



**THE IMPORTANCE OF ENDOTHELIAL DYSFUNCTION IN THE DEVELOPMENT OF
DISORDERS OF THE HEMOSTASIS SYSTEM IN PATIENTS WITH RHEUMATOID
ARTHRITIS**

Musayeva Nargiza Bakhtiyarovna
Tashkent Medical Academy The Great Teacher,
Department of Hematology, Transfusiology and Laboratory Work

Annotation: Chronic inflammatory diseases are associated with accelerated atherosclerosis and increased risk of cardiovascular diseases (CVD). As the pathogenesis of atherosclerosis is increasingly recognized as an inflammatory process, similarities between atherosclerosis and systemic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel diseases, lupus, psoriasis, spondyloarthritis and others have become a topic of interest. Endothelial dysfunction represents a key step in the initiation and maintenance of atherosclerosis and may serve as a marker for future risk of cardiovascular events. Patients with chronic inflammatory diseases manifest endothelial dysfunction, often early in the course of the disease.

Keywords: endothelial dysfunction; endothelium; atherosclerosis; inflammation; inflammatory disease; arthritis

INTRODUCTION

An expanding body of evidence demonstrates that chronic autoimmune inflammatory diseases are associated with accelerated atherosclerosis and increased cardiovascular morbidity and mortality compared to the general population [1,2]. Although rheumatoid arthritis has been most extensively studied, an abundance of data now exists demonstrating excess cardiovascular risk in a multitude of other inflammatory diseases, including systemic lupus erythematosus, the seronegative spondyloarthropathies, psoriasis and inflammatory bowel disease [3].

Endothelial dysfunction has been postulated to represent an initial step in the pathogenesis of atherosclerosis in the general population. Accordingly, efforts to elucidate unique mechanisms driving increased cardiovascular risk in patients with inflammatory diseases have often focused on the endothelium, which serves as an interface for multiple converging risk factors. In this review, we outline the evidence for and the significance of endothelial dysfunction in several chronic inflammatory diseases. We review the epidemiology and potential mechanisms of endothelial dysfunction in inflammatory diseases, highlighting shared features. Finally, we summarize the available data regarding the efficacy of anti-inflammatory therapies in reducing endothelial dysfunction and potentially mitigating cardiovascular risk.

MATERIALS AND METHODS

We queried the PubMed database (NCBI, Bethesda, MD, USA) using the MESH searches for relevant studies using the following search terms in various combinations: rheumatoid arthritis; systemic lupus



erythematosus; psoriasis; seronegative spondyloarthritis; inflammatory bowel disease; endothelial function; endothelial dysfunction; endothelial activation; forearm blood flow; flow-mediated vasodilation; cardiovascular disease (CVD); cardiovascular mortality; myocardial infarction; inflammation. Because of the limited number of relevant studies, there were no defined inclusion or exclusion criteria. Studies were screened informally for size and methodological quality. Studies reviewed ranged over the period of 1982–2014, with preference given to more recent data. Systematic reviews and meta-analyses were incorporated when available.

RESULTS AND DISCUSSION

Rheumatoid arthritis, systemic lupus erythematosus, the seronegative spondyloarthropathies, psoriasis and inflammatory bowel disease have all been associated clinically with excessive cardiovascular risk [1]. Over the last several decades, there has been considerable interest in characterizing this excess cardiovascular risk in an attempt to identify potential risk factors and mechanisms responsible for the genesis of atherosclerosis in these populations (Table 1).

Table 1. Relative risk of cardiovascular morbidity and mortality.

Disease	CAD Risk (RR or OR)	Cardiovascular Mortality (RR)
Rheumatoid Arthritis	1.5–2.0 [26,27]	1.5 [28]
Systemic Lupus Erythematosus	2.2–2.6 [29,30]	1.7 [31]
Psoriasis (severe)	1.5–7.1 [7,25]	1.1–1.6 [7,25]
Ankylosing Spondylitis	1.9 [32,33]	1.3–2.1 [5]
Inflammatory Bowel Disease	1.2–1.4 [6,34]	1.0 [34,35]

Abbreviations: RR: Relative risk; OR: Odds ratio; CAD: Coronary artery disease.

Rheumatoid Arthritis (RA)

It has been known for many years that coronary artery disease is largely responsible for the excess morbidity and mortality in patients with RA. Endothelial dysfunction in RA was first described in a seminal 2012 study demonstrating impaired brachial artery responsiveness to ACh by FBF in patients with early disease [36].

Efforts to characterize endothelial function by measuring soluble plasma biomarkers in patients with rheumatoid arthritis have been largely unsuccessful. Littler *et al.* [4] first described an expression profile of intercellular adhesion molecules in 22 patients with RA. While ICAM-1, ICAM-3, VCAM-1, L-selectin and P-selectin were found to be elevated in sera of patients with RA, only P-selectin correlated with disease activity. Others have identified unique expression profiles in RA patients [2], although ICAM-1 and P-selectin were also found to be elevated in RA patients in these studies. Several investigators have failed to demonstrate differences in adhesion molecule expression between patients and healthy controls [3]. There is also discordance with regard to the correlation between adhesion molecule expression and markers of disease activity. Plasma levels of ADMA have also been found to be elevated in patients with RA. ADMA levels correlate inversely with FMD and directly with markers of systemic inflammation [2]. In general, the clinical utility of biomarkers for endothelial dysfunction



in inflammatory diseases remains unclear. While it appears unlikely that cellular adhesion molecules will serve as important prognostic indicators for CVD, ADMA is more promising. Other biomarkers currently under investigation, such as circulating endothelial progenitor cells, may prove to be useful markers of endothelial dysfunction.

CONCLUSION

Patients with chronic inflammatory diseases are at high risk for cardiovascular morbidity and mortality. In many inflammatory diseases, this heightened risk of CVD is reflected in early endothelial dysfunction as assessed by vasoreactivity studies, even in the absence of detectable atherosclerosis. The endothelium therefore represents an integrator of vascular risk and the study of its dysfunction may help elucidate mechanisms driving accelerated atherosclerosis in these populations.

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