Lupus (1998) 7, Suppl 2, S132–S134
 0961-2033/98 $12.00
http://www.stockton-press.co.uk/lup

REVIEW

Antiphospholipid antibodies and myocardial infarction

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In prospective studies, increased levels of cardiolipin-biding antibodies and autoantibodies to oxidized low-density lipoprotein (LDL) have been observed in patients with myocardial infarction (MI). These findings suggest that antiphospholipid antibodies may contribute to the development of MI. The 'oxidative-modification hypothesis' in the pathogenesis of atherosclerotic heart disease is based on the oxidation of LDL, its accumulation into arterial wall, and the development of chronic inflammation in the atheroma. Evidence of enhanced lipid peroxidation and its association with antiphospholipid antibodies has been recently reported in SLE patients. There is also epidemiological data showing a remarkably increased risk of MI in SLE. In this review, the role of different types of antiphospholipid antibodies in the development of atherosclerotic heart disease is evaluated with particular attention to their potential pathogenic mechanisms and the possibilities in the prevention of MI associated with antiphospholipid antibodies.

Keywords: antiphospholipid antibodies; oxidized LDL; prothrombin; β_2-glycoprotein I; atherosclerosis; myocardial infarction

Introduction

Myocardial infarction (MI) is a clinical manifestation of coronary atherothrombosis. The basic feature in the atherosclerotic coronary vessel is the accumulation of lipids, lipoproteins and inflammatory cells in the arterial intima and the proliferation of the smooth-muscle cells. Atherosclerosis can be considered as a systemic disease characterized by narrowing arteries with endothelial dysfunction affecting the vascular function and the hemostatic balance. Inflammatory reaction in the atheroma seems to be an important determinant for the development of clinical complications of the atherosclerotic disease, such as atherothrombosis.

Anticardiolipin antibodies and MI

Elevated levels of antibodies binding to cardiolipin (a phospholipid purified from heart tissue but found ubiquitously in all mitochondrial membrane) were described in young patients with myocardial infarction by Hamsten et al. in 1986.[1] The authors suggested that cardiolipin-binding antibodies could contribute to the development of coronary occlusion in patients with coronary heart disease without a lupus-like syndrome. This finding has been confirmed by prospective studies showing that elevated levels of cardiolipin-binding antibodies in a non-systemic lupus erythematosus (non-SLE) population imply an increased risk for the development of MI.[2–5] Some evidence supports the view that cardiolipin-binding antibodies are a risk for MI, especially in young individuals.[1,4,6] The prevalence of cardiolipin-binding antibodies in patients with MI seems to be between 5% and 15%, which indicates that the possible etiological fraction of these antibodies in the development of MI is not large in a general population.[1–6] In some prospective studies the association of cardiolipin-building antibodies with MI has not be seen.[7] In patients with SLE cardiolipin-binding antibodies are a frequent finding and the clinical significance of these antibodies in the development of MI in the SLE population may indeed be more pronounced.

The antibodies binding to cardiolipin on solid-phase immunoassay may be directed against several different antigenic structures available in the assay. Some recognize phospholipids, some bind to plasma

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phospholipid proteins such as β_2-glycoprotein I or prothrombin, and some of these antibodies may be directed against cross-reactive epitopes common with oxidized low-density lipoprotein (LDL).[8,9] The heterogeneity of cardiolipin-binding antibodies makes it difficult to compare the results from different studies. Some anticardiolipin assays may more specifically detect antibodies directed against phospholipid-binding plasma proteins and be less sensitive for antibodies showing cross-reactivity with oxidized LDL. More antigen-specific and standardized assays are needed for evaluation of the possible pathogenic role of antiphospholipid antibodies in MI. In conclusion, cardiolipin-antibodies are associated with MI but in non-SLE populations these antibodies cannot be used for screening of individuals with increased risk for MI.

Antibodies to oxidized LDL and MI

Occurrence of antibodies binding to oxidized low-density lipoprotein (LDL) are considered as markers of atherosclerosis.[10] Two prospective studies have shown that these antibodies are predictive for MI.[5,11] Although some of these antibodies seem to be cross-reactive with antibodies binding to cardiolipin, these antibodies represent a separate entity.[9] Antibodies to oxidized LDL comprise antibodies binding to oxidized lipids (probably resposible for cross-reactivity with cardiolipin) and antibodies that recognize oxidized apolipoprotein B. Some of the antibodies binding to oxidized LDL may actually be antibodies to β_2-glycoprotein I that recognize their antigen in association with LDL.[12] Although cardiolipin-binding antibodies were associated with antibodies to oxidized LDL, the joint effect of these two antibodies for the risk of MI was additive,[11] suggesting that these two antibodies have at least partly different antibody specificities with different pathogenic pathways.

The generation of antibodies to oxidized LDL probably reflects the increased oxidation of LDL in atherosclerosis. However, the magnitude of the immune response may rather reflect the individual's responsiveness to the chronic inflammatory process in the arterial wall than the amount of *in-vivo* oxidized LDL. In this respect, the increased levels of antibodies to oxidized LDL may be considered as markers of the active atherosclerotic process, that is atherosclerosis characterized by intensive inflammatory reaction. Accumulating evidence indicates that an intensive inflammation in the atheroma makes the plaque more vulnerable for rupture and subsequent development of atherothrombosis.[13] In a series of patients with coronary heart disease, the levels of antibodies to oxidized LDL represented an independent determinant of impairment of both endothelium-dependent and endothelium-independent vasodilatation detected in the forearm vasculature with strain-gauge plethysmography.[14] The other independent determinants of impaired endothelium-dependent vasodilatation were elevated C-reactive protein levels and ICAM-1 expressing CD8 lymphocytes, both of which represent markers of inflammation. The question of the direct involvement of antibodies to oxidized LDL in the development of atherothrombosis is still open, but several studies indicate that these antibodies serve as markers of pathogenic determinants of atherothrombosis, such as oxidation of LDL, endothelial dysfunction and arterial inflammation.

Antibodies to β_2-glycoprotein I

Although antibodies to β_2-glycoprotein I have not been associated with the development of MI in clinical studies,[15] *in vitro* studies suggest that these antibodies may be involved with the development of atherosclerosis. Antibodies to β_2-glycoprotein I have been shown to enhance the accumulation of oxidized LDL into macrophages.[12] Antibodies to β_2-glycoprotein I may react with β_2-glycoprotein I–LDL complexes and increase LDL uptake by Fc receptors. This mechanism may be important in the development of premature atherosclerosis in patients with antibodies to β_2-glycoprotein I. The occurrence of antibodies to β_2-glycoprotein I in patients with MI who do not have autoimmune diseases seems to be rare, however.

Antibodies to prothrombin

In a prospective follow-up of healthy dyslipidemic men from the Helsinki Heart Study, a twofold risk of MI was found in middle-aged men with antibody levels to prothrombin in the highest tertile when compared to the men with antibody levels in the lowest tertile.[15] This risk was increased in an additive manner when the joint effect with other risk factors for MI was accounted. Especially when combined with high Lp(a) levels, which alone did not imply an increased risk for MI in this study, high antibody levels to prothrombin increased the coronary odds ratio from 1.8 to 3.8.

The possible pathogenic mechanisms of antibodies to prothrombin is a complex issue since these antibodies bind to a procoagulant plasma protein and

some of them even cause a prolongation of blood clotting time *in vitro* (lupus anticoagulant phenomenon).[8] Recently we demonstrated that these antibodies in sera from patients with MI in the Helsinki Heart Study cross-reacted with plasminogen.[16] Plasminogen has an important role in fibrinolysis. The antibodies binding to prothrombin on solid phase were inhibited by plasminogen and its peptide containing the conservative pentapeptide common to kringle proteins, such as prothrombin and plasminogen. Monoclonal antibodies to plasminogen have been shown to inhibit the activation of plasminogen.[17] Although functional studies with human polyclonal antibodies are lacking, it can be speculated that antibodies with cross-reactivity to prothrombin and plasminogen could have a dual function by causing prolongation of the blood clotting time *in vitro* or the inhibition of fibrinolysis *in vivo*.

Spreading of antiphospholipid antibodies in atherosclerosis

It seems that several subspecificities of antiphospholipid antibodies may occur in the patients with MI, and some evidence suggest that these antibodies may contribute to the development of MI. It is possible that antiphospholipid antibodies are initiated as a consequence of the underlying systemic arterial inflammatory disease and reflect the spreading of the autoimmune response against several antigens modified in the atherosclerotic vessel wall.

Antioxidants in the prevention of MI in antiphospholipid syndrome

Convincing evidence of an increased risk of cardiovascular events in SLE patients has been reported by Manzi *et al.*[18] Highest risk was observed in women with SLE in the 35- to 44-year age group, the rate ratio of cardiovascular events being over 50 times higher than in healthy women of similar age. Older age at SLE diagnosis, longer disease duration, longer duration of corticosteroid use, hypercholesterolemia, and postmenopausal status were more common in the women with SLE who had a cardiovascular event than in those who did not have an event. Indications for the use of low-dose aspirin and anticoagulant therapy as well as treatment of hypercholesterolemia exist in patients with antiphospholipid syndrome. Both epidemiological studies and recent clinical trials suggest the beneficial effect of antioxidants in the prevention of atherosclerotic heart disease in the nonautoimmune population.[19] In patients with SLE, antiphospholipid antibodies have been reported to correlate with the markers of lipid peroxidation, suggesting that increased oxidative stress could be a trigger of these antibodies.[20] Clinical trials for the prevention of myocardial infarction and atherosclerosis in patients with antiphospholipid syndrome are necessary. To achieve statistical power, these kinds of intervention studies should be planned as international multicenter trials.

References

1 Hamsten A *et al.* Antibodies to cardiolipin in young survivors of myocardial infarction: an association with recurrent cardiovascular events. *Lancet* 1986; **1**: 113–116.
2 Vaarala O *et al.* Anti-cardiolipin antibodies and risk of myocardial infarction in a prospective cohort of middle-aged men. *Circulation* 1995; **91**: 23–27.
3 Zuckerman E *et al.* Anticardiolipin antibodies and acute myocardial infarction in non-systemic lupus erythematosus: a controlled prospective study. *Am J Med* 1996; **101**: 381–386.
4 Levine SR *et al.* IgG anticardiolipin antibody titer > 40 GPL and the risk of subsequent thrombo-occlusive events and death. A prospective cohort study. *Stroke* 1997; **28**: 1660–1665.
5 Wu R *et al.* Antibodies against cardiolipin and oxidatively modified LDL in 50-year-old men predict myocardial infarction. *Arterioscler Tromb Vasc Biol* 1997; **17**: 3159–3163.
6 Adler Y *et al.* The presence of antiphospholipid antibodies in acute myocardial infarction. *Lupus* 1995; **4**: 309–313.
7 Sletnes KE *et al.* Antiphospholipid antibodies after myocardial infarction and their relation to mortality, reinfarction, and non-haemorrhagic stroke. *Lancet* 1992; **339**: 451–453.
8 Roubey RA. Autoantibodies to phospholipid-binding plasma proteins: a new view of lupus anticoagulants and other 'antiphospholipid' autoantibodies. *Blood* 1994; **84**: 2854–2867.
9 Vaarala *et al.* Affinity-purified cardiolipin-binding antibodies show heterogeneity in their binding to oxidized low-density lipoprotein. *Clin Exp Immunol* 1996; **10**: 269–274.
10 Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet* 1994; **344**: 793–795.
11 Puurunen M *et al.* Antibodies to oxidized low-density lipoprotein predicting myocardial infarction. *Arch Intern Med* 1994; **154**: 2605–2609.
12 Hasunuma Y *et al.* Involvement of β_2-glycoprotein I and anticardiolipin antibodies in oxidatively modified low-density lipoprotein uptake by macrophages. *Clin Exp Immunol* 1997; **107**: 569–573.
13 Libby P. Molecular bases of the acute coronary syndromes. *Circulation 12995;* **91**: 2844–2850.
14 Sinisalo J *et al.* Relation of inflammation to vascular function in patients with coronary heart disease (submitted for publication).
15 Vaarala O *et al.* Antibodies to prothrombin imply a risk of myocardial infarction in middle-aged men. *Thromb Haemost* 1996; **75**: 456–459.
16 Puurunen M *et al.* Antibodies to prothrombin crossreact with plasminogen in patients developing myocardial infarction. *Br J Haematol.* 1998; **100**: 374–379.
17 Church WR, Messier TL. Inhibition of plasminogen activation by monoclonal antibodies to the kringle 5-B chain segment of human plasminogen. *Hybridoma* 1991; **10**: 659–72, 1991.
18 Manzi S *et al.* Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997; **145**: 408–15.
19 Diaz MN *et al.* Antioxidants and atherosclerotic heart disease. *N Engl J Med* 1997; **337**: 408–416.
20 Iuliano L *et al.* Enhanced lipid peroxidation in patients positive for antiphospholipid antibodies. *Blood* 1997; **90**: 3931–3935.