Review Article

Plaque regression and plaque stabilisation in cardiovascular diseases

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ABSTRACT

Atherosclerosis is characterized by formation of plaques on the inner walls of arteries that threatens to become the leading cause of death worldwide via its sequelae of myocardial infarction and stroke. Endothelial dysfunction leads to cholesterol uptake and accumulation of inflammatory markers within the plaque. The stability of a plaque eventually depends on the balance between vascular smooth muscle cells that stabilize it and the inflammatory cells like macrophages and T lymphocytes that make it prone to rupture. The current approach to manage atherosclerosis focuses on the treatment of a ruptured plaque and efforts have been made to reduce the risk of plaque rupture by identifying vulnerable plaques and treating them before they precipitate into clinical events. New diagnostic approaches such as IVUS and CIMT ultrasound are now being preferred over traditional coronary angiography because of their better accuracy in measuring plaque volume rather than the level of stenosis caused. The present review highlights the literature available on two prevalent approaches to manage a vulnerable plaque, namely, plaque stabilization and plaque regression, and their validation through various treatment modalities in recent plaque management studies. Plaque stabilization focuses on stabilizing the content of plaque and strengthening the overlying endothelium, while plaque regression focuses on the overall reduction in plaque volume and to reverse the arterial endothelium to its normal functional state. Although earlier studies contemplated the practicality of plaque regression and focused greatly on stabilization of a vulnerable plaque, our review indicated that, aided by the use of superior diagnostics tools, more intensive lipid modifying therapies have resulted in actual plaque regression.

Key words: Atherosclerotic plaque, plaque regression, plaque stabilisationstabilization, vulnerable plaque

Introduction

Atherosclerosis is a systemic disease characterized by narrowing of blood vessels due to the formation of atheromatous plaque or atheroma (Plural: Atheromata). Atheroma is the deposition of fatty material and cholesterol within the inner wall of arteries that makes arterial lumen stenotic.[1] The major clinical manifestations of atherosclerosis are angina, myocardial infarction (MI), transient cerebral ischemic attacks, and strokes.[2] In the year 2008, out of 17.3 million cardiovascular (CV) deaths, MI alone was responsible for 7.3 million deaths and stroke alone caused 6.2 million deaths.[3]

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Pathophysiology of atherosclerotic plaque

Arterial endothelial activation is the first step in the pathophysiology of atherosclerotic plaque where there is an increased expression of adhesion molecules which attracts and internalizes the circulating monocytes and leukocytes from the bloodstream[4] and gets converted into macrophages by macrophage-colony stimulating factor (M-CSF).[5] In addition, cholesterol uptake from apolipoprotein B containing lipoproteins such as low-density lipoprotein-cholesterol (LDL-C) and oxidation of native LDL-C by oxygen-free radicals stimulates the expression of several inflammatory markers, which play a crucial role in development of plaque [Figure 1].[6] The stability of atherosclerotic plaque depends on the interplay of vascular smooth muscle cells (VSMCs) and inflammatory cells (macrophages and T lymphocytes). The VSMCs synthesize structurally important collagens that provide

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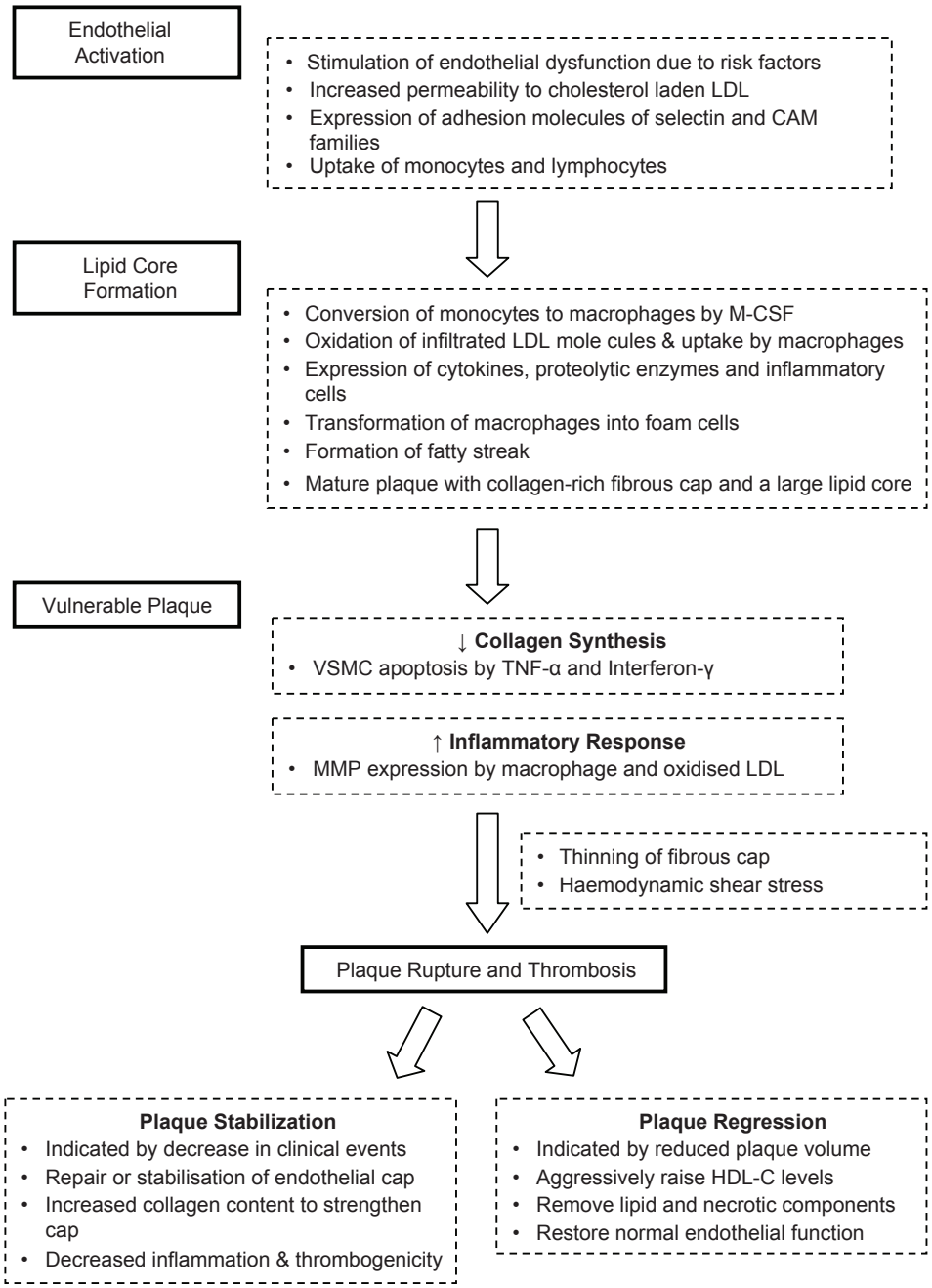

Figure 1: Evolution of atherosclerotic plaque

stability to the plaque while inflammatory cells release matrix metalloproteinases (MMPs), which degrade collagen and extracellular matrix, potentially weakening the plaque.[7] In unstable plaque, the balance among these competing factors favors collagen breakdown rather than synthesis. With plaque rupture, lipid fragments and cellular debris are released into the vessel lumen resulting in the formation of a thrombus.

Diagnosis of plaque

While studying plaque regression, it is quintessential to identify accurate changes in plaque composition and volume to treat ruptured plaque and to indicate plaque vulnerability in asymptomatic individuals.[8] A crucial factor impeding the diagnosis of plaque is the effect of arterial wall remodeling. In the early stages of plaque formation, plaque growth is eccentric, and due to expansive (positive) remodeling, there occurs compensatory outward enlargement of the vessel wall in order to accommodate considerable plaque volume without much compromise on the vessel lumen.[9] Coronary angiography is the traditional gold standard for atherosclerotic plaque assessment, but since its assessment is based on the imaging of arterial lumen stenosis, it fails to detect the effect of expansive remodeling[4] and hence,

lacks the ability to measure accurate changes in atheroma volume.

Intravascular ultrasound (IVUS) depicts the lumen size as well as thickness of the entire vessel wall but is invasive in nature. Ultrasound measurement of the carotid intima media thickness (CIMT) is a non-invasive technique that accurately assesses changes in the wall thickness and, more importantly, correlates these changes with future clinical events.[10] High resolution magnetic resonance imaging (MRI) has emerged as a leading non-invasive imaging technique that has monitored changes in plaque volume.[11] However, MRI studies correlating changes in atheroma volume with reduction in events are lacking.[4] Other emerging diagnostic techniques of plaque imaging such as computed tomography (CT) luminal coronary stenosis assessment, ECG-gated single-photon emission computed tomography (SPECT), infrared spectroscopy, and intra-coronary thermography have effectively detected changes in anatomical and functional information in an unstable plaque, but these results are yet to be validated in larger studies.[5]

Purpose of this review

The current modalities of plaque management are based on the treatment of ruptured plaque that precipitates into acute clinical events. The present review focuses on the need of preventive approaches for plaque management by impeding the progression of plaque before rupture and stabilizing the composition of plaque to prevent rupture (plaque stabilization), and if possible, to reverse the growth of plaque altogether (plaque regression).

Search strategies used in this review

We identified electronic databases, mainly MEDLINE, HighWire, Cochrane, and Google Scholar for articles from 2001 through December 2011 by using keywords "Atherosclerotic plaque," "plaque regression," "plaque stabilization," and "vulnerable plaque." In MEDLINE, we used the Medical Subject Heading (MeSH) terms: "Atherosclerotic plaque," AND the Subheadings "diagnosis," "pathophysiology," "prevention and control," and "therapy." Reference lists of screened articles were also searched to identify additional data.

Predisposing Factors of Atherosclerosis

Dyslipidemia, hypertension, obesity, smoking, diabetes, genetic predisposition, homocysteinaemia, immune complexes, and infectious agents are few of the risk factors, which favor progression of atherosclerosis.[12,6] Risk factors for atherosclerosis as per the latest WHO Report on cardiovascular disease (CVD)[1] are shown in [Table 1]. In the first decade of life, atherosclerosis begins as "fatty streaks,"[13] which progress to unstable or vulnerable plaques by the next two decades on continuous exposure to CV risk factors.[2] These vulnerable plaques may further cause obstruction of blood flow to vital organs, resulting in heart attack, stroke, and other CV complications.

Table 1: Risk factors for atherosclerosis

Behavioral risk factors
Tobacco use
Physical inactivity
Unhealthy diet (rich in salt, fat, and calories)
Harmful use of alcohol
Metabolic risk factors
Raised blood pressure (hypertension)
Raised blood sugar (diabetes)
Raised blood lipids (e.g., cholesterol)
Overweight and obesity
Other risk factors
Poverty and low educational status
Advancing age
Gender
Inherited (genetic) disposition
Psychological factors (e.g., stress, depression)
Emerging risk factors (e.g., excess homocysteine)

Therapeutic Strategies for Atherosclerotic Plaque

Interventions that target lipid metabolism are the primary interventions for prevention of CV morbidity and mortality.[14] Other therapeutic strategies include anti-thrombotic agents, anti-oxidants, and diet management; these strategies have been used either alone or in combination with lipid-lowering agents. Based on the stage of plaque, there are different treatment options. For example, in a patient with acute coronary syndrome (ACS), the destabilized plaque would require a different treatment approach and strategy than the plaque that has not yet destabilized. The recent approaches to plaque management primarily focus on the need for early plaque detection and their treatment before any clinical event occurs. Hence, it is imperative to identify plaques at an early stage where they have not yet ruptured but are highly susceptible to rupture, commonly referred to as the vulnerable plaque. The characteristics of vulnerable plaque are enumerated in Table 2.[7,15]

As evident in Table 2, a variety of intrinsic and extrinsic factors predisposes plaque to instability and acute disruption. In order to prevent complications of plaque rupture, it is important not only to identify vulnerable patients based on traditional risk factors but also to identify vulnerable plaques in asymptomatic individuals.[15]

Plaque stabilization

Plaque stabilization is an approach towards altering the structure, content, or function of the plaque and/or

Table 2: Vulnerable atherosclerotic plaque

Major characteristics
Increased inflammatory cell infiltration (more than 26% macrophage infiltration)
A thin cap (<65 μ)
A large lipid core (>40% of the plaque's total volume)
Minor characteristics
Superficial platelet aggregation on the endothelium
Low VSMC and collagen contents
Higher levels of VSMC apoptosis
Increased expression of matrix degrading MMP
Reduced expression of tissue inhibitor of MMP (TIMP)
Increased concentrations of macrophage colony stimulating factor (M-CSF)
Hemodynamic shear stress (due to increased blood pressure and vasospasm)

VSMC: Vascular smooth muscle cell, MMP: Matrix metalloproteinase, M-CSF: Macrophage-colony stimulating factor, TIMP: Tissue inhibitor of metallo proteinases

its overlying endothelium to either prevent or reduce the severity of plaque rupture.[16] Once the plaque has disrupted/eroded with overlying thrombus, stabilization is possible by percutaneous coronary intervention (PCI), with interventions such as lipid-lowering, anti-thrombotic, and anti-coagulant agents.[17]

In the 1990s, several angiography trials on lipid lowering demonstrated significant reduction in clinical events despite a small amount of plaque regression.[18] A series of post-mortem and angiographic studies identified that the probability of MI incidence was not reflected by corresponding increase in arterial stenosis.[19] Hence, it was considered that the stability of the plaque rather than its absolute size determined the likelihood of rupture, making a change in plaque composition rather than plaque regression a worthwhile clinical goal.[7] The basic idea of plaque stabilization is to make the plaques more fibrous and reduce their lipid content. Several *in vivo* studies have reported the role of macrophages, MMP expression, and interstitial collagen content in plaque stability.[20] Decreased macrophage counts and MMP expression, and increased interstitial collagen content had led to increase the plaque stability.

Clinical studies of statin therapy have consistently demonstrated increase in hyperechogenicity index (suggesting an increase in fibrous tissue), and reductions in the plaque lipid pool, but only modest reductions in plaque volume.[21] These changes in plaque structure may have improved the endothelial function and reduced the platelet thrombogenicity, translating into improved outcomes in both Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering with Atorvastatin (MIRACL)[22] and the Pravastatin Acute Coronary Treatment (PACT)[23] early cholesterol reduction studies in ACS patients. Plaque stabilization may also lead to significant reduction in the rate of progression of carotid intima-medial thickening, which may be due to either up-regulation of type III collagen synthesis[24] or anti-atherogenic effect.[25]

Niacin and fibrates have shown increase in high-density lipoprotein cholesterol (HDL-C), either alone or in combination with simvastatin, leading to improved CV outcomes in high-risk groups with low HDL-C.[26] Other cholesterol-reducing agents, such as nicotinic acid and ezetimibe, may improve plaque stabilization by reducing the lipid pool and improving the endothelial function, but whether this will translate into improved outcomes in ACS is yet to be ascertained.[15]

Plaque stabilization can also be achieved by various anti-thrombotic therapies, including anti-platelets and anti-coagulants. Anti-platelet therapies (aspirin, clopidogrel or prasugrel, intravenous anti-platelet drugs [glycoprotein IIb/IIIa inhibitors]) reduce platelet activation and aggregation, which are integral steps in the formation of a thrombus after plaque disruption.[27] The anti-coagulant therapies (unfractionated heparin, low molecular weight heparins, fondaparinux, and bivalirudin) target the clotting cascade to prevent deposition of fibrin strands in the clot. Both anti-platelet and anti-coagulant therapies heal the intimal tear and retard the endothelium activation, leading to plaque stabilization. Aspirin has anti-platelet and anti-inflammatory properties. It covalently binds cyclo-oxygenase and reduces interleukin-6, C-reactive protein (CRP), and macrophage colony stimulating factor.[15] Recent advances in the molecular biology of the platelets have demonstrated that the platelet integrin GP IIb/IIIa plays a pivotal role in the final common pathway leading to platelet aggregation.[28] Clopidogrel and ticlopidine are two adenosine diphosphate receptor antagonists (Gp IIb/IIIa inhibitors) that reportedly inhibited platelet activation, degranulation, and release of pro-thrombotic and inflammatory mediators and prevented activation of the glycoprotein (Gp) IIb/IIIa receptor.[15] These Gp IIb/IIIa inhibitors exhibited maximum benefit in patients who underwent PCI for destabilized plaque.[29] Aspirin, alone or in combination with heparin and clopidogrel, served as a treatment option in ACS. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, striking benefit of the combination of clopidogrel and aspirin over aspirin alone was observed in patients with unstable angina and non-ST elevation myocardial infarction in terms of reduced clinical events.[30]

The Heart Outcomes Prevention Evaluation (HOPE) study had shown ACE inhibitors such as ramipril to improve plaque stability by inhibiting endothelial dysfunction and

oxygen-free radical production by angiotensin; by decreasing macrophage activity, or by inhibiting VSMC lipoxygenase activity.[25] The ACE inhibitors not only potentiate vasodilator bradykinin and decrease platelet adhesion but also inhibit pro-atherosclerotic agents like plasminogen activator inhibitor. There is enough accumulated evidence that chronic ACE inhibitor therapy stabilizes plaque and decreases vascular reactivity.[28] Calcium antagonists such as amlodipine have shown anti-atherogenic role in patients with ACS where they had stabilized plaques by interfering with the lipid oxidation process, reducing the foam cell formation, and significantly increasing the trans-membrane calcium transport mechanism. Amlodipine also significantly reduced the rate of CIMT and reduced ACS admissions in high CV risk groups.[31]

Oral anti-oxidants also contribute to plaque stabilization by inhibiting LDL-C oxidation and stabilizing vascular reactivity. However, trials assessing the effects of treatment with the anti-oxidant probucol, either alone or in concert with lovastatin, on restenosis rates after PCI have yielded mixed results.[32,33] Oral treatment with corticosteroids improved clinical outcomes and reduced in-stent restenosis in patients with high CRP concentrations.[34]

Diets rich in anti-oxidants have high concentrations of omega-3 class of essential fatty acids, which have been reported to reduce CV events. One such example of an anti-oxidant rich diet is the Mediterranean-type diet,[35] which has been reported to significantly lower the saturated fat content and ACS events in CAD patients in the Lyon Diet Heart Study. Dietary intake of saltwater fish rich in omega-3 polyunsaturated fats confer cardio-protective effects mediated in part by reductions in platelet aggregation as well as other beneficial effects on arterial-wall endothelial function.

Plaque regression

Plaque regression, as viewed today, delves over the prospect of treating vulnerable plaques beyond just stabilization. It emphasizes on aggressive and/or long-term therapy in removing lipids and necrotic material, restoring normal endothelial function and repair of denuded areas to bring about changes beyond just stabilization of vulnerable plaques. Although critics had earlier refuted the concept of plaque regression, recent studies by Nissen *et al*.[36-38] have showed atherosclerosis regression to be a realistic goal in some patients. In addition, earlier angiography studies, which were unable to show aggressive and long-term treatment (usually 1 and 2 years) with statins, has been the most widely studied approach to treat plaque regression. It has been shown to reduce LDL-C and elevate HDL-C levels;[4] the combination of which has been found to be an effective clinical strategy to regress atherosclerosis in the Arterial Biology for the Investigation for the Treatment Effects of Reducing Cholesterol series of studies.[39,40] Another retrospective analysis found that aggressive LDL-C lowering with statins significantly correlated with the reduction in coronary calcium-volume score by electron-beam CT, indicating that coronary artery calcifications can shrink.[4]

Besides inhibition of HMG-CoA reductase, statins show pleiotropic effects and considerably reduce the plaque burden by: (1) diminution of the plaque lipid-rich core; (2) reduction in the inflammation with decreased macrophage and foam cell formation; (3) promotion of fibrous cap thickening; and (4) decreasing platelet reactivity.[41] All these effects translate to an overall improvement in endothelial function, which can play a crucial role in preventing plaque formation altogether.

Three recent landmark trials that utilized IVUS to show regression of plaque with intensive statin therapy are the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound Derived Coronary Atheroma Burden (ASTEROID), and Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN). In the REVERSAL trial,[37] high dose statin group had 0.4% decrease (regression) in the median atheroma volume in comparison to 2.7% increase (progression) in the moderate-dose group over an 18-month period. A sub-analysis of the REVERSAL study by Nicholls and colleagues[42] reported that aggressive lipid-lowering therapy was effective in suppressing the development of coronary plaques associated with an increase in body mass index (BMI). In the ASTEROID study, 63.6% of patients experienced regression with a decrease in mean total atheroma volume by 7% after 24 months of 40 mg/day rosuvastatin treatment.[38] Notably, 84% of the patients in ASTERIOD study received a beta-blocker during the study, which may also have some effects on plaque regression. The most recent study focusing on intensive statin therapy for plaque regression was the SATURN trial, which compared the effect of rosuvastatin (40 mg daily) and atorvastatin (80 mg daily) in 1039 patients with coronary disease for 104 weeks. Results showed that maximal doses of both rosuvastatin and atorvastatin resulted in significant plaque regression in majority of the patients, with a relatively higher percentage of patients showing regression with rosuvastatin.[43]

Another potential intervention that can raise HDL-C was the inhibition of cholesteryl ester transfer protein (CETP). Various trials, including Investigation of Lipid Level

Management to Understand Its Impact in Atherosclerotic Events (ILUMINATE),[44] Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE),[45] Radiance 1 (Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor)[46] have shown no improvements in coronary or carotid anatomy despite significant increase in HDL-cholesterol levels in the statin–torcetrapib groups.

ApoA-1 oral peptides have been developed based on the observation that certain genetic polymorphisms were associated with high HDL-C levels. When administered to patients with ACS, 5 weekly infusions of a reconstituted version of ApoA-I resulted in marked plaque regression as assessed by coronary IVUS.[36] A major limitation of current ApoA-I mimetics was that they required parenteral administration because of gastrointestinal proteases that may prevent their effective oral use.[4]

Conclusion

The current literature on management of atherosclerotic plaque suggests that numerous associations have been made between systemic factors important in plaque evolution, thereby creating diverse avenues for disease prevention. Of equal importance is the parallel development of non-invasive imaging techniques that can accurately confirm the effect of different treatment modalities. Improvements in our understanding of rupture-prone vulnerable plaques will help us choose the right strategy to manage plaque progression. While plaque stabilization mainly focuses on repairing the endothelial cap and strengthening collagen content, plaque regression mainly focuses on aggressive lipid management to remove necrotic components and restore normal endothelial function of the arterial wall. Plaque stabilization has already been proven to reduce clinical events and studies with statins, HDL-C increasing agents, anti-thrombotic agents, ACE inhibitors, calcium antagonists, oral anti-oxidants, and diet modifications have shown that reduction in clinical events need not be reflected by reduced plaque volume. The major studies supporting plaque stabilization included MIRACL, PACT, CURE, HOPE, and Lyon Diet Heart Study. However, recent IVUS studies have shown the incompetence of angiography to precisely measure plaque volume. New insights into the possibility of plaque regression have been elicited by the ASTEROID, REVERSAL, and SATURN studies that utilized intensive statin therapy and demonstrated plaque regression in majority of study patients. However, these trials showed less than 10% regression in overall plaque volume only, which may not explain CV event reduction. This highlights the practical importance of plaque stabilization as the treatment approach to manage plaque disruption. Nonetheless, the growing interest in treating vulnerable plaque has substantially raised the bar on current treatment approaches and, if complemented by confirmatory imaging techniques and markers, can possibly help regress plaque evolution and eradicate the possibility of atherosclerosis altogether.

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