Plasma fibrin clot structure and risk of thrombosis in rheumatoid arthritis

To the Editor Recently, Ząbczyk et al[1] have presented an interesting overview of studies on fibrin clot structure and an in vitro measurement of fibrin clot permeability in such clinical conditions as stroke, myocardial infarction, and some other diseases associated with an elevated risk of thrombosis. The authors concluded that assays testing clot properties may improve identification of patients at high thromboembolic risk. Because in their extensive overview the authors omitted some data and did not discuss prothrombotic conditions associated with systemic inflammatory diseases, I would like to address these issues and refer to a study showing unfavorably altered fibrin clot properties, including lower clot permeability, faster clot formation, thicker fibrin fibers, and prolonged fibrinolysis in patients with rheumatoid arthritis (RA).[2] It was found that clot permeability in these patients inversely correlated with C-reactive protein and fibrinogen levels and with disease activity measured by the Disease Activity Score 28.

Currently, there is strong evidence for the interaction between the systemic inflammatory state in RA and the hemostatic system, which leads to a hypercoagulable state and increases thromboembolic and cardiovascular risk in these patients.[3] However, alteration of fibrin clot properties associated with disease activity was reported for the first time in 2010 by Kwaśny-Krochin et al.[2] Several factors contribute to the prothrombotic state in active RA, including inflammatory mediators and elevated levels of fibrinogen, D-dimers, tissue plasminogen activator, and plasminogen activator inhibitor 1.[3] An increased risk of thrombosis reported in RA is at least in part determined by elevated blood levels of factor VIII (FVIII).[4] Simulations of thrombin generation suggest that blood plasma composition, that is, elevated FVIII levels, partly counterbalanced by free tissue factor pathway inhibitor (TFPI) derived from the damaged endothelium, may accelerate coagulation. It was also reported that disease activity positively correlated with FV, FVIII, FIX, FX, antithrombin, and free TFPI levels, while it correlated negatively with protein Z levels.[4]

As reported by Ząbczyk et al,[1] the use of medications may alter fibrin clot permeability in various disorders. In fact, there are scarce data on cardiovascular and venous thromboembolic risks in patients with RA, as well as on the treatment of RA. van den Oever et al[3] cited only one study showing clinical improvement associated with the reduction of activated coagulation in patients with RA treated with anti–tumor necrosis factor α (anti–TNF-α) antibody. At least one more study has shown clinical improvement accompanied by significant downregulation of elevated acute-phase protein levels within the first 16 days of anti–TNF-α treatment, with a simultaneous decrease in plasma concentrations of thrombin–antithrombin and plasmin–antiplasmin complexes during the next 44 days of infliximab therapy.[5]

The risk of thromboembolism in active RA is high.[3] The effects of systemic treatment of RA on fibrin clot structure and risk of thrombosis remain unknown. Therefore, we hope that our comments will stimulate further research in this area.

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Authors' reply Thank you for your valuable comment. Our review of December 2017 focused on recent observations regarding altered fibrin clot phenotype associated with thromboembolic events, including myocardial infarction, stroke, and venous thromboembolism.[1] In patients with systemic inflammatory diseases, such as rheumatoid arthritis (RA) as well as chronic obstructive pulmonary disease (COPD), a prothrombotic state involving reduced clot permeability and prolonged lysis time has been shown to be associated with disease activity.[2,3] One might speculate that such prothrombotic fibrin clot phenotype contributes to the elevated risk of thrombosis in patients with active RA. However, to what extent altered fibrin clot structure and function may increase the risk of arterial and venous thrombosis in RA remains to be established in large prospective studies. Such impact of fibrin variables has been shown for recurrent venous thromboembolism during follow-up.[4]

Although many antiplatelet, anticoagulant, or cholesterol-lowering agents have been shown to favorably modulate fibrin properties,[1,2] the influence of steroids or specific antibodies (ie, infliximab) on fibrin clot phenotype, especially in patients with systemic inflammatory diseases, is unknown. Growing evidence indicates that the treatment with anti–tumor necrosis factor α antibodies can suppress blood coagulation.[3] Similarly, patients with RA treated with tocilizumab, an interleukin-6 receptor inhibitor, showed a reduction in the levels of inflammatory markers, followed by a decrease in prothrombin fragment F1+2 and D-dimer levels.[5] This suggests that immunothrombosis is involved in RA-induced thrombosis, but the role of fibrin properties is unclear in this context. Therefore, we absolutely agree that further studies of patients with RA, with long-term follow-up, and with thromboembolic events as primary endpoints are warranted.

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