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Chronic arthritis and cardiovascular disease: Altered blood parameters give rise to a prothrombotic propensity

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ABSTRACT

Objective: Rheumatoid arthritis, and to a lesser extent ankylosing spondylitis and psoriatic arthritis, associates with increased morbidity and mortality due to cardiovascular complications. We hypothesized that the increased risk of cardiovascular disease is reflected by changes in blood parameters that are compatible with a prothrombotic propensity. To substantiate this notion, we performed an extensive literature search identifying such parameters.

Methods: A search through PubMed (1970–2013) was done to find primary articles with the following search terms: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or synovial fluid. These were combined with keywords reflecting processes of atherothrombosis: atherosclerosis, cardiovascular disease, coagulation, endothelial, fibrinolysis, mean platelet volume, microparticle, platelet, platelet count and mass, thrombosis, and thrombus.

Results: The published studies point to a multitude of blood-related processes that can contribute to a prothrombotic propensity in chronic inflammatory diseases. These include an increase in platelet mass; low-level platelet activation, enforced by interaction with leukocytes and the formation of proinflammatory cytokines; a locally activated endothelium; and an increased coagulant activity. Patient treatment with methotrexate or TNF-α blockers appears to result in normalization of several of these prothrombotic parameters.

Conclusion: This analysis provides a first identification of the mechanisms by which inflammatory arthritis can aggravate cardiovascular disease.

Introduction

Chronic inflammatory arthritides like rheumatic and spondyloarthritis are differentiated through their clinical manifestations, but they have in common disabling inflammatory symptoms of the joints. The treatment options for these diseases are partly different and rely on the efficacy of disease-modifying drugs to suppress radiographic changes and specific clinical manifestations. On the other hand, all forms of chronic arthritis are associated with an increased risk of cardiovascular disease [1]. Furthermore, meta-analyses reveal that patients with rheumatic arthritis (RA) may have a 50% increase in mortality due to cardiovascular disease, while patients with spondyloarthritis, either ankylosing spondylitis (AS) or psoriatic arthritis (PsA), display a 25–40% higher mortality as a consequence of cardiovascular complications [2,3]. This insight has prompted the American College for Rheumatology and the European League Against Rheumatism (ACR/EULAR) to issue specific recommendations for cardiovascular risk management in patients with inflammatory arthritis [4]. The prevalence of cardiovascular disease in these patient groups is no more than partly explained by the classical Framingham risk factors, *i.e.*, male sex, age, systolic blood pressure, smoking, diabetes mellitus, plasma cholesterol, and body mass index [5]. This suggests that other likely blood-related disease factors contribute to the prothrombotic propensity.

For this article, we hypothesized that the higher risk of cardiovascular disease in patients with chronic inflammation of the joints is reflected by changes in blood parameters that are compatible with a prothrombotic propensity. To confirm this, we searched the published literature on relevant changes in blood-related parameters in patients with RA, AS, or PsA, categorized in changes in platelet activation, leukocyte function, endothelial activation, coagulation, and fibrinolysis. From this analysis, we deduced potential mechanisms on how these changes in blood parameters can link chronic arthritis to cardiovascular disease.

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Methods

A search through PubMed (1970–2013) was performed on primary articles with the following search terms: RA, AS, PsA, or synovial fluid. This search was combined with keywords reflecting processes of atherothrombosis: atherosclerosis, cardiovascular disease, coagulation, endothelial, fibrinolysis, mean platelet volume, microparticles, platelet, platelet count and mass, thrombosis, and thrombus. Together, this comprehensive search resulted in 55 articles, containing data on changes in blood-related parameters from patients with RA, AS, or PsA, with respect to platelet count or function, leukocyte function, and markers of inflammation, endothelial activation, coagulation, or fibrinolysis. Table 1 lists the findings and indicates the numbers of studies, where specific prothrombotic or proinflammatory changes have been reported.

Table 1
Reported blood-related parameters reflecting a prothrombotic or proinflammatory state in patients with chronic arthritis

Parameter	RA	AS	PsA
Platelet mass			
Mean platelet volume ↑	2/3 [57–59]	1/2 [58,60]	1/1 [61]
Platelet count ↑	11/13 [10,20,21,27,57–59,62–67]	3/4 [21,58,60,68]	0/1 [21]
Platelet microparticles ↑	1/4 [26,27,67,69]	0/1 [70]	
Platelet activation			
Platelet aggregation ↑	4/5 [20–24]	1/1 [21]	2/2 [21,25]
Integrin $\alpha_{IIb}\beta_3$ activation ↑	1/1 [53]	–	–
P-selectin (CD62P) expression ↑	2/3 [27,53,71]	1/1 [68]	0/1 [72]
CD63 expression ↑	1/1 [71]	1/1 [68]	–
Platelet-derived mediators			
β-Thromboglobulin (CXCL7) ↑	0/1 [53]	–	–
Platelet factor 4 (CXCL4) ↑	0/1 [64]	–	–
RANTES (CCL5) ↑	1/1 [26]	–	–
sCD40L ↑	1/1 [27]	–	0/1 [72]
Leukocyte activation			
CD11b and CD64 expression ↑	5/5 [26,27,53,57,59]	1/1 [60]	–
Platelet–monocyte complexes ↑	2/2 [27,53]	–	1/1 [72]
Platelet–neutrophil complexes ↑	1/2 [27,53]	–	0/1 [72]
sL-selectin (sCD62L) ↑	1/3 [73–75]	–	–
sICAM-3 (sCD50) ↑	1/1 [73]	–	–
Proinflammatory mediators			
C-reactive protein (CRP) ↑	16/16 [21,26,27,39,53,57–59,65–67,71,76–79]	7/7 [21,58,60,70,71,80,81]	1/1 [21]
ESR ↑	14/14 [21,26,27,53,58,59,65–67,71,76–78,82]	5/5 [21,58,60,68,80]	1/1 [21]
IL-1β ↑	2/2 [10,39]	–	–
IL-4 ↑	1/1 [10]	–	–
IL-6 ↑	8/8 [10,26,39,53,57,66,76,78]	1/1 [81]	–
IL-8 ↑	1/1 [26]	–	–
IL-18 ↑	1/1 [83]	–	0/1 [83]
MCP-1 ↑	1/1 [26]	–	–
MPO ↑	2/2 [57,79]	–	–
TNF-α ↑	3/3 [39,53,78]	–	–
Vascular adaptation			
Intima–media thickness ↑	2/2 [77,82]	1/2 [80,84]	–
Macrovascular dilatation ↓	1/2 [66,85]	2/2 [80,84]	–
Microvascular dilatation ↓	2/4 [66,79,86,87]	1/1 [88]	–
Angiogenesis ↑	–	1/1 [88]	–
Thrombomodulin ↑	1/1 [89]	1/1 [81]	–
Endothelial activation			
sE-selectin (sCD62E) ↑	3/7 [27,39,65,66,73,75,76,82,90]	–	1/1 [72]
sP-selectin (sCD62P) ↑	4/6 [53,57,73–75,90]	–	–
sICAM-1 (sCD54) ↑	6/7 [26,39,66,73,76,82,90]	–	–
sVCAM-1 (sCD106) ↑	3/4 [39,66,73,90]	–	–
VEGF ↑	1/2 [26,66]	–	–
Coagulation and fibrinolysis			
D-dimer ↑	5/5 [53,76,78,82,91]	–	–
Factor VIII ↑	1/1 [92]	–	–
Fibrinogen ↑	3/3 [53,91,92]	0/1 [80]	–
Fragment 1+2 ↑	2/3 [53,69,78]	–	–
PAI-1 ↑	3/4 [76,82,91,93]	0/1 [81]	–
TFPI ↑	1/1 [92]	–	–
Tissue factor ↑	–	1/1 [94]	–
Thrombin generation ↑	1/1 [95]	1/1 [96]	–
Thrombin–antithrombin complex ↑	1/2 [27,69]	0/1 [81]	–
tPA ↑	1/4 [76,82,91,93]	0/1 [81]	–
uPA ↑	1/1 [97]	–	–
vWF ↑	4/7 [66,76,77,82,91,93,98]	1/1 [81]	–

ESR, erythrocyte sedimentation rate; IL, interleukin; MCP, monocyte chemotactic protein; MPO, myeloperoxidase; PAI-1, plasminogen activator inhibitor-1; s, soluble; TFPI, tissue factor pathway inhibitor; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.