque volume regression were significantly associated with the incidence of myocardial infarction or revascularization but not with major adverse cardiovascular events (39). Moreover, these IVUS studies have shown evidence of greater regression as LDL cholesterol is lowered well below 70 mg/dl (40).

More limited outcomes benefit with plaque regression has also been demonstrated by carotid ultrasonography. Carotid intima media thickness is a validated measure of carotid atherosclerosis that predicts future cardiovascular events (41). Several randomized trials of lipid-lowering therapy (particularly niacin) have shown significant regression of carotid intima media thickness (41–45) with some associated reduction in clinical cardiovascular events (46); however, larger-scale studies demonstrating reduction in events are lacking.

Other imaging techniques have shown regression as well but lack outcomes data. Optical coherence tomography is a newer intravascular imaging technique that provides higher resolution than IVUS, especially in its ability to image the intima, and thus better visualizes high-risk, thin-cap fibroatheroma, at the expense of poorer definition of the external elastic lamina. To date, one prospective randomized trial has evaluated patients with angina and intermediate, lipid-rich plaque by optical coherence tomography before and after therapy with ezetimibe and fluvastatin versus fluvastatin alone. After nine months, fibrous cap thickness significantly increased in both groups, but the change in cap thickness was significantly greater in the ezetimibe–fluvastatin group, suggesting that greater LDL cholesterol reduction is associated with more favorable plaque morphology (47). Near-infrared spectroscopy is another intravascular imaging technique that can evaluate the extent of plaque lipid content, reported as the lipid-core burden index. In a small prospective randomized trial of short-term high-intensity statin therapy versus standard-of-care statin therapy of patients with multivessel coronary artery disease referred for percutaneous coronary intervention with at least one other severely obstructive lesion, median reduction in lipid-core burden index (reduction in lipid content) was greater in the high-intensity statin group (89).

Noninvasive imaging techniques have similarly demonstrated atheroma regression and favorable changes in plaque composition. Coronary commuted tomography angiography (CCTA) can visualize luminal stenosis as well as plaque composition (calcification versus noncalcification) and arterial remodeling. Noncalcified plaque with spotty calcification, a surrounding ring of high attenuation, positive remodeling, and low Hounsfield units are associated with high risk (48). In one large retrospective study of patients being evaluated for coronary artery disease, those on statin therapy had features of plaque regression with reduction in low-attenuation plaque, reduction in noncalcified plaque, and increase in calcified plaque (49). A randomized trial of lipid-lowering therapy versus placebo in HIV patients showed a significant reduction in noncalcified plaque volume and favorable remodeling of high-risk plaque features with significantly fewer low-attenuation plaques and significantly less positive remodeling in the statin group, as measured by CCTA at baseline and at one year of follow-up (50).

Other noninvasive imaging modalities have highlighted the ability to regress plaque as well. Unlike CCTA, magnetic resonance imagining (MRI) and magnetic resonance angiography (MRA) have trouble imaging coronary anatomy and plaque characteristics in detail, as motion artifact and technical difficulties reduce contrast-to-noise ratio, spatial resolution, and volumetric coverage (38). Therefore, the use of coronary MRA remains largely limited to the proximal portion of all major coronary arteries (38, 51). Imaging of plaque characteristics by MRI has been more successful than lumen analysis (51). No clinical trials to date have been completed to demonstrate

coronary artery plaque regression with this technique. However, the use of MRI and MRA to visualize carotid atherosclerosis is more feasible, given that the carotid arteries are of larger caliber and stationary (38, 48). Randomized trials of lipid-lowering therapy have demonstrated significant regression of carotid plaque as assessed by MRI after 18 months of therapy in terms of reduction of vessel wall area and volume (52, 53), and after two years and three years of therapy in terms of reduction in lipid-rich necrotic core (54, 55).

Both perfusion and molecular imaging with cardiac positron emission tomography (PET) have also demonstrated plaque regression. Prospective trials of intensive lifestyle intervention with and without pharmacologic therapy demonstrated reduction in size and severity of perfusion abnormalities as compared to antianginal therapy alone. Progressively more aggressive lifestyle intervention approaches were associated with fewer coronary events on follow-up (56, 57). Molecular imaging of plaque inflammation has been validated by PET with the radiotracer ^{18}F-FDG (fluorodeoxyglucose) and has shown reduced inflammation associated with reduced clinical cardiovascular events with use of statin therapy (38).

An important clinical goal should be to use clinical imaging, reductions in plaque size, and indices of instability to predict individual response to therapy. Most vulnerable plaques likely rupture without any clinical significance; therefore, focusing on isolated lesions, e.g., the most advanced plaques, might not be predictive. In contrast, risk of cardiovascular events associates with cardiovascular risk factors, exclusive of imaging (58). Probably because of the multiplicity of lesions, most of which are nonobstructive, medical therapy would be predicted to have advantages over lesion-based therapy in patients with stable coronary artery disease. Thus, while patients with angina have more rapid symptomatic improvement with surgery or stent placement, landmark studies show that medical treatments offer similar long-term benefit (31, 59). This contrasts with the great benefit of interventional approaches during an acute event.

While marked cholesterol reduction will reduce and remodel atherosclerotic lesions in the majority of patients, it is important to identify patients who require additional approaches. Subgroup analysis of the IVUS studies has assessed a number of markers associated with increased CVD and greater inflammation. However, neither higher C-reactive protein (60) nor lipoprotein (a) (61) levels negate the benefits of reducing LDL cholesterol to induce regression. Although patients with diabetes also benefit from marked LDL reduction (62), higher on-treatment LDL levels, hypertension, hyperglycemia, and elevated triglycerides continue to contribute to atherosclerosis progression (33, 35, 62).

MOUSE MODELS AND THE BIOLOGY LEARNED FROM THEM

Animal models allow for elucidation of the pathophysiology underlying the benefits of cholesterol reduction. IVUS studies in humans suggest that cholesterol reduction leads to a rapid reduction in necrotic core and lipid infiltration of the lesions (60), and multiple methods have been developed in mouse models to reproduce this biology, obtain more detailed molecular dissection of the pathology, and identify interventions that improve or inhibit regression. These methods include the transplantation of atherosclerotic aortic segments from a hypercholesterolemic to a low-cholesterol recipient mouse (63), genetic conditional induction of defective liver production of ApoB lipoproteins (64), and transient inhibition of LDL receptors using antisense oligonucleotides (9). These studies have shown that marked cholesterol reduction leads to a rapid decrease in vascular lipid and initiates multiple inflammation-resolving programs in the immune system. For example, the inflammatory (M1) and often cholesterol-loaded macrophages can exit the lesions, and most of the remaining macrophages, which continue to be recruited from monocytes in the circulation, are required for tissue remodeling and creation of a vascular scar (65, 66). As in

humans, the regressed lesion may not be altered in size, but its pathology, as reflected by cellular composition and extracellular matrix content, is markedly altered.

From these models, we can learn of many metabolic and cellular factors that prevent normal regression. Increased atherogenesis, however, due to diabetes has been difficult to reproduce in mice. One reason for this is the exacerbation of the hypercholesterolemia in $ApoE^{-/-}$ and $LDLr^{-/-}$ mouse models, which likely swamps out effects of diabetes per se. Experiments in which early lesions are assessed in non-hypercholesterolemic mice have illustrated a role of the receptor for advanced glycation endproducts (RAGE) (67) and the fatty acid metabolizing enzyme acyl CoA synthetase 1 (ACSL1) (68) in enhancing lesion formation in diabetic mice.

In contrast to the confounding effects of extreme hypercholesterolemia in diabetic mouse models of atherosclerosis progression, in regression studies a simpler setting is possible, because to initiate plaque resolution, plasma lipids are returned to normal in both the normoglycemic and hyperglycemic mice (e.g., 69). The defect in atherosclerosis regression due to diabetes is very robust, ~50% impairment (69, 70), and has been tied to hyperglycemic activation of the bone marrow (71). Defective regression is exacerbated by overexpression of the human form of the aberrant glucose metabolizing enzyme aldose reductase (72) and is ameliorated by increasing the production of ApoA-I (73), the major protein of high-density lipoprotein (HDL), which in certain contexts suppresses the proliferation of bone marrow precursors of neutrophils and monocytes (74).

ApoA-I also promotes the regression of atherosclerosis in nondiabetic mice (75). Presumably this is related to its ability to form functional HDL particles, as the lowering of ApoB-containing lipoproteins was ineffective in promoting regression when ApoA-I (and HDL) was deficient (75). Consistent with this was the finding that infusions of functional, but not dysfunctional, HDL promoted plaque regression in $ApoE^{-/-}$ mice (76). These types of studies emphasize the difference between HDL particle functionality and HDL cholesterol. The former is still considered clinically important as an atheroprotective factor by many, and the latter is now considered to be an inadequate marker in intervention trials, despite its inverse association with CVD in observational studies. Besides promoting cholesterol efflux from plaque macrophages, other protective properties of HDL may be promoting these cells to adopt an M2-like state, which is inflammation resolving (65), and reorganizing lipid rafts to make macrophages less responsive to inflammatory stimuli (77–79).

The effect of HDL on macrophage phenotype is a reminder of the broad role of macrophages in atherosclerosis. Historically, they have been shown to be the central cell in the formation and progression of atherosclerotic plaques, and we refer the reader to other reviews for more comprehensive information (e.g., 80–82). One highlight for the purposes of the present review is that the recruitment of $CCR2^+$ circulating monocytes (termed LY6Chi in mice or $CD14^+CD16^-$ in humans) to the plaque is a major step in atherogenesis because these cells become plaque macrophages. This explains why CCR2 inhibitors have attracted attention as anti-inflammatory agents of potential value in atherosclerosis and other inflammatory diseases (e.g., 83, 84).

What is less well appreciated is that to resolve inflammation in atherosclerotic plaques, the recruitment of $CCR2^+$ cells is also required—even with a dramatic lowering of plasma levels of ApoB-containing lipoproteins (65). In contrast to the fate of the cells recruited in a progression environment, in regression, the LY6Chi monocytes become macrophages with M2-like properties, which then exert processes that serve to dampen inflammation (e.g., by secretion of IL-10) and to clean up dead and dying cells (by efferocytosis). There have been other inflammatory diseases (e.g., 85) in which newly recruited $CCR2^+$ (LY6Chi) monocytes become inflammation resolving. Although these monocytes have traditionally been thought to become only M1 cells,

atherosclerosis regression may be an example of the hypothesis (86) that a "burst" of inflammatory cells is required to jump start the inflammation resolution process.

A series of elegant studies (reviewed in 87) has shown the importance of efferocytosis in plaque pathology. It has been known for some time that as plaques advance, macrophage apoptosis is part of a homeostatic mechanism to regulate the population size of these cells. In early stages of atherosclerosis, apparently there are enough healthy macrophages to efferocytose the dying ones, which protects the plaque microenvironment from the release of inflammation-inciting damage-associated molecular patterns (DAMPS), prothrombotic tissue factor, and a variety of chemo- and cytokines. As plaques advance, however, efferocytosis efficiency wanes, which promotes the formation and expansion of the necrotic core. Thus, by the time a regression stimulus is applied in the typical mouse models, this process of failed efferocytosis and necrotic core expansion is well entrenched. The favorable change in the plaque microenvironment from the rapid reversal of hyperlipidemia apparently allows the newly recruited LY6Chi monocytes to polarize toward the M2 state and exert robust efferocytosis activity. In the diabetic setting, both in vitro and in vivo, assumption of the M2 state by macrophages is inhibited despite lipid lowering (69, 71). This defect in macrophage biology is a likely contributor to the impaired regression in diabetic mouse models of atherosclerosis.

CONCLUSIONS

Information obtained from animal experiments and the effects of marked cholesterol reduction in humans have changed our view of the natural history of atherosclerosis. A reversal of the hypercholesterolemia that commonly develops in humans in the United States and Western Europe initiates the repair of the vessel. This process, termed regression, is responsible at least in part for the marked reduction in angina and acute events in patients with coronary artery disease. Regression involves loss of lesional lipids, but for success, there also has to be infiltration and conversion of macrophages from an inflammatory to a reparative phenotype, and increased collagen accumulation. That these processes are integral to the maximal response to the regression stimulus of lipid lowering is clear from mouse studies, in which reversal of hypercholesterolemia alone did not fully accomplish favorable plaque remodeling, especially in diabetic mice. A similar phenomenon may be reflected in the CANTOS study, which revealed that in some subjects, CVD risk reduction was observed with aggressive lipid lowering and an anti-inflammatory therapy (88). Thus, augmentation of each of these processes should reduce plaque vulnerability and reduce CVD events.

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