Systemic inflammation as a risk factor for atherothrombosis

S. I. van Leuven¹, R. Franssen¹, J. J. Kastelein¹, M. Levi¹, E. S. G. Stroes¹ and P. P. Tak²

Several chronic inflammatory disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and chronic infections that are associated with a chronic inflammatory state, such as human immunodeficiency virus (HIV) infection, are associated with an increased incidence of cardiovascular disease (CVD). Cardiovascular mortality is a major cause of death in patients with these disorders. Direct effects and indirect sequelae of systemic inflammation promote atherothrombotic vascular disease. Pathophysiological processes promoting atherogenesis can initiate years before the diagnosis of a chronic inflammatory disease is made, and since exposure to risk factors in this pre-clinical phase is widespread, early cardiovascular protection in these patients seems warranted.

KEY WORDS: Systemic inflammation, Atherosclerosis, Thrombosis, SLE, RA.

Introduction

During the last decades it has become well established that inflammation plays a major role during all stages of atherosclerosis, from fatty streak formation up to plaque destabilization and subsequently atherothrombosis [1]. Recently, it has become clear that systemic inflammation, principally outside the vascular system, can enhance atherogenesis. This is illustrated by the increased incidence of cardiovascular disease (CVD) in patients with chronic inflammatory disorders, such as systemic lupus erythematosus (SLE) [2], rheumatoid arthritis (RA) [3], inflammatory bowel disease [4], human immunodeficiency virus (HIV) [5] or even periodontitis [6].

Systemic inflammation and CVD: epidemiology

It has been known for up to 30 yrs that patients with SLE have an increased risk of developing CVD [7]. This holds particularly true for pre-menopausal women with SLE, who are 50 times more likely to have a myocardial infarction compared with healthy women [8]. Indeed, subclinical atherosclerosis is present in 40% of all SLE patients [9], who overall have a 5–10 times increased risk of developing CVD [10]. Similarly, the association between RA and atherosclerotic vascular disease was identified decades ago and these patients have a 4-fold increased risk of CVD [11]. In fact, cardiovascular mortality is currently the main cause of death in RA patients [12]. In the relatively short period of time that HIV is now being diagnosed, it has become clear that also in these patients the atherosclerotic process is accelerated, partly independent of the use of anti-retroviral therapy [13]. In fact, atherogenesis appears to also be enhanced in Sjogren’s disease [14], systemic sclerosis [12, 15] and vasculitis [16]. In addition, it has recently been suggested that Crohn’s disease is also associated with enhanced atherogenesis [17, 18]. Indeed, having an inflammatory disorder is an independent risk factor for vascular comorbidity [2, 11, 13] which suggests that the association between systemic inflammation and CVD is universal. In line with this, in several studies disease activity appears to be linked with atherosclerosis progression [19, 20] although this could not be confirmed by other studies [21]. It is highly likely that in the near future an association with CVD will be confirmed in other inflammatory disorders as well.

Systemic inflammation and the arterial wall

In general, exacerbations of inflammatory disorders are characterized by activation of leukocytes as well as increased concentrations of cytokines and other inflammatory mediators. This may impose injury on the arterial wall accelerating the atherosclerotic process [13, 22, 23]. The suggestion that systemic inflammation can enhance atherogenesis has been substantiated by the observation that various anti-inflammatory interventions can protect the vascular wall. Blockade of tumour necrosis factor-α (TNF-α) or chemokine receptors, for instance, results in attenuated atherosclerosis [16, 24, 25].

The atherogenic effects of a systemic inflammatory state can manifest at different levels. First, systemic inflammation can induce endothelial dysfunction. Under physiological circumstances the endothelium produces mediators such as the vasodilator nitric oxide (NO) that protect the arterial wall against atherothrombosis. An inflammatory state results in reduced expression of endothelial NO synthase (eNOS) in conjunction with increased expression of inducible NOS (iNOS). This dysbalance results in the production of excessive amounts of NO and underlies endothelial dysfunction. In addition, an imbalance between various endothelium-derived prostanoids has also been implicated in the origin of endothelial dysfunction [26]. Endothelial functioning can be measured non-invasively by means of flow-mediated dilation (FMD). Following deflation of an occluding forearm cuff, the ensuing reactive hyperaemia causes increased shear stress and subsequent production of NO. The ensuing diameter increase of the brachial artery can be measured using ultrasound diameter measurements [27]. Endothelial dysfunction is a sensitive and early marker for atherosclerotic vascular disease and occurs before the morphological changes of the arterial wall are present [28]. In several chronic inflammatory disorders, an endothelial dysfunction has been demonstrated [29, 30].

Second, systemic inflammation induces secondary dyslipidaemia; an atherogenic lipid profile characterized by reduced high-density lipoprotein (HDL) cholesterol and increased triglycerides [10, 31]. Indeed dyslipidaemia is more common in SLE and RA as exemplified by an increased incidence of the metabolic syndrome [32, 33]. In addition to lowering HDL levels, systemic inflammation can also modify the protein and enzyme composition of the HDL particle [17, 34]. Subsequently, HDL can acquire devious functional characteristics and may even exert pro-atherogenic effects [35]. In a number of studies, however, it has been shown that after correction of classical risk factors for CVD, such as...
dyslipidaemia, there is still a significantly increased risk of atherosclerotic vascular disease in patients with a chronic inflammatory disorder [11, 36]. Hence, although secondary dyslipidaemia is likely to contribute to enhanced atherogenesis, it does not appear to be the most important mediator.

Third, systemic inflammation can activate the coagulation cascade and vice versa [37]. In addition to tissue factor (TF), platelets play an important role in this bidirectional activation. A systemic inflammatory state results in thrombin generation and activation of platelets, and these processes are closely connected to the development of atherothrombosis [38]. Platelets can adhere to the endothelium well before an atherosclerotic plaque is formed as has been shown in apoE−/− mice, an animal model for atherogenesis [39]. Moreover, following binding to the endothelium, platelets can release a plethora of inflammatory mediators including adhesion molecules, chemokines and coagulation factors that subsequently mediate a pro-inflammatory environment as well as recruitment of leucocytes to the vascular wall and the subendothelial space. Over 300 proteins have been identified that can be released by activated platelets [40]. The atherogenic potential of platelets has been confirmed in a study in which administration of activated platelets to ApoE-deficient mice resulted in a 40% increase in atherosclerotic lesion size [41].

In addition to secretion of mediators of vascular inflammation and thrombosis, activated platelets also express P-selectin, an adhesion factor that facilitates binding to leucocytes (predominantly monocytes) via the receptor P-selectin glycoprotein ligand-1 (PSGL-1) receptor. These so-called platelet–monocyte complexes (PMC) are a sensitive marker for the activation of platelets [42] and it has been suggested that they play a causal role in plaque instability, thrombosis and inflammation [43]. An increased number of circulating PMCs have not only been shown in patients with atherosclerotic vascular disease [42, 44] but also in patients with a chronic inflammatory disorder such as SLE or RA [45]. Moreover, P-selectin induces tissue factor expression, the most important initiator of the coagulation cascade.

In conclusion, a systemic inflammatory state can lead to endothelial dysfunction, secondary dyslipidaemia and activation of coagulation. These mechanisms contribute to the pathogenesis of atherothrombotic vascular disease and represent potential targets for treatment strategies.

**Additional mechanisms, specific for chronic inflammatory disorders**

In conjunction with these general effects of systemic inflammation which may occur in various degrees in the different inflammatory disorders, there are additional mechanisms anchored within the pathophysiology of the individual inflammatory disorders that are specific to that particular disorder (Fig. 1).

In SLE, there is a pro-inflammatory and pro-oxidative state that can accelerate atherosclerosis [46]. This results for instance in enhanced oxidation of low-density lipoprotein- (LDL) cholesterol to the very atherogenic ox-LDL [47]. In addition, several antibodies have been reported that can enhance atherogenesis, such as antibodies directed against apolipoprotein H [48] or against the endothelium [49] which may indeed be clinically significant as increased apoptosis of the endothelium has been observed in SLE [50]. Finally, activation of complement has also been suggested to accelerate atherosclerosis in SLE patients. In 91 SLE patients, genotyping was performed of mannose-binding
lectin (MBL), which activates the lectin pathway of complement. Homozygosity for variant alleles of MBL, resulting in reduced serum levels was associated with a hazard ratio of developing arterial thrombosis of 7.0 [95% confidence interval (CI) 1.9–25.4] [51]. Interestingly, in healthy volunteers increased MBL levels appear to pre-dispose to atherothrombotic disease [52]. It remains unclear whether the role of MBL in atherothrombosis differs between people with or without SLE.

In RA, a reduced number of circulating endothelial progenitor cells (EPCs) has been reported. The number of these precursors of mature endothelium is negatively correlated with CVD and a reduction of EPC may be causally related to enhanced athrogenesis in RA [53]. A second cell type that may be involved is a T-lymphocyte subtype, the so-called CD4+CD28- T-cell. These cells have a high pro-inflammatory and tissue damaging potential and are increased in patients with unstable atherosclerotic plaques [54]. In RA, the number of circulating CD4+CD28- cells has been reported to be increased which was correlated to pre-clinical atherosclerotic disease including endothelial dysfunction [55]. Finally, a genetic risk factor for both RA and myocardial infarction has been reported [56]. The expression of major histocompatibility complex (MHC) class II is regulated by MHC2TA, the gene that encodes the class II transactivator (CIITA). An A-168G single nucleotide polymorphism (SNP) in the promoter region of MHC2TA, which leads to decreased MHCII expression, was recently analysed. Although decreased MHCII expression may lead to reduced antigen presentation, and thus attenuation of immune-driven responses within the arthritic joint as well as the atherosclerotic plaque, this mutation was associated with an increased susceptibility to both RA and myocardial infarction [56]. The authors hypothesized that the pathogenic mechanism may be related to a less efficient presentation of antigens to protective, regulatory T cells. Indeed, regulatory CD4+CD25+ T cells appear to play a protective role against both RA [57] and atherosclerosis [58].

Further elucidation of the pathophysiological mechanisms of these chronic inflammatory disorders may result in the identification of the specific processes, within the wide spectrum of immune activation, which accelerate atherosclerosis.

Systemic inflammation and CVD: clinical consequences

The observation that systemic inflammation can enhance the atherosclerotic process and thereby underlies an increased incidence of CVD has important clinical consequences. It implies that, when composing therapeutic strategies for patients with a chronic inflammatory disorder, cardiovascular protection will have to be part of the management strategy. For several autoimmune disorders this is further strengthened by the observation that the pathophysiological process has started years before manifestation of the disease or the time of diagnosis. In a number of studies it has been shown that in apparently healthy blood donors or soldiers, who were in a later stage diagnosed with RA [59] or SLE [60], various antibodies were present in the years preceding their diagnosis. In the case of RA it has even been shown that in the years prior to diagnosis, the serum levels of CRP [61] and sPLA2 [62], important markers of cardiovascular morbidity, are increased. Moreover, future RA patients have a significantly more atherogenic lipid profile in comparison with RA [63]. As such, the pre-clinical phase is not only characterized by the production of autoantibodies but there also appears to be an acute phase response as well as dyslipidaemia. This suggests that there may be prolonged exposure to risk factors that can accelerate the atherosclerotic process and emphasizes the significance of cardiovascular protection in these patients, perhaps even from the time of diagnosis.

The characterization of atherosclerosis as an inflammatory disorder has sparked considerable interest in anti-inflammatory or immunosuppressive medication as an anti-atherosclerotic strategy [24]. This holds true for patients with a chronic inflammatory disorder, in particular considering these patients are by definition assigned to these classes of drugs. One of the most well-known anti-inflammatory interventions is treatment with non-steroid anti-inflammatory drugs (NSAIDs). However, in addition to inhibition of inflammation, this group of drugs has a much broader range of actions including that on the prostaglandin metabolism in which also atheroprotective mediators (e.g. prostacyclin) are inhibited [64]. Several studies have also evaluated the anti-atherogenic potential of immunosuppression. Blockade of TNF-α in patients with RA [65] or vasculitis [16] for instance has indeed been shown to result in a significant improvement of endothelial function. Hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) also fulfill an interesting role. These drugs are effective in lowering LDL-cholesterol and thereby cardiovascular risk. In addition, several immunomodulatory properties have been ascribed to statins [66]. In animal models for SLE [67] and RA [68], it has indeed been shown that statins can inhibit the pathophysiology of these disorders although it should be mentioned these effects were achieved with dosages that exceed human use. Immunomodulatory actions of statins have also been shown in patients with RA [69] and short-term treatment significantly improved endothelial function [70]. In SLE, two randomized, placebo-controlled studies have been initiated to evaluate the potential cardiovascular risk reduction of statins in these patients. One of them was terminated prematurely, however, due to difficulties with recruitment and retention of participants [71]. A similar study in children and adolescents with SLE has recently been initiated and results are expected in early 2010 [72]. Interestingly, mycophenolate mofetil (MMF) has recently also emerged as a potential anti-atherosclerotic strategy [73]. MMF has a strong cytostatic effect on T lymphocytes by interfering with DNA synthesis in activated T cells [74, 75]. This may significantly attenuate plaque formation since T cells have a prominent role in athrogenesis illustrated by the observation that ablation of replicating T cells, by incorporation of a suicide gene active upon cell division, was shown to result in a 55% reduction of lesion development in mice [76]. In addition, MMF also induces apoptosis in activated T cells [77] and has beneficial effects on regulatory T cells [78], which are considered atheroprotective [58]. Furthermore, MMF interferes with the expression of adhesion molecules not only on T cells [74, 79] but also on monocytes/macrophages [80] and the endothelium [81]. MMF can inhibit leucocyte recruitment to the subendothelium and the subsequent reduced activation of leucocytes will translate into attenuation of subendothelial cross-talk between T cells and macrophages. This cascade of events will interrupt the self-perpetuating pro-inflammatory environment within the arterial wall, the hallmark of atherosclerotic vascular disease [82]. Indeed, in several animal studies MMF has been shown to inhibit the atherosclerotic process [83–85] and human studies are therefore warranted.

Conclusion

Improvements in diagnostic and treatment strategies have led to a significant increase in the life expectancy of patients with chronic inflammatory disorders. This has contributed to the current situation, where now cardiovascular comorbidity represents a considerable source of mortality and morbidity. Direct and indirect consequences of a systemic inflammatory state mediate atherothrombotic disease. Pathophysiological mechanisms specific to SLE or RA can, however, also contribute to this. Especially considering the fact that pathophysiological processes involved in these disorders can occur at a subclinical level years before a diagnosis is made, early cardiovascular prevention seems essential in these patients.
Disclosures: The authors have declared no conflicts of interest.

References


