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Review Article

Diagnosis and Treatment of Atherosclerosis: A Review Article

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Abstract

Atherosclerosis is a pathological process occurring in the major arteries that leads to many cardiac disorders. The development of atherosclerotic lesions can be regarded as a modified form of chronic inflammation which is multi factorial. This review briefly discusses the factors that influence the growth and development of atherosclerotic lesions. It also focuses on the recent advances in diagnoses. Finally the review summarizes the major and recent therapeutic strategies that are used for the treatment of atherosclerosis.

Keywords: Atherosclerosis; Pathogenesis; Diagnosis; Treatment

Introduction

Atherosclerosis represents the leading cause of morbidity and mortality in industrialized countries. It was initially defined as a process caused by the passive accumulation of lipids in the vessel wall, whereas nowadays it is considered as a complex condition where multiple pathogenic factors contribute to trigger and sustain vessel wall damage [1]. Experimental studies have clearly demonstrated that atherosclerosis is a progressive inflammatory process that frequently affects large- and medium-sized arteries leading to cardiovascular diseases such as coronary heart disease (CHD) and stroke [2].

Factors that influences atherosclerotic lesions

Inflammation plays a key role in all stages of the pathogenic process, including formation of atherosclerotic plaques consisting of necrotic cores, calcified regions, accumulated modified lipids, and inflamed smooth muscle cells (SMCs), endothelial cells (ECs), leukocytes, and foam cells. The imbalance between anti-inflammatory mechanism and pro-inflammatory factors, in favor of the proinflammatory factors, would result in the progress or rupture of atherosclerotic plaque [2-4].

The pathophysiology of atherosclerosis is multi factorial. Hyperlipidemia, critical condition of elevated lipid levels in the body, is considered a major classical risk factor resulting in the development and progress of atherosclerosis. A variety of risk factors have been found to be associated with hyperlipidemia like cholesterol rich food, overweight, alcohol abuse, diabetes and stress [5].

Clinical and experimental data have demonstrated that cells of both the innate (monocyte-derived macrophages and dendritic cells) and the acquired immune system (T and B lymphocytes) are implicated in the atherogenic process, producing a wide array of cytokines that can exert both pro and anti-inflammatory effects [6-8]. Several studies have implicated the role of these cells in progression and destabilization of the atherosclerotic plaque [9,10]. Deficiency in both T and B cells determines a reduction in atherosclerotic lesion development, as shown in apolipoprotein (Apo) E-deficient mice [11,12]. In accordance with these results, transfer of $CD4^+$ T cells aggravates atherosclerosis in immunodeficient ApoE knockout mice, indicating a proatherogenic role for T cells [13].

Furthermore, the majority of pathogenic T cells in atherosclerosis are of the Th1 profile, producing pro-inflammatory mediators such as IFN-γ and activating macrophages [14,15]. Th1-driven responses are detrimental to the atherosclerotic process. IFN-γ inhibits the synthesis of collagen by the vascular smooth muscle cells, damaging the protective thick fibrous cap of the plaque. It also activates monocytes/macrophages and dendritic cells, leading to the perpetuation of the pathogenic Th1 response [16]. Deficiency in IFN-γ or in its receptor significantly reduces lesion development and enhances plaque collagen content, whereas exogenous administration of IFN-γ enhances lesion development [17].

A recent category of auto antigens that have been implicated in atherosclerosis are the stress-induced heat shock proteins (HSPs) [18]. HSPs act as molecular chaperons facilitating refolding of denatured proteins in stressed cells and increase in response to many environmental stresses, including oxidative stress [19]. Under stress conditions, HSPs are expressed not only within cells, but also on the cell surface and can be released into the intercellular space. In atherosclerotic lesions, human HSPs appear to stimulate an immune response leading to the development and progression of atherosclerosis [20-22]. Antibody levels against HSP60/65 are increased in subjects with cardiovascular disease and are associated with disease outcome. Recently, human HSP90 was reported as a possible auto antigen involved in the pathogenesis of carotid atherosclerosis [23].

Diagnosis and assessment of severity

Multiple methods have been used in the assessment of atherosclerosis beginning from catheterization, carotid intima-media thickness, analysis of flow-mediated vaso dilation, X-ray contrast angiography, ending by the most recent ones like intravascular ultrasonographic and molecular imaging with positron emission tomography.

Catheterization is the gold standard for diagnosis of atherosclerosis, but it is relatively expensive and carries significant risk. Evidence accumulated over the last 15 years demonstrates that subtle increases in biomarkers of inflammation (such as C-reactive protein, CRP) can augur prospective cardiovascular events in apparently well people [24,25]. Among inflammatory molecular mediators, a key role is played by cytokines and chemokines, which modulate all aspects of vascular inflammation by altering the proliferation, differentiation, and function of vascular and immune cells. These regulatory

mediators and their receptors have been demonstrated in atheromatous tissue where they modulate plaque morphology and stabilization [26].

Several studies have demonstrated that serum levels of pro-inflammatory T helper (Th) 1-related cytokines positively correlated with the severity of atherosclerotic disease [27,28] In particular, high circulating levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6 were predictors of incident coronary and cardiovascular events, whereas high levels of the anti-inflammatory cytokine IL- 10 were associated with a significantly improved outcome of patients with acute coronary syndromes [27-29]. Moreover, prospective epidemiological studies found increased risk of incident or recurrent coronary heart disease associated with increased baseline levels of monocyte chemo-attractant protein- (MCP-) 1 [30]. Elevation of IL-18 and IL-2 serum levels in carotid atherosclerosis revealed an association of these cytokines with intimae media thickness [31-33].

Carotid intima-media thickness (CIMT), recorded with B-mode sonography, is an important marker to quantify atherosclerotic burden in the common carotid artery (CCA). The last twenty years, the value of CIMT-measurement for risk estimation of atherosclerotic events (for e.g., myocardial infarction, stroke, and sudden cardiac death) increased more than ever [34]. Carotid plaque formation is defined as an increase of CIMT about at least 0.5 mm or an increase about 50% compared the adjacent CIMT as well as an increase of thickness about more than 1.5 mm [35]. It is certain that carotid plaque formation is always pathologic. In a meta-analysis about 11 population-based studies, carotid plaque formation had a significantly higher diagnostic precision in the prediction of myocardial infarction compared to an increased CIMT [36]. The additive inclusion of plaque formation in CIMT-measurements may improve risk prediction of coronary heart disease [37].

Analysis of flow-mediated vasodilation (FMV) of the brachial artery by use of ultrasound allows assessing endothelial function, and provides pathophysiological, diagnostic and prognostic information. In individuals known to have peripheral atherosclerosis, the FMV technique reinforces the role of endothelial dysfunction in the pathogenesis of cardiovascular disease and is likely to become a surrogate marker of cardiovascular risk [38].

Conventional anatomic imaging modalities, such as X-ray contrast angiography, gives information about site and severity of disease but not the more important plaque composition [39]. It can detect coronary stenosis accurately and serve to guide percutaneous and surgical coronary revascularization. This approach can relieve ischemia, but only prevents events or prolongs life in selected subsets of patients. Indeed, autopsy studies indicate that lesions that do not cause a flow-limiting stenosis (<50%) cause most fatal MIs [40]. Thus, we need imaging approaches that reach beyond the visualization of stenosis to develop, validate, and apply novel therapies rapidly and effectively. More recent technologies, like intravascular ultrasonography (IVUS) and carotid ultrasound, have improved the observation of plaques by detecting qualitative differences in plaque composition. But these techniques remain based on contrast analysis, and do not inform specifically on the active cellular and molecular processes that drive the evolution of atherosclerotic lesions [41].

Noninvasive assessment of atherosclerotic plaques is needed to better predict events in the at-risk but asymptomatic, provide information regarding the underlying vascular biology, and track the effect of novel interventions, which will rely on interference with key identified pathways. Molecular imaging with positron emission tomography (PET) is sensitive enough to detect inflammation within atherosclerotic plaques. The tracer 18F-fluorodeoxyglucose (18F-FDG) is taken up by macrophages and has proven to be a robust noninvasive surrogate of plaque composition and activity [39]. All together, no current molecular imaging technology by itself is ideal, but co-registration imaging with two or more modalities (e.g., PET/CT, PET/MRI) allows us to combine the benefits of different imaging platforms. For atherosclerosis, researchers and clinicians have developed and tested many imaging strategies that report on the mechanisms involved in plaque formation and destabilization [41].

Treatment of atherosclerosis

Looking at the etiology of atherosclerosis, multiple therapeutic strategies could be adopted for the management of the disease. The treatment of atherosclerosis is currently based on lipid lowering. If lipid lowering agents are used in combination with anti-inflammatory or immunomodulatory agents, this could slow the progression of atherosclerosis. The reversal of atherosclerosis has also become a new attractive target for cardiovascular therapy and coronary device development [42,43].

Targeting elevations in low-density lipoprotein cholesterol (LDL-C), remains the cornerstone of treatment in clinical practice, whereas lowering elevated triglyceride (TG) levels and elevating low levels of high-density lipoprotein cholesterol (HDL-C) are secondary targets to slow progression, or even partially reduce the total atheroma volume [44].

Furthermore, the anti-inflammatory and immunomodulatory strategies have become the preferred emerging treatments to target the root causes of atherosclerosis [45,46]. The purpose of these therapies is to interfere with lipoprotein metabolism, [47] and also to modulate specific immune responses that play key roles in the development of the inflammatory processes involved in the pathogenesis of the disease [48,49].

Lipid Lowering Agents:

HMG-CoA Reductase Inhibitors (Statins)

The statins competitively inhibit the enzyme HMG-CoA reductase, the initial rate-limiting step in cholesterol synthesis. Inhibition of cholesterol synthesis, particularly in hepatocytes, decreases intracellular pools, which triggers an increase in LDL receptor number and activity [50]. Statins lower plasma lipids, including LDL-C and triglycerides, by inhibition of hepatic VLDL synthesis, resulting in decreased numbers of VLDL, IDL, and LDL particles. Beyond their lipid-lowering activity, statins also exert anti-inflammatory effects. Statins have also been reported to lower serum levels of C-reactive proteins together with their LDL and cholesterol lowering properties [51,52].

Fibric Acid Derivatives

Fibrates appear to activate transcription factors belonging to the nuclear hormone receptor superfamily, the peroxisome proliferator-activated receptors (PPARs). PPAR-α mediate the action of fibrates on HDL-C levels via transcriptional induction of synthesis of major HDL apolipoproteins (ApoA-I and ApoA-II) and increased synthesis of lipoprotein lipase. Fibrates decrease hepatic ApoC-III transcription,

reducing inhibition of lipoprotein lipase and enhancing clearance of triglyceride-rich lipoproteins. Other functions altered by the actions of fibrates on PPAR-a result in increased fatty acid uptake, decreased fibrinogen and high sensitivity C-reactive protein, and increased cholesterol efflux. Increasing the activity of endothelial lipoprotein lipase enhances release of VLDL surface fragments to form nascent HDL and increases production of ApoA-1. Decreasing triglyceride content and number of VLDL remnants reduces the cholesterol ester transfer protein transfer of triglycerides to HDL particles in exchange for cholesterol [53].

Bile Acid Sequestrants

They are large copolymers that act by exchanging Cl for negatively charged bile salt anions. They are poorly absorbed and pass out of the gastrointestinal tract with the stool. These bile resins are particularly of value in patients intolerant to statins and in combination with statins and niacin when the additional lowering of LDL-C is sought [54].

Cholesterol Absorption Inhibitors

They act at the brush border of the small intestine to inhibit cholesterol absorption, leading to a decreased delivery to the liver. This reduces hepatic cholesterol and increases LDL receptor mediated clearance of cholesterol from the blood. This distinct mechanism is complementary to that of the HMG-CoA reductase inhibitors [55].

Niacin

Niacin is unique among all available lipid modifying agents in exerting multidimensional beneficial effects across the entire lipid/lipoprotein spectrum. Niacin is the most effective agent available for raising HDL-C levels [56,57]. Niacin also has a beneficial effect on scavenger receptor class B type IY mediated cholesterol efflux and on adenosine triphosphate-binding cassette transporter A1Y mediated cholesterol efflux from macrophages, an effect that can contribute to reverse cholesterol transport via niacin mediated increases in HDL-C [58]. Emerging evidence also suggests that the beneficial effects of niacin may be mediated in part by its effects on acute atherosclerotic inflammation [59]. Niacin reduces release of fatty acids from fat stores, decreasing the rate of hepatic triglyceride synthesis and VLDL production. It also increases hepatic clearance of HDL-C but inhibits uptake of ApoA-1, resulting in its increased availability for development of HDL particles. The decrease in anabolism of VLDL triglyceride-rich particles, which are metabolized to IDL and LDL, results in decreased LDL-C and LDL particle numbers and an increase in the less atherogenic, larger, more buoyant LDL particles [60].

Anti-inflammatory and immunomodulators

Local adiponectin

Adipose has been considered a simple energy storage tissue, but mounting evidence suggests that it can produce and secrete many bioactive substances, collectively referred to as adipocytokines. One of these, adiponectin, has significant roles in regulating the metabolism of glucose and fatty acids, and in protecting against atherosclerosis. Adiponectin is a collagen-like protein, whose gene is located on human chromosome 3q27 and is named as apM 1 gene [61]. Adiponectin has been shown to reduce atherosclerosis through attenuating endothelial inflammatory response and macrophage-to-foam cell transformation [62]. Adiponectin has been reported to inhibit TNF-α-induced expression of adhesive molecules by blocking NF-κB, and it could inhibit proliferation of smooth muscle cells induced by growth factors by inhibiting mitogen-activated protein pathways. Meanwhile, adiponectin suppresses the expression of NF-κB-inducible genes, including VCAM-1, in endothelial cells and class A scavenger receptor expression in monocyte-derived macrophages [63,64].

Tumor necrosis factor-α blockade

A common feature of TNF antagonists is that they reduce cellularity in inflamed tissues and inhibit expression of pro-inflammatory cytokines and chemokines IL-1B, IL-6, IL-8, MCP-1, GM-CSF, VEGF. Furthermore, they dampen the TNF-α-driven production of matrix-degrading enzymes MMP-1 and MMP-3 [65]. These enzymes are considered to be contributing factors to plaque instability. The pleiotropic cytokine IL-6 acts as a major inducer of the acute-phase response (i.e. C reactive protein) and impacts on the function of diverse inflammatory and vascular cells [66].

Interleukin-1 receptor antagonism

Interleukin-1 receptor antagonism (IL-1Ra) has shown beneficial effects in several inflammatory diseases and recently also stroke [67]. Genetic evidence documented a significant correlation between a variant in the IL1-Ra gene and carotid atherosclerosis [68].

Leukotrienes Modifiers

Leukotrienes belong to the family of eicosanoids and constitute potent pro-inflammatory and smooth muscle constrictive lipid mediators [69]. Marked reduction in inflammatory biomarkers has been observed after administration of an inhibitor of the 5-lipoxygenase activating protein (FLAP) to patients carrying at-risk variants in the FLAP gene or the LTA4H gene [70].

Expansion of Regulatory T Cells

Treg cells were detected in all stages of atherosclerotic lesions. Expansion of the Treg cell pool can be achieved either by promoting Treg cell development and survival in vivo by administering drugs or by adoptive transfer of Treg cells following ex vivo expansion. A monoclonal antibody directed at the CD3-e chain of T cells showed remarkable efficacy in type 1 diabetic patients and reduced atherosclerosis in mice [71,72]. A critical role was recently identified for the co-stimulatory molecules ICOS, PD-1, OX40L, and CD137 in Treg and cytotoxic T cell function in mice, suggesting further targets for modulation of immune homeostasis in atherosclerosis [73].

Cytokine administration in vivo may be a valid short-term strategy to enhance Treg cells. Interleukin-10 and TGF-β have important roles in Treg cell generation and function. TGF-β, however, appears as a less interesting candidate due to its pleiotropic effects. Adoptive immunotherapy to rapidly increase the circulating Treg cell pool by re-infusion of autologous Treg cells after in vitro expansion constitutes an interesting approach. Treg cells directed against antigens relevant in atherosclerosis can be achieved by in vitro expansion of isolated antigen-specific (adaptive) Treg cells, by means of expanding natural Treg cells isolated from patients against specific antigens in vitro or by induced expansion of naive T cells against specific antigens under tolerable conditions in vitro [74].

Atherosclerosis-specific immunization

Immunization has emerged as a promising therapeutic regimen against atherosclerosis enhancing protective antibody titers, altering the balance of pro- and anti-inflammatory T cell subtypes and expanding Treg cells. Several antigens have been identified and investigated for immunization against atherosclerosis in animal models using active immunization or antibody infusion. Among those, epitopes recognized in the LDL particle including apolipoprotein B-100 appear most interesting from a clinical perspective in light of the role of LDL in the pathogenesis of atherosclerosis [75].

Lipid-Based Vaccination

Since lipids are key biomolecules in atherosclerosis, several vaccination strategies have targeted different proteins considered central in lipid metabolism. Over the past decade interest has turned to modulation of cholesteryl ester transfer protein (CETP) activity. This strategy resulted in the inhibition of atherosclerotic lesion formation, associated with increased CETP antibodies, decreased CETP activity, and modified lipoprotein profiles [49].

It has been suggested that antibodies reactive to oxidized LDL may contribute to the pathogenesis of atherosclerosis; however, anti-oxidized LDL IgM antibodies may protect against atherosclerosis possibly because they can scavenge the oxidized LDL particles [76]. Grosso et al. have reported that the passive immunization with xenogeneic polyclonal antibodies, xenogeneic Fab fragments, and allogeneic monoclonal IgG antibodies, reactive to electronegative LDL (minimally modified LDL), significantly reduced atherosclerosis in LDL-receptor-deficient mice [77].

Recombinant human antibodies against MDA-ApoB100, 2D03-IgG, were very effective in promoting atherosclerotic lesion regression in ApoB100-expressing LDL receptor deficient mice, which has been suggested to come about as a result of reduced macrophage infiltration and enhanced cholesterol efflux [78]. Inverse association between antibodies to malondialdehyde- (MDA-) modified fibronectin and a risk of cardiovascular events has been reported. The immunization of apoprotein E- (ApoE-) deficient mice with MDA-modified fibronectin resulted in a 70% decrease in plaque area and a less inflammatory phenotype of remaining plaques. Immunization converted a weak naturally occurring Th1 antibody response against MDA-fibronectin into a Th2 antibody response. Cytokine expression and flow cytometry analyses of spleen cells from immunized mice showed an activation of regulatory T cells. Immunization with MDA-fibronectin was also found to reduce plasma fibronectin levels [45].

Heat Shock Proteins

Autoimmunity to heat shock proteins (HSPs) is one element in atherosclerosis-induced immune responses. HSPs are a class of functionally related, highly conserved proteins that function as sentinels in the so-called cellular stress response [79]. Repeated mucosal administration of Mycobacterium HSP60/65, both orally and nasally, inhibited atherosclerotic lesion formation in LDL-receptor-deficient mice when compared to the control group. The observed attenuation of atherosclerosis was associated with decreased macrophage and T-cell numbers and enhanced IL-10 intimal expression [80].

B-Cell Modulation

Although limited vascular B-cell infiltration is detectable in the early stages of atherosclerosis, B-cell accumulation substantially increases with time. It localizes within and around advanced atherosclerotic coronary lesions and atherosclerotic abdominal aortic aneurysms of mice and humans and is even prominent in vascular inflammation associated with other immune mediated diseases [81]. Inhibition of excessive B-cell activation either through depletion or immune modulation might substantially limit vascular inflammation and atherosclerotic lesion development [82].

Alternative Therapies

Plasmonic photothermal therapy (PPTT) using near-infrared (NIR) laser irradiation

Is the novel invasive approach in cardiology. The noble-metal nanoparticles are the only type of optically active composite spherical particles on the nanoscale for needs of PPTT [83].

Therapies Based on Response-to-Retention Hypothesis

The aorta is an abundant tissue source of the heparin sulfate proteoglycan (PG) collagen XVIII and its proteolytically released endostatin (ES) fragment, which has previously been shown to inhibit angiogenesis in cancer and atherosclerosis models. A recent data has shown that collagen XVIII is differentially degraded in blood vessels affected by atherosclerosis. Loss of collagen XVIII/ES resulted in enhanced plaque neovascularization and vascular permeability to lipids in mice prone to developing atherosclerosis [84]. ES indirectly inhibits the macrophage uptake of biglycan-associated LDL by interfering with LDL retention to biglycan, but it has no direct effect on th macrophage uptake of native or modified lipoproteins. Immunization with the chP3R99 monoclonal antibody has been reported to prevent the development of atherosclerosis lesions, and this effect was associated with its capacity to induce antibodies capable of blocking the binding of LDL to chondroitin sulfate (CS) and their oxidation, thus acting as an idiotypic vaccine. It has been shown that antiatherosclerotic effects are associated with the capability of preserving the aortic redox state [85].

Eicosapentaenoic Acid from Fish Oil:

Supplements that contain the long-chain omega-3 eicosapentaenoic acid found in fish oil at doses up to 3 g/day reduce TG levels by as much as 30%. Evidence supports a role for omega-3 fatty acid supplements in reducing risk factors for atherosclerosis. The benefits of omega-3 fatty acids include reduced serum TGs, lower risk of sudden cardiac death and all-cause mortality, mildly lower blood pressure, and reduced risks of inflammation and thrombosis [86].

Conclusion

Atherosclerosis is one of the most widespread health problems which is characterized by hyperlipidemia and chronic inflammation. Many methods have been implicated in the diagnosis of atherosclerosis like catheterization and X-ray contrast angiography. Moreover, recent techniques like PET, have shown much better sensitivity in inflammation detection within atherosclerotic plaques. Many therapeutic strategies like HMG CoA reductase inhibitors, bile acid sequestrants, fibrates, and nicotinic acid derivatives have been

widely used to reduce atherosclerotic lesions. However, recent therapies targeting to blockade of inflammatory cytokines and others as atherosclerosis-specific immunization, succeeded to provide significant reduction of the risk of atherosclerosis. However, further studies are mandatory in order to provide more novel therapeutic agents for complete protection of atherscleosis.

Conflict of interest

The authors have no conflict of interest to declare.

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