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Citation for published version (APA):

Beinsberger, J., Heemskerk, J. W. M., & Cosemans, J. M. E. M. (2014). Chronic arthritis and cardiovascular disease: Altered blood parameters give rise to a prothrombotic propensity. *Seminars in Arthritis and Rheumatism*, 44(3), 345-352. <https://doi.org/10.1016/j.semarthrit.2014.06.006>

Document status and date:

Published: 01/12/2014

DOI:

[10.1016/j.semarthrit.2014.06.006](https://doi.org/10.1016/j.semarthrit.2014.06.006)

Document Version:

Publisher's PDF, also known as Version of record

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

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ARTICLE INFO

Keywords:

Rheumatoid arthritis
Ankylosing spondylitis
Psoriatic arthritis
Platelets
Coagulation
Cardiovascular disease
TNF- α

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.

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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.

This work was supported by Grants from the Center for Translational Molecular Medicine (INCOAG) to J.W.M.H. and J.M.E.M.C.; the Netherlands Heart Foundation (2011T6) to J.M.E.M.C.; and ZonMW (MKMD 114021004) to J.W.M.H. and J.M.E.M.C.

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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-1 β ↑	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.

Fig. 1. (A) Non-inflammatory regulation of hemostatic processes. At a resting vessel wall, platelets and leukocytes are prevented from adhesion to endothelial cells by endothelial-produced inhibitory mediators (IM, e.g., prostacyclin and nitric oxide) and the absence of cellular adhesion molecules (CAM) at the endothelial surface, respectively. Endothelial injury leads to exposure of collagen and tissue factor (TF), causing platelet activation and fibrin formation, respectively, and formation of a thrombus. (B) Inflammatory modulation of hemostatic processes leading to a prothrombotic propensity. Under conditions of chronic inflammation, proinflammatory mediators (PM) are produced by activated leukocytes (PM1), platelets (PM2), and endothelial cells (PM3). Platelets become activated by adhesion onto activated and retracted endothelial cells, bind to leukocytes, and may enhance leukocyte transmigration. Locally, microthrombi may be formed with activated platelets and fibrin, triggered by collagen and tissue factor (TF), respectively. Coagulation and fibrinolysis products are released in the plasma. The PM also stimulate smooth muscle cell (SMC) proliferation.

Results

Blood cell–vessel wall interactions in normal hemostasis

Before discussing the aberrations in blood parameters reported in cases of chronic inflammation, we briefly recapitulate the fundamentals how blood cell interactions with the vessel wall are regulated in normal hemostasis [6]. In the non-inflamed, healthy vessel wall, the endothelial secretion of inhibitory mediators prevents adhesion of platelets, while leukocyte adhesion is limited by the absence of cellular adhesion molecules (CAMs) at the endothelial surface (Fig. 1A). Vascular damage results in exposure of subendothelial matrix proteins such as collagens to which platelets adhere and form aggregates and a secluding thrombus [7]. Exposed vascular tissue factor triggers the formation of thrombin and fibrin to consolidate the formed thrombus. These processes may also lead to limited leukocyte adhesion.

Increased platelet mass and circulating microparticles in chronic arthritis

The mass of circulating platelets has been identified as a blood parameter that associates with cardiovascular disease [8,9]. In 14 articles, a rise in platelet count or in mean platelet volume has been reported for patients with RA, AS, or PsA (Table 1). The increased mass of circulating platelets likely is a consequence of chronic inflammation, given the fact that several inflammatory

mediators influence platelet production from megakaryocytes or can prolong platelet survival. A key mediator in this respect is interleukin-6 (IL-6), which has been shown to stimulate platelet production from megakaryocytes and is up regulated in blood from RA and AS patients [10]. However, mechanistic studies to demonstrate such a role of IL-6 in arthritis are still missing.

In 2 breakthrough studies with mice, a role of platelet-derived microparticles has been shown in experimental arthritis [11,12]. However, in clinical studies with RA or AS patients, increased circulating levels of microparticles were observed in only 1 out of 5 articles. Given the knowledge that microparticle shedding can be considered as a marker of platelet activation [13,14], this argues against an overall high activation state of the circulating platelets in chronic arthritis. On the other hand, local effects such as accumulation of platelet-derived as well as neutrophil- and monocyte-derived microparticles in the synovial fluid of the joints have been reported in RA patients [11,15]. By implication, activation of both platelets and leukocytes in the joints may lead to microparticle formation and subsequent aggravation of local inflammatory and procoagulant reactions [16,17]. To which extent these local processes integrate to a systemic prothrombotic propensity of the patients is unclear.

Activated platelets interacting with leukocytes

Platelets contain a large pool of bioactive proteins that are secreted from their α -granules and can regulate a variety of

Fig. 2. Interactions between activated leukocytes, platelets, and endothelial cells in inflammatory arthritis. Leukocyte adhesion to inflamed endothelium can be accomplished by the indicated endothelial cell adhesion molecules (CAM), selectins, and their counter receptors. Leukocyte tethering to platelets occurs via integrin $\alpha_M\beta_2$, P-selectin, and CD40-CD40L. Soluble (s) forms of several of these glycoproteins can be released into the plasma and mark cellular activation. Platelets furthermore adhere to subendothelial fenestrae via glycoprotein (GP)Ib and GPVI, interacting with von Willebrand factor (vWF) and collagen, respectively. Proinflammatory mediators (PM) are produced by activated leukocytes (PM1), platelets (PM2), as well as endothelial cells (PM3). Key mediators are indicated in boxes.

intravascular processes, such as thrombus formation, vascular repair, and leukocyte activation [18]. Vice versa, inflammatory mediators derived from leukocytes can also potentiate the activation of platelets [19]. Hence, it is understandable that, in many studies with chronic inflammatory arthritis patients, evidence has been found for an increase in platelet activation. Mostly reported are higher tendencies in platelet aggregation and platelet secretion (Table 1).

In patients with RA, elevated $\alpha_{IIb}\beta_3$ integrin activation and platelet aggregation has been documented for all common platelet agonists: adenosine diphosphate (ADP), arachidonic acid, collagen, epinephrine, and thrombin receptor-activating peptide (TRAP) [20–25]. With respect to the P2Y₁₂ receptor agonist ADP, aggregation is reported to be increased in 4 out of 5 articles studying RA patients (Table 1). Flow cytometric studies support these findings by showing that dense granule secretion (expression of P-selectin/CD62P) and α -granule secretion (expression of CD63) are increased in platelets from RA or AS patients.

Interestingly, circulating levels of the platelet secretion products (β -thromboglobulin and platelet factor 4) seem to be unchanged in patients' blood samples, implying that the extent of systemic secretion is limited. Yet, 2 studies report elevated plasma levels of 2 other platelet products, namely CCL5 (RANTES) and soluble CD40L [26,27]. These mediators can be produced by non-classical secretion pathways, for example, via protease-induced shedding of soluble CD40L from the platelet membrane.

Platelets extensively interact with leukocytes in vascular diseases such as atherosclerosis and are regarded as central players in the pathophysiology of vascular inflammation [28]. Upon activation, platelets release a range of chemotactic cytokines and lipid mediators that influence the activation state of monocytes and other leukocytes [29]. Evidence for a proinflammatory role of platelets in RA comes from reports on increased levels of platelet-monocyte and platelet-neutrophil complexes in blood from these patients (Table 1). This is compatible with an increase in P-selectin expression at the platelet surface, as this glycoprotein is of key importance for the establishing of platelet-leukocyte contacts [16,30]. Conversely, activated leukocytes produce cytokines that can also modulate the platelet-activation process.

In particular, levels of monocyte-derived proinflammatory cytokines, such as IL-6, IL-8, and MCP-1, appear to be increased in RA plasma. Also, shedding of the leukocyte receptors, L-selectin, and ICAM-3 is increased in 2 out of 3 studies with patients with RA (Table 1). In the formation of these mediators, platelet activation may also play an intermediary role. For example, platelet inhibition was found to counterbalance the rises in IL-6 and the acute-phase reactant C-reactive protein in patients with acute cardiovascular disease [31]. Together with the erythrocyte sedimentation rate (ESR), plasma levels of C-reactive protein are the most frequently used markers for disease activity in patients with arthritis. As expected, the plasma levels of C-reactive protein and ESR were found to be increased in 22/22 studies examining patients with RA, AS, or PsA (Table 1). Platelets may further be implicated in the dissociation of the circulating pentameric form of C-reactive protein into monomers with more proinflammatory properties [32]. Taken together, these findings indicate that, in chronic arthritis, many of the reported changes in blood parameters point to an increase in platelet-leukocyte crosstalk linked to enhanced activation of these blood cells (Fig. 2).

Leukocyte and endothelial activation

Activated leukocytes strongly modulate the activation state of the vascular endothelium. Relevant mediators in this respect are IL-6 and TNF- α , the levels of which are consistently found to be elevated in plasma from RA patients (Table 1). Endothelial cells as well as monocytes that are stimulated with interleukins or TNF- α display increased procoagulant activity. Mechanistically, TNF- α induces the up-regulation of tissue factor and inhibits the activation of protein C, both of which effects promote the coagulation process [33,34]. The cytokines IL-1 β and IL-8 have similar effects on monocytes. In line with a procoagulant propensity, IL-6 stimulates the hepatic production of fibrinogen, thus resulting in elevated plasma levels of this coagulant protein [35–37].

As reviewed elsewhere, there is consistent evidence that the pathogenesis of rheumatic diseases depends on persistent endothelial activation and vascular adaptation [38]. Literature reports indicate increases in arterial intima-media thickness, arterial

stiffness, and angiogenesis (Table 1). Correspondingly, several studies with RA patients report on increased plasma levels of markers of endothelial activation, such as soluble fragments of ICAM-1, VCAM-1, and E-selectin, although this is not confirmed in all studies. The difference between studies may be explained by the small sample size and heterogeneity among the disease state of the patients. Mechanistically, there is evidence that elevation in leukocyte-derived TNF- α and IL-1 β induces the up-regulation and shedding of CAM and selectin isoforms on the endothelium [39]. Once expressed at the endothelial surface membrane, these glycoproteins regulate leukocyte adhesion and infiltration [29]. Furthermore, activated endothelial cells can contribute to the inflammation process by producing mediators like IL-1, -6, -8, TNF- α , MCP-1, and CCL5 [40]. Endothelial activation also leads to retraction of these cells and exposure of the subendothelial matrix to the blood stream, thus providing sites for platelet adhesion and activation [28,41].

Taken together, this leads to a model in which chronic arthritis drives and is driven by leukocyte interactions with platelets and endothelial cells, mediated by multiple proinflammatory mediators, many of which also have a role in prothrombotic reactions (Fig. 2). Jointly, these interactions thus create a proinflammatory and prothrombotic environment.

Plasmatic coagulation, fibrinolysis, and immunity

In the literature, ample support is provided for increased activity of the plasmatic coagulation and fibrinolytic systems in patients with inflammatory joint diseases (Table 1). An increase in thrombin generation has been noticed in plasmas from RA and AS patients. This is considered to be relevant, since thrombin is a central enzyme in the coagulation cascade that activates platelets and cleaves fibrinogen into fibrin [6]. In agreement with this, plasma levels of the thrombin-generation products, fragment 1 + 2, and thrombin-antithrombin (TAT) complex are increased in RA patients (Table 1). The reported increases in plasma levels of coagulation factor VIII and fibrinogen may also point to an increased procoagulant potential in these patients (Table 1 and Fig. 1B).

In 4 out of 6 studies with RA and AS patients, increased plasma levels of von Willebrand factor (vWF) have been reported (Table 1), which is an indication of endothelial activation and links to increased procoagulant activity. Once released by activated endothelial cells, vWF acts as a carrier in plasma for factor VIII and plays an important role in shear-dependent platelet adhesion and thrombus formation [6].

There is limited evidence for altered fibrinolytic activity in RA patients. The degradation of fibrin relies on plasminogen activation by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Increased levels of uPA but not of tPA have been found in the synovial fluid and blood plasma from RA patients (Table 1). The fibrin degradation product, D-dimer, commonly used as a marker of fibrinolysis, is consistently high in RA plasma. On the other hand, also the anti-fibrinolytic protein, plasminogen activator inhibitor-1 (PAI-1), released by activated endothelium, is higher in these patients.

Several recent studies point to connections between inflammation and alterations in innate and adaptive immunity in RA. In a mouse model of spontaneous autoantibody-driven arthritis, a role of the proinflammatory complement factor C5 has been identified in supporting the coagulation process [42]. In another study, cleavage of complement factor C5a by carboxypeptidase B in a thrombomodulin (endothelium)-dependent way was found to suppress the inflammation process [43]. Recently, citrullinated histone 4, present in pathogen-killing neutrophil extracellular traps (NETs), was identified as a substrate for RA-specific

anti-citrullinated peptides antibodies [44]. Taken together, these data point to coagulation, fibrinolysis, and immunity-induced procoagulant changes in the blood from arthritis patients, which at least partly can be linked to an increased activation state of the endothelium.

Normalization of prothrombotic propensity by anti-arthritis medication

Non-steroidal anti-inflammatory drugs (NSAIDs) are conventionally used as a first-line treatment of chronic arthritis to relieve pain, but they may promote cardiovascular risk. The latter effect has been attributed to NSAID-mediated inhibition of the COX2-dependent formation of prostacyclin in the endothelium, thereby abrogating the platelet-inhibiting activity of prostacyclin [45,46]. Other compounds used to slow down the progression of RA are the so-called disease-modifying anti-rheumatic drugs (DMARDs), with methotrexate as a standard. These drugs, targeted at T cells, are considered to have a beneficial effect on cardiovascular disease-related mortality [47]. However, because methotrexate (or other DMARDs) is often given in combination therapy with NSAIDs, a normalizing effect regarding cardiovascular risk is not always apparent [1].

An improved effect on cardiovascular disease is also reported for the biopharmaceutical TNF- α inhibitors (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab), which are prescribed either as first-line treatment or to patients who are non-responsive to other treatments [1]. Considering that TNF- α is a master regulator of inflammation, TNF- α blockers thus help to suppress the onset of this process [48–52].

From the analyzed literature, it is evident that at least several of the prothrombotic parameters become normalized in rheumatoid patients who are treated with methotrexate or TNF- α blockers (Table 2). As aimed for, all types of therapy reduce the plasma levels of key inflammatory mediators (ESR, C-reactive protein, TNF- α , and IL-6). A consistent decrease in platelet mass and a reduction in endothelial activation markers (soluble selectins and ICAM) so far have only been reported for conventional or TNF- α -directed therapy. A single, small-sized study reported no more than minimal effects on platelet-activation processes after treatment with methotrexate or TNF- α blockers [53]. Interestingly, all current treatments appear to normalize coagulation- and fibrinolysis-related parameters (Table 2).

Although anti-platelet agents may effectively suppress inflammatory processes [54,55], treatment strategies to reduce platelet-dependent inflammation processes in arthritis are not available yet. A potentially interesting target in this respect is platelet P-selectin, given its key role in forming interactions of leukocytes with platelets and endothelial cells. So far, the effects on arthritis of common platelet inhibitors targeted at cyclooxygenase (aspirin) or the P2Y₁₂ receptor for ADP (clopidogrel and prasugrel) have not systematically been studied.

Discussion and conclusion

Overviewing the literature, it appears that the prothrombotic propensity in patients with inflammatory arthritis is a consequence of the combined activation of the platelets, leukocytes, and endothelium, thereby affecting the coagulation system. Proinflammatory mediators released by leukocytes, platelets, and endothelial cells may drive the intercellular cross talk. The fragmented evidence so far indicates that in these patients, the mass of platelets is increased; the platelet-activation tendency is higher; platelet-leukocyte complexes are formed; coagulation factors accumulate; and (local) activation of the coagulation and

Table 2
Reported normalizing effects of anti-arthritis medication on blood-related prothrombotic and proinflammatory parameters

Parameter	Medication		
	Conventional ^a	Medication methotrexate	TNF- α directed
Platelet mass			
Mean platelet volume ↓	2/3 [58–60]	–	1/2 [60,100]
Platelet count ↓	4/5 [58–60,90,99]	–	2/2 [60,100]
Platelet mass ↓	1/1 [60]	–	1/1 [60]
Platelet activation			
CD62P expression ↓	–	0/1 [53]	0/1 [53]
β -Thromboglobulin (CXCL7) ↓	–	0/1 [53]	1/1 [53]
Proinflammatory mediators			
C-reactive protein (CRP) ↓	5/5 [58–60,90,99]	1/1 [78]	5/5 [53,60,78,88,101]
ESR ↓	4/4 [58–60,99]	1/1 [78]	7/7 [53, 60, 78, 85, 88, 100, 102]
TNF- α ↓	–	1/1 [78]	1/1 [78]
IL-6 ↓	–	–	2/2 [53,101]
Leukocyte count ↓	–	1/1 [53]	–
Endothelial activation			
sE-selectin ↓	1/1 [99]	–	–
sP-selectin ↓	1/1 [90]	–	1/1 [53]
sICAM-1 ↓	1/1 [90]	–	–
Vascular adaptation			
Intima-media thickness ↓	–	–	1/1 [85]
Macrovascular dilatation ↑	–	–	6/6 [85,88,102–105]
Angiogenesis ↓	–	–	0/1 [88]
Coagulation and fibrinolysis			
D-dimer ↓	–	2/2 [53,78]	1/1 [78]
Fibrinogen ↓	–	–	3/3 [53,101,105]
Fragment 1 + 2 ↓	–	2/2 [53,78]	1/1 [78]

Abbreviations: see Table 1.

^a Treatment with conventional disease-modifying anti-rheumatic drugs (DMARD), non-steroidal anti-inflammatory drug (NSAID), or steroids.

fibrinolysis systems results in the circulation of thrombin and fibrin products (Fig. 1B). The moderately activated platelets, leukocytes, and endothelial cells shed soluble forms of CAM and selectin receptors—perhaps in a manner dependent on the actual disease state—that serve as cell activation markers and may have biological properties themselves. Yet, there is little evidence for high in-situ platelet activation and massive release of platelet-activation products, such as observed in acute prothrombotic situations, e.g., in overt peripheral arterial disease. Together, this points to a mechanism of moderate or local blood cell activation, e.g., mediated and enforced by proinflammatory cytokines, which stimulates platelet interaction with leukocytes and endothelial cells and enhances leukocyte recruitment.

Because of their multi-faceted interactions with other cells of the cardiovascular system, platelets are nowadays considered as central regulatory cellular effectors of inflammation in vascular diseases [19,56]. From the current analysis, it seems that platelets—in crosstalk with leukocytes, the endothelium, and the coagulation system—are also important in the switch from chronic inflammatory into prothrombotic conditions linked to cardiovascular disease. However, more systematic trials are needed to identify the key markers of platelet or coagulation activation for assessment of the risk of cardiovascular disease in patients with rheumatoid disorders. This may lead to more personalized therapy to reduce the comorbidity and improved long-term outcome of these patients in terms of disability, hospitalization, and mortality.

The effectiveness of pharmacological treatment of arthritis, especially with TNF- α blockers, appears to be accompanied with normalization not only of leukocyte function but also of vascular, platelet, and coagulant activities. Hence, it seems that recuperation of the leukocyte-driven inflammation process leads to readjustment of many of the prothrombotic changes in patients with

chronic arthritis. Yet, the evidence for this scenario is scattered among articles, mostly analyzing small groups of patients. Larger and more coherent studies are required to confirm this treatment effect further.

Acknowledgments

We thank Dr. A.E. Boonen and Dr. A.M. van Tubergen, Division of Rheumatology, Maastricht University Medical Center for reading the article and for valuable suggestions.

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