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REVIEW ARTICLE

Relationship between Inflammation and Cardiovascular Diseases

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ABSTRACT

Inflammation is a part of complex biological response of vascular tissue to harmful stimuli such as pathogens, damaged cells or irritants. Recent advance in basic science have established a fundamental role for inflammation immediating all stages of cardiovascular diseases from initiation, progression and complications. Inflammation is thread linking to cardiovascular diseases. Clinical studies have shown that this emerging biology of inflammation play important role in pathogenesis of acute thrombotic events. The article reviews that there is relationship between inflammation and cardiovascular diseases. Also inflammation is important contributor to atherosclerosis. Certain markers such as Interlukin 1 (IL-1), Interlukin-6 (IL-6), tumor necrosis factor-α (TNF-α), etc. of inflammation both systemic and local play important role in the development of atherosclerosis. Prognostic method includes invasive and non invasive techniques, also includes detection of systemic inflammation and prevention of atherosclerosis caused by inflammation. Relation of inflammation to cardiovascular disease aids in identification of individuals at risk of cardiovascular diseases events with goals of lessening dependence on late stage and invasive treatment.

KEYWORDS

Inflammation, Cardiovascular diseases, Atherosclerosis, Endothelial dysfunction

INTRODUCTION

An estimated 26 million people are living with the effects of heart disease and is a major cause of death in western society. Until recently the widely held belief was that the cardiovascular disease (CVD) is simply the process as a buildup of fat on the surface of artery walls. Eventually, this builds up of fat blocks the artery and a heart attack or stroke occurs. However, the process has now been identified as a disease of the inner artery wall (intima) and inflammation is a key factor in its progression.

The source of inflammation in CVD is not completely understood. However, numerous factors are thought to initiate the complex inflammatory process such infectious agents for example herpes viruses and Chlamydia pneumoniae. Other promoters and stimulators of inflammation leading to endothelial injury include smoking, hyperglycaemia, oxidised low-density lipoprotein (LDL) or sheer stress on the vessel wall by hypertension. Genetic factors may also play a role in the degree and duration of the inflammatory response, although this still needs to be fully explored.

Once stimulated by a promoter or stimulator (including those mentioned above), endothelial cells of the intima interpret their presence as unwanted and activate the immune system to deal with the problem. The gene transcription factor NF-*k*B is released, serving as a promoter

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of early cytokines such as TNF-α and IL-6, chemokines such as MCP-1 and adhesion molecules. The chemokines attract monocytes and T lymphocytes (T cells) from the blood stream allowing monocytes to travel across the endothelial barrier and become macrophages. Entry of monocytes into the vessel wall is a key factor in the development of atherosclerosis, as blocking monocyte migration has ameliorated atherosclerosis in *in vivo* models. Once inside the intima, these mononuclear cells produce pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α to stimulate the inflammatory cascade. Metalloproteinases are also released, promoting smooth muscle cell proliferation and uptake of LDL by these macrophages to form foam cells.

Through uptake of LDLs, a fatty streak can develop into a necrotic plaque that is sealed off from the blood flow by the fibrous cap and is held in balance by collagen deposition and degradation. Fissuring or rupturing of this cap can occur when the balance is disrupted by increased inflammation leading to thinning of the collagen cap. The plaque rupture exposes thrombotic substances to the blood, leading to local thrombus formation and downstream microemobolization. Furthermore, inflammatory cytokines activate platelets expressing P-selectin and CD40, thus increasing platelet-platelet adhesiveness. Cytokines also signal the production of acute phase proteins such as fibrinogen serum amyloid A and C-reactive protein. These are systemic downstream markers which can be useful in assessing cardiovascular risk in patients. The role of inflammation in cardiovascular disease is not strictly limited to the innate inflammatory response. The adaptive immune response particularly lymphocytes are also involved in CVD. Prevention of the initial development of CVD and progression over time is the goal of any prevention program. With increasing knowledge, the approach to identifying the underlying causes of heart disease is changing rapidly. Much research has identified inflammation as an underlying or active factor in the development of the disease. For the past two decades, clinical trials of antiatherosclerotic drug therapies have sought to reduce CVD morbidity and mortality. This includes the use of a group of drugs called statins (atorvastatin and rosuvastatin) to treat high cholesterol levels which have been shown in large randomised trials, to reduce cardiovascular events in risk patients. Research has demonstrated that at higher doses, statins slow or even reverse plaque progression as demonstrated during intravascular ultrasound. Recently however, clinical findings have indicated that statins may slow progression of disease at a rate and to an extent that cannot be attributed to lower LDL alone. The proposed mechanisms for such pleiotropic actions include endothelial-dependent nitric oxide bioavailability, inhibition of oxidative stress and anti-inflammatory activity. In particular a number of clinical trials have shown that statins reproducibly lower circulating levels of C reactive protein (CRP) an inflammatory biomarker associated with acute coronary syndromes. Reducing inflammation may therefore be a key mechanism by which statins alter the biology of the plaque and slow down disease progression. Although statins are currently the most popular and widely prescribed drugs to help treat CVD, evidence indicates side effects such as a higher risk of drug interactions in elderly, muscle pain or memory related problems are linked to their use. It is therefore necessary to continue the investigation into inflammation and in inflammatory cell-cell interactions to help develop more effective therapies.

Inflammation and Atherosclerosis

Inflammation plays a major role in all phases of atherosclerosis. Stable plaques are characterized by a chronic inflammatory infiltrate, whereas vulnerable and ruptured plaques are characterized by an “active” inflammation involved in the thinning of the fibrous cap, predisposing the plaque to rupture. Although a single vulnerable atherosclerotic plaque rupture may cause the event, there are many other types of plaques, several of which are vulnerable. The existence of multiple types of vulnerable plaques suggests that atherosclerosis is a diffuse

inflammatory process. Atherosclerosis has a broad spectrum of clinical presentation. Some patients are asymptomatic for life, even though they have atherosclerotic plaques in their vasculature. Others have ischemic symptoms, such as myocardial infarction and stroke. The first condition is usually characterized by slowly growing, silent lesions defined as "stable plaques." In the second condition, clinical events are associated with one or more "unstable plaques." Stable angina is associated with smooth fibrous coronary artery plaques, whereas unstable angina, acute myocardial infarction (AMI), and sudden cardiac death are almost invariably associated with irregular or ruptured plaques. Similarly, in patients with carotid artery disease, plaque irregularity and rupture are associated with cerebral ischemic events. Patients with irregular or ulcerated plaques have a higher risk of ischemic stroke irrespective of the degree of stenosis of the vessel lumen. Inflammation is a component of all forms of plaque .A topographic relationship among an inflammatory infiltrate, plaque rupture, and thrombosis is a pathogenetic role for macrophages at the site of cap rupture in patients with fatal Acute Myocardial Infarction. Further observations demonstrated the role of activated macrophages and activated T lymphocytes in plaque destabilization.

The combination of macrophages and lymphocytes in vulnerable plaque is associated with the secretion of cytokines and lytic enzymes that result in thinning of the fibrous cap, predisposing a lesion to rupture.

Inflammation as a Key Pathogenic Mechanism in Atherosclerosis

Inflammation participates in atherosclerosis from its inception and development to its ultimate endpoint, thrombotic complications.

Initiation of Atherosclerosis

Endothelial dysfunction: Endothelial cells (ECs), which form the inner most surface of the artery wall, resist adhesion by leukocytes. However, triggers of atherosclerosis, such as consuming a high saturated fat diet, smoking, hypertension, hyperglycemia, obesity, or insulin resistance, can initiate the expression of adhesion molecules by Endothelial cells , thus allowing the attachment of leukocytes to the arterial wall.

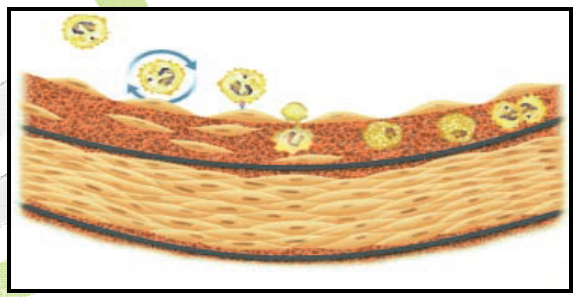

Figure 3: Initiation of atherosclerosis

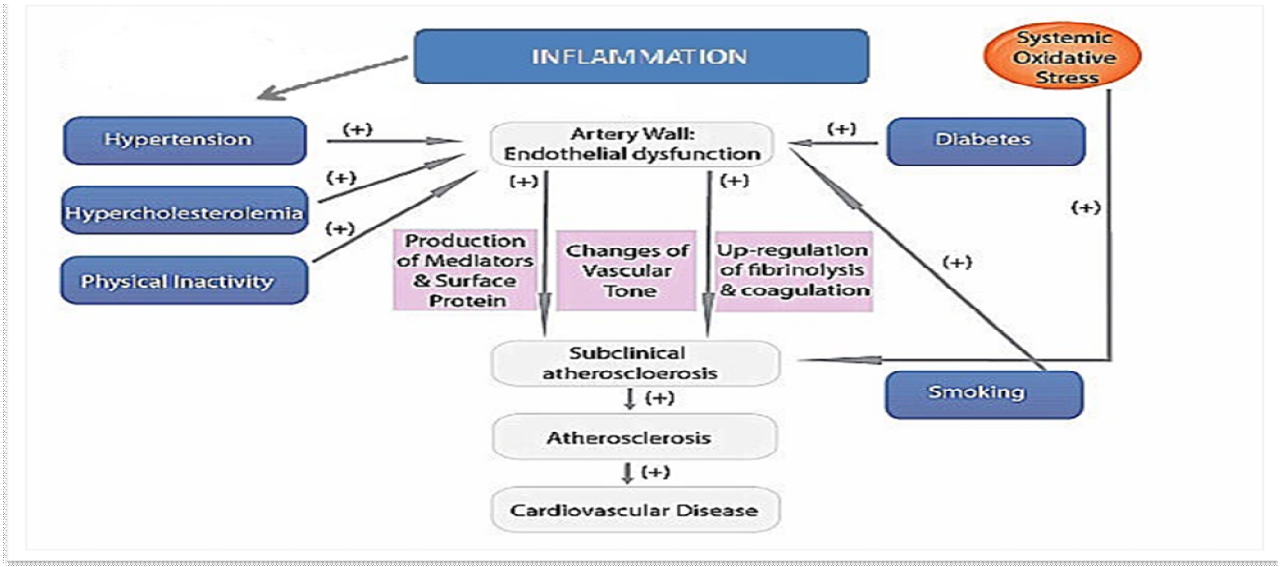

Figure 1: Relation between Inflamation and Cardiovascular diseases

Adhesion molecule: One likely culprit in this interaction between the endothelium and leukocytes is vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 binds monocytes and T lymphocytes, the types of leukocytes found in early atherosclerotic plaques.

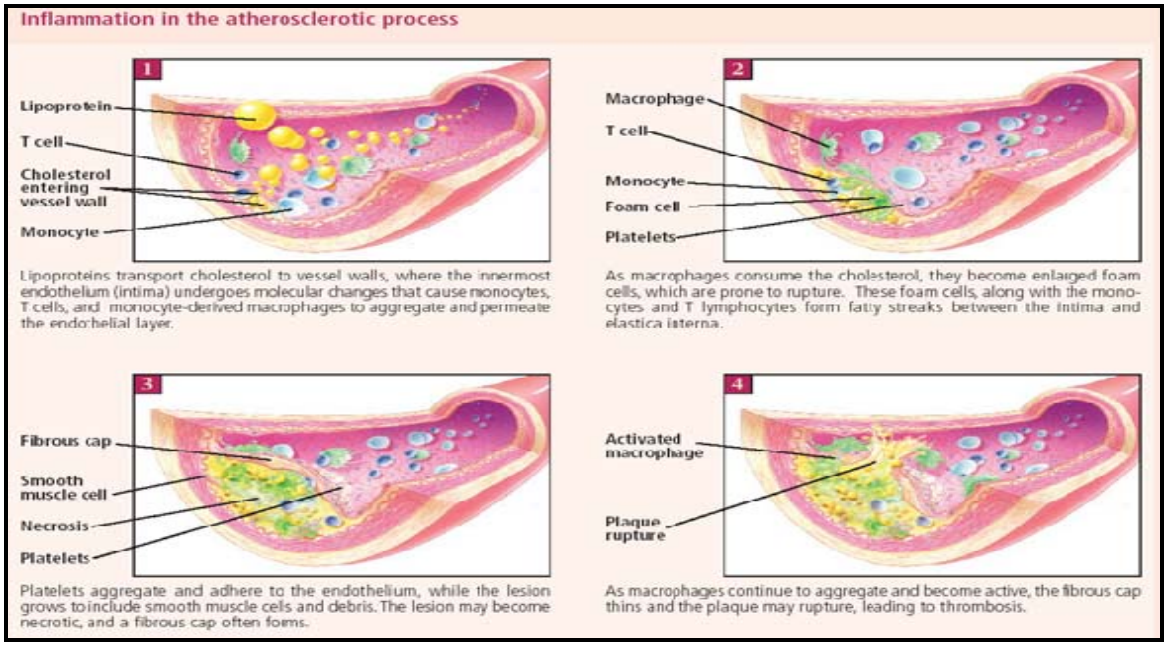

Figure 2: Inflammtion and atherosclerosis

Expression of VCAM-1: In the case of an atherogenic diet, the initiating event is likely the accumulation of modified lipoprotein particles in the arterial intima. Oxidized lipids can induce VCAM-1 expression through a pathway mediated by nuclear factor B, as can proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). Interestingly, lesions tend to develop in specific areas only, likely because of the type of blood flow they experience. Laminar blood flow produces shear stress, which elicits several atheroprotective mechanisms, such as expression of a form of the antioxidant enzyme superoxide dismutase or increased nitric oxide synthase expression. This endogenous vasodilator nitric oxide molecule also has anti-inflammatory properties and can limit expression of VCAM-1. The resulting increase in production of the vasodilator nitric oxide can limit VCAM-1 gene expression by inhibiting nuclear factor-B activation and combating platelet clumping. Areas of the vasculature prone to lesion formation experience disturbed flow, and the lack of laminar flow may reduce the activity of such atheroprotective mechanisms.

Development of the Fatty Streak

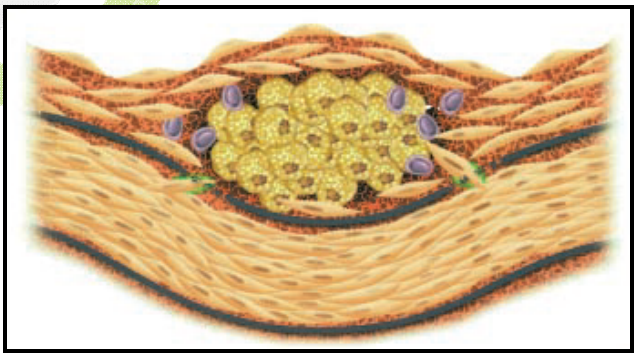

Figure 4: Development of fatty streak

Once adhered to the arterial endothelium, monocytes penetrate the endothelial lining and enter the intima of the vessel wall by diapedesis between endothelial cells, a process that requires a chemoattractant gradient, likely due in large part to monocyte chemoattractant protein-1 (MCP-1). Human and experimental atheroma overexpress MCP-1. This chemoattractant cytokine (chemokine) can recruit monocytes, the type of inflammatory

white blood cell that characteristically accumulates in early atheromas. Within the intima, monocytes mature into macrophages, exhibit increased expression of scavenger receptors, and engulf modified lipoproteins. Cholesterol esters accumulate in the cytoplasm, and the macrophages become foam cells, ie, lipid laden macrophages that characterize the early stages of atherosclerosis. At the same time, the macrophages multiply and release several growth factors and cytokines, thus amplifying and sustaining proinflammatory signals.

One key mediator of this transformation and proliferation, macrophage colony-stimulating factor (M-CSF), is also overexpressed in experimental and human atherosclerotic plaques. T lymphocytes, the cells of the adaptive immune response, also participate critically in atherogenesis. A trio of interferon inducible chemokines, IP-10, MIG, and I-TAC, beckon these lymphocytes to enter the inflamed artery wall. These chemokines interact with the CXCR3 receptor, which is highly expressed by T lymphocytes in the atherosclerotic plaque. Several additional adhesion molecules, chemokines, cytokines, and growth factors participate in this process. The atherosclerotic plaque over expresses eotaxin, which is traditionally associated with eosinophil chemoattraction. Eotaxin binds to the receptor CXCR3, which localizes predominantly in macrophage rich areas, thus suggesting that eotaxin modulates macrophage function in the plaque. Small numbers of mast cells inhabit the plaque as well, and these also express CXCR3. Therefore, eotaxin may mediate mast cell migration to the site of the lesion. VCAM-1, MCP-1, and M-CSF, however, appear to be the key mediators in the initiation and development of the initial lesion of atherosclerosis, the fatty streak. They also illustrate some of the complex tapestry of inflammatory signaling that leads to atherosclerotic plaque development.

Progression to Complex Plaque

The fatty streak seen in teenagers to the complex plaque that causes cardiovascular complications in adults. Human endothelial cells exposed to Escherichia coli endotoxin, a proinflammatory stimulus, express IL-1 and IL-1 messenger RNA, which raises the possibility that vascular Endothelial cells are not merely passive responders to immunologic stimuli from leukocytes but are actively involved in the process. Since then, a range of cytokines expressed by vascular wall cells has been identified, including IL-1, TNF-α, IL-6 (an important messenger cytokine), and the very factors important to the recruitment and activation of the monocytes, i.e., M-CSF, MCP-1, and IL-1. Another proinflammatory cytokine, CD40 ligand (CD154), can contribute to this phase of atherogenesis as well. Interruption of CD40/CD154 signaling can slow the initiation of atherosclerosis. So muting inflammatory signaling not only prevents the formation of new lesions but also halts the evolution of existing atherosclerosis.

Plaque Rupture

The development of atheromatous plaques would not be such a major health issue were it not for plaque rupture and thrombosis. In coronary arterial thromboses, the underlying lesion often does not produce critical arterial narrowing. Indeed, serial angiogram data show that extreme narrowing of the artery occurs weeks or months before Myocardial Infarction in only 15% of cases. Additionally, coronary arteries can enlarge and compensate for the developing plaque, thus preserving the flow of blood to the myocardium. This mechanism becomes overwhelmed only when the stenosis occupies 40% of the arterial lumen.

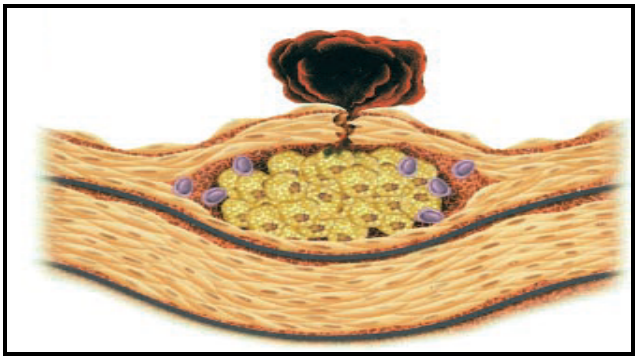

Figure 5: Plaque development and rupture

We now know that physical disruption of the atherosclerotic plaque, most often a fracture of the fibrous cap that ordinarily protects the blood from contact with the lipid core, causes most acute coronary syndromes, resulting in thrombus formation and sudden expansion of the lesion, perhaps to the extent that blood flow through the affected artery becomes compromised or even completely blocked. Given the critical importance of such events in clinical practice, has investigated the role of inflammation in plaque disruption, with a particular focus on the structure of the fibrous cap.

The fibrous cap owes its biomechanical strength and stability to interstitial collagen. One characteristic of plaques that have ruptured and caused fatal thrombosis is their tendency toward thin fibrous caps. Inflammation interferes with the integrity of the interstitial collagen matrix by blocking the creation of new collagen fibers and by stimulating the destruction of existing collagen. In the arterial wall, collagen is produced mostly by smooth muscle cells, stimulated by transforming growth factor, platelet-derived growth factor, and, to a lesser extent, IL-1. However, the cytokine interferon, which is produced by T lymphocytes in the plaque, inhibits both basal collagen production and the stimulatory effects of transforming growth factor, platelet-derived growth factor, and IL-1.

T lymphocytes also participate in the inflammatory processes that promote the destruction of existing collagen in vulnerable plaques. CD40 ligand and IL-1 produced by T-lymphocytes promote the production of collagen-degrading enzymes by macrophages, including members of the matrix metalloproteinase MMP family, specifically MMP-1, MMP-8, and MMP-13. In addition, mast cells in the plaque may release the MMP inducer TNF-α as well as the serine proteinases tryptase and chymase, which can activate MMP proenzymes. Other causes of physical disruption of the fibrous cap are possible, but these appear to be the most common. T lymphocytes also promote the thrombogenicity of the lipid core through the expression of CD40 ligand, which stimulates macrophage production of tissue factor, a potent procoagulant that, once exposed to factor VII in the blood, initiates the coagulation cascade. Therefore, inflammation promotes not only the initiation of the atherosclerotic lesion but also its progression to complex plaque; the weakening of the fibrous cap, which renders the plaque prone to rupture; and finally, boosting of the thrombogenicity of the lipid core.

Emerging Diagnostic Techniques

The inflammatory cascade is potentially capable of being a risk of at various stages of atherosclerosis. Invasive and noninvasive techniques for detecting local inflammation are currently being explored.

Invasive Techniques

Temperature Heterogeneity

Most descriptions of atherosclerotic plaques have been structural, having to do with thickness, density, etc. However, functional characterizations, based on physiological variables such as temperature and pH, may also provide important information. Atherosclerotic plaques at risk for ulceration or rupture display temperature heterogeneity. Monocytes and inflammatory cells in plaque release heat. When intimal surface temperatures were measured with a thermistor, temperatures varied from 0.2° to 0.3°C up to 2.2°C and correlated positively with the macrophage density, suggesting that heat is generated by the increased metabolism of inflammatory cells. Many specimens contained “hot spots” foci of increased heat, characteristic of plaques that are denuded and inflamed. To detect whether temperature heterogeneity is observable in vivo, a catheter with an expandable, externally controllable basket with 9 thermo sensors was developed. Using this catheter, which is capable of detecting temperature heterogeneity to 0.01°C in various conditions of blood flow, temperature, and luminal stenosis, such temperature heterogeneity has been detected in atherosclerotic dogs and rabbits, in which

increased temperature was correlated with increased total macrophage mass. Temperature was constant in the normal arteries, but there was a higher temperature in the atherosclerotic arteries. Thermal techniques might potentially be combined with intravascular ultrasound or optical coherence tomography to provide both functional and anatomic information.

pH Heterogeneity

Although metalloproteinases are thought to be the principal contributors to plaque degradation, the pH content of plaque may also play a role. As inflammation increases metabolic activity and temperature, it also reduces pH. An acidic, low pH environment can promote apoptosis of smooth muscle cells, leading to plaque vulnerability. Fluorescence microscopic imaging confirmed pH heterogeneity in both humans and rabbits, but not in human umbilical arteries. pH of lipid-rich areas was significantly lower than pH in calcified areas , and had a higher temperature, reflecting increased metabolic activity and a more acidic environment in the lipid-rich segments. There was a general correlation between increased pH heterogeneity and excessive lactate accumulation. Thus, there may be a role for detection of low pH in determining plaque vulnerability. The potential clinical utility of this measure remains to be evaluated.

Noninvasive Techniques

Although it is useful to be able to measure cap thickness, modified LDL, temperature, and pH, for clinical use, it is important to be able to characterize plaque noninvasively to identify high risk plaques. Two imaging techniques, MRI and computed tomography (CT), have been used successfully for this purpose. High resolution, multicontrast imaging MRI is currently the leading imaging modality for plaque characterization in vivo; it can differentiate plaque components based on both physical and chemical variables, provide high resolution images of the coronary artery wall, and identify thin fibrous caps and lipid cores of atherosclerotic plaques. Signal from flowing blood has been eliminated using a high-resolution black blood sequence. In this method, signal from blood flow is rendered black using preparatory pulses to delineate the vessel wall. Black blood MRI provides images with excellent flow suppression and high contrast and signal to noise. This technique can be combined with MR angiography. Raman spectroscopy is an optical technique that characterizes the chemical composition of tissue. Raman spectra are obtained by processing collected light that is scattered by a tissue illuminated with a laser. It can potentially quantify cholesterol in plaque and can monitor the effects of atheroma modifying therapy. Raman spectroscopy is limited by the fact that blood absorbs laser light and that it is 1-dimensional. It can, however, be combined with other imaging techniques to provide important information about plaque composition. Targeted contrast enhanced ultrasound using microbubble contrast agents is in the early stages of development but also holds potential as a technique that can be used clinically to evaluate vascular inflammation.

Detection of Systemic Inflammation

Predictive Value of Various Inflammatory Markers

Raised circulating concentrations of acute phase proteins, cytokines, and cell adhesion molecules suggest that inflammatory processes are occurring systemically. Recently, the role of several markers in the prediction of coronary events has been studied in apparently healthy men and women, as well as among patients with stable angina, acute coronary syndromes, and in secondary prevention. These markers include IL-6, serum amyloid A (SAA), TNF-α, soluble intercellular adhesion molecule-1 (sICAM-1), macrophage inhibitory cytokine-1, sP-selectin, and CD 40 ligand. Of these various markers, however, only high-sensitivity (hs) CRP, which has a well-standardized assay, is so widely available as to be clinically useful at this time.

Predictive Value of C-Reactive Protein

CRP is an acute-phase reactant that has been shown in prospective cohort studies worldwide to be a reliable measure of underlying systemic inflammation and a strong predictor of future MI and stroke. Although CRP levels may increase up to 1000-fold in response to major infection or trauma, levels are remarkably stable over long periods of time when measured in asymptomatic adults, in whom CRP in the high-normal range has been found to be a potent, independent predictor of future vascular events.[41] CRP are synthesized mainly in the liver cells, induced by various inflammatory cytokines which are produced by activated macrophages/monocytes at the inflammatory sites. C-reactive protein is a principal acute phase protein, and increased most significantly upon various inflammations.[17] There are two different tests for CRP standard test and hs-CRP test. Standard test measures a much wider range of CRP levels but is less sensitive in the lower ranges and hs-CRP test can more accurately detect lower concentrations of the protein (it is more sensitive), which makes it more useful than the CRP test in predicting a healthy person's risk for cardiovascular disease. People with higher hs-CRP values have the highest risk of cardiovascular disease, and those with lower values have less of a risk. Specifically, individuals who have hs-CRP results in the high end of the normal range have 1.5 to 4 times the risk of having a heart attack as those with hs-CRP values at the low end of the normal range. A high-sensitivity CRP (hs-CRP) test measures low levels of CRP using laser nephelometry. The test gives results in 25 minutes with a sensitivity down to 0.04 mg/L[19].

Implication for Therapy

The association of inflammatory markers with increased risk for coronary heart diseases suggests the use of anti inflammatory treatment to reduce the risk for future Coronary heart diseases events. However, no prospectively designed studies have so far assessed clinical benefits after specific treatment of these markers. Such studies would indicate whether inflammatory markers could be used not only in risk stratification but also to determine therapeutic efficacy.

Effects of Statins on C-reactive protein

In several trials, the effects of statins on CRP levels appeared unrelated to their effects on lipid levels, suggesting that statins may exert an anti inflammatory action. The well documented lipid regulating effects of statins in conjunction with their possible antiinflammatory properties may therefore provide a theoretical double benefit. In a study of atorvastatin in high risk patients with combined hyperlipidemia, CRP concentrations decreased significantly with statin treatment. These reductions were unrelated to decreases in total cholesterol and LDL cholesterol, but were directly related to triglyceride changes and inversely related to changes in HDL cholesterol levels. The effects of pravastatin, simvastatin, and atorvastatin were compared in a crossover study of a small number of patients with elevated triglycerides and LDL cholesterol. The three drugs were equally effective in significantly decreasing CRP, and none reduced plasma levels of IL-6 or its soluble receptor. Changes in CRP levels were correlated with changes in triglycerides but not with changes in LDL cholesterol or HDL cholesterol. During the washout period between treatments, LDL cholesterol increased but CRP did not, providing further evidence of the dual activity of statins. In another small study, atorvastatin decreased CRP and SAA, whereas simvastatin did not. Both statins decreased the inflammatory marker soluble phospholipase A2, but they had no reproducible effect on intercellular adhesion molecule-1 or IL-6. A recent study with simvastatin showed a reduction in CRP within 14 days, an effect that was independent of LDL-cholesterol reduction. The mechanisms by which statins may counteract inflammation are still undergoing investigation. In an animal model of atherosclerosis, atorvastatin reduced inflammation by decreasing the expression of the proinflammatory molecule cyclooxygenase-2 (COX-2). Atorvastatin also decreased the activity of nuclear factor-B, a transcription

factor controlling proinflammatory genes, in circulating mononuclear cells. This finding suggests that atorvastatin may affect the activity of inflammatory mediators in circulating monocytes before they enter the vascular wall, differentiate into macrophages, and contribute to the atherosclerotic process.

Angiotensin Converting Enzyme Inhibition

By interrupting the expression of adhesion molecules and cytokines, angiotensin converting enzyme (ACE) inhibitors exert antiinflammatory effects on the development of atherosclerosis and on the plaque rupture that initiates acute coronary syndromes. In the future, identification of specific markers of inflammation may identify a subpopulation of high risk post MI patients and others for whom therapy with an ACE inhibitor will be more effective than it is for the total patient population.

Cyclooxygenase Inhibitors

Cyclooxygenase exists in two isoforms, COX-1 and COX-2, and plays an important role in inflammation. COX-1 is constitutively expressed in most tissues. COX-2 is induced at sites of inflammation and is expressed by cells in human atherosclerotic lesions. Aspirin, which inhibits both COX isoenzymes, has antiplatelet and antiinflammatory activities. The ability of aspirin to decrease the incidence of a first thrombotic event, including MI, ischemic stroke, and venous thrombosis, was measured with respect to CRP levels. Men with the highest CRP levels had an increased risk for MI and ischemic stroke, but not venous thrombosis, independent of other risk factors. Aspirin significantly reduced the risk for MI among men in the highest quartile of CRP levels, but not among those in the lowest quartile. This result suggests that the relation of CRP mediated inflammation to vascular risk is confined to the arterial circulation, that aspirin acts as an antiinflammatory agent, and that CRP levels may identify persons who are more likely to respond to aspirin therapy. The expression of COX-2 is induced by cytokines, growth factors, and prostaglandins secreted by macrophages in the vessel wall. COX-2 expression can lead to production of proinflammatory eicosanoids that in turn induce the production of IL-6. COX-2 promotes the development of early atherosclerotic lesions in LDL-receptor deficient male mice fed a Western diet, whereas inhibition of COX-2 decreases atherogenesis. In a rabbit model of atherosclerosis and in cultured vascular smooth muscle cells, atorvastatin decreased COX-2 but not COX-1 expression induced by cytokines, suggesting COX-2 as a therapeutic target in atherosclerosis. Selective inhibitors of COX-2 are used clinically as antiinflammatory and analgesic drugs. In patients treated with COX-2 inhibitors for arthritis, cardiovascular events occurred at a higher or equal rate compared with patients treated with other classes of antiinflammatory drugs or placebo. Nevertheless, it is possible that selective use of COX-2 inhibitors combined with an antiplatelet agent might reduce the substrate for thrombotic events and inhibit thrombosis. This hypothesis remains to be tested in clinical trials.

Fish Oil

In animal studies as well as in human populations, consumption of large amounts of fish and of highly unsaturated fatty acids in general (and omega-3 fatty acids [n-3 FA] in particular) reduces the risk of CHD. In a study monitoring 22 071 men with no prior CHD for up to 17 years, higher baseline blood levels of n-3 FA were strongly associated with a reduced risk of sudden death, even after controlling for confounding factors.41 In a study monitoring 84 688 women over 16 years, a higher intake of fish or n-3 FA was associated with a lower risk for CHD after adjustment for standard risk factors. In secondary prevention trials, increased consumption of fatty fish or dietary supplementation with n-3 FA reduced coronary events. The cardioprotective effect of n-3 FA may result from reductions in endothelial activation or expression of cell adhesion molecules. In vitro, the n-3 FA docosahexaenoic acid, but not saturated fatty acids, protected human endothlial cells from

activation by inflammatory cytokines and inhibited the expression of cell adhesion molecules, including vascular cell adhesion molecule-1 and E-selectin. Effective concentrations of docosahexaenoic acid can be achieved by nutritional supplementation. The protective effect of n-3 FA may also be due in part to an antiarrhythmic effect, reduction of triglycerides, decreased platelet aggregability, and possibly inhibition of COX. However, aspirin is a much stronger COX inhibitor than fish oil.

CONCLUSION

Inflammation and oxidation are crucial to the pathogenesis of atherosclerosis. Inflammatory markers such as CRP and SAA may predict risk for CHD. The role of inflammation in clinical decision making related to cardiovascular prevention, however, requires further research. Inflammatory markers, especially CRP, may prove to be useful adjuncts to traditional risk assessment to help determine the intensity of intervention, but should not supplant other risk factors when considering the initiation of treatment. That certain pharmacological interventions reduce inflammatory parameters helps illustrate the biological plausibility of the inflammation hypothesis, but the precise contribution of these effects to clinical benefit has proved difficult to analyze. For now, clinical event data from randomized trials represent the best guides for identifying treatment strategies. By this standard, statins, ACE inhibitors, aspirin, and dietary supplementation with n-3 fatty acids are among the appropriate drug approaches with putative anti-inflammatory effects that have been shown to reduce CHD risk. Lifestyle modification and proven medical therapies must join stenting and coronary bypass surgery. If we are to embrace fully our new appreciation of inflammation in the initiation and development of atherosclerosis, we must reduce new biological insights to practice to aid in the identification of individuals at risk of cardiovascular events, with the goal of lessening our dependence on late stage and invasive treatments.

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