

# THE ROLE OF INFLAMMATION IN ENDOTHELIAL DYSFUNCTION AND PROGRESSION OF ATHEROSCLEROSIS IN METABOLIC SYNDROME

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## REZUMAT

Sindromul metabolic joacă un rol important între factorii de risc cardiovasculari. Este deja cunoscut faptul că unii autori descriu boala aterosclerotică drept boală inflamatorie. Modificările apărute în cadrul sindromului metabolic determină disfuncționalități de ordin celular și molecular, generând disfuncția endotelială. Există studii care descriu o strânsă asociere între disfuncția endotelială și creșterea nivelului plasmatic de proteină C reactivă. Identificarea valorilor crescute ale CRP ca un factor de risc independent pentru disfuncția endotelială poate furniza o dovadă importantă pentru a lega un marker sistemic al inflamației de progresia aterosclerozei.

**Cuvinte cheie:** disfuncție endotelială, ateroscleroză, inflamație, sindrom metabolic

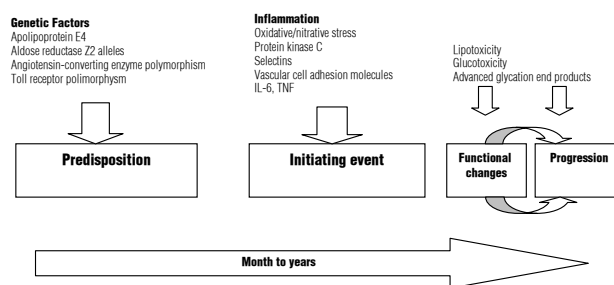
## ABSTRACT

The metabolic syndrome plays an important role as a risk factor for cardiovascular disease. It is known that the atherosclerotic disease can be described as an inflammatory disease. The changes generated by the metabolic syndrome modify the highly specific cellular and molecular responses and the endothelial function is disturbed. Many studies described the elevated C reactive protein associated with the endothelial dysfunction, some of them as an independent risk factor for endothelial dysfunction. This could be an important link between systemic marker of inflammation and the progression of atherosclerosis.

**Key Words:** endothelial dysfunction, atherosclerosis, inflammation, metabolic syndrome

## INTRODUCTION

One of the major risk factor for cardiovascular disease is the metabolic syndrome. Its components: dyslipidemia, hypertension, insulin resistance and abdominal obesity are linked with an inflammatory and protrombotic states. This could generate the cardiovascular disease, the first changes being the endothelial dysfunction. (Figure 1)



**Figure 1.** Evolution of the metabolic syndrome and diabetes.<sup>9</sup>

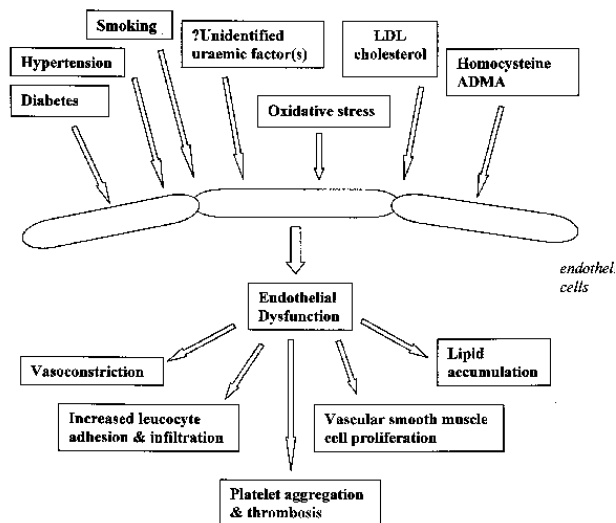
It is generally accepted that endothelial dysfunction plays an early pathogenic function in atherosclerosis, arterial thrombosis, pulmonary hypertension, myocardial infarction, stroke and deep vein thrombosis. Endothelial dysfunction is defined as a change towards injurious processes and it contributes to vasospasm, vasoconstriction, excessive thrombosis and abnormal vascular proliferation.<sup>1</sup> In some particular conditions, the endothelium response through release of vasoactive mediators and growth

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factors disturb the normal vasomotricity, permeability, the balance between coagulation and fibrinolysis, the composition of the subendothelial matrix, leukocyte extravasations and the proliferation of vascular smooth cell. (Figure 2)



**Figure 2.** Cause and effect of endothelial dysfunction.<sup>9</sup>

## ENDOTHELIAL DYSFUNCTION AND DEVELOPMENT OF ATHEROSCLEROSIS

Atherosclerosis, through the cellular and molecular modifications, can be described as an inflammatory disease. The main relaxing factor (NO) is secreted by the normal endothelium as a response to physiological and pharmacological stimuli. Some physiological states, as well as some diseases, can alter the regulation of the relaxing and the contracting factors. Endothelial dysfunction implies leukocyte adhesion and infiltration of monocytes, macrophages and lipoproteins into the arterial wall. This is the first stage in the formation of foam cells into an atherosclerotic process.<sup>2</sup>

The decreased secretion of NO and prostacyclin by the endothelium increases platelet adhesion and the secretion of platelet growth factors. The enhanced secretion of platelet-derived growth factor (PDGF) leads to the migration of smooth muscle cells and their proliferation by growth factors (VEGF, TGFβ).<sup>3,4</sup> (Table 1)

The main feature of the initial events in the development of vascular disease is the endothelial dysfunction, characterized by a decrease in relaxing factors and an increase in contracting factors. Several authors have demonstrated that the physiological impairment of endothelial function is linked to age, hypercholesterolemia, smoking, hypertension, diabetes mellitus and heart failure.<sup>5-10</sup> Clarkson et al found that healthy young subjects, with a family

history of premature coronary disease and free of other cardiovascular risk factors had impaired endothelium-dependent vasodilation.<sup>11</sup> There is an impaired endothelium-dependent vasodilatation linked to a defect in nitric oxide pathway in patients with cardiovascular risk factors.

**Table 1.** Properties of endothelium.

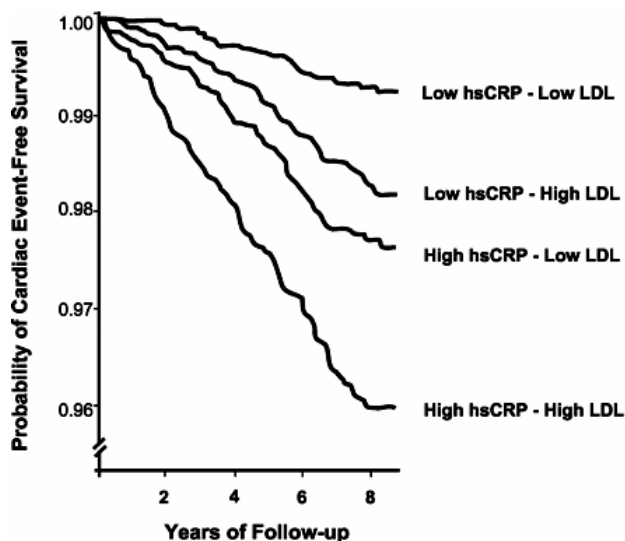
Function	Substances and factors
<b>Vasoregulation</b>	
-Relaxation	NO, EDHF, PGI2
-Contraction	ET-1, PGH2, TxA2
<b>Permeability</b>	
-Inflammation and leukocytes extravasation	VCAM-1, ICAM-1, PCAM-1, P and E selectin
<b>Vasculogenesis/angiogenesis</b>	VEGF, TGF-β
<b>Hemostasis</b>	
-Coagulation	PGI2, TxA2, vWF
-Fibrinolysis	t-PA, PAI-1

## STRONG RELATION BETWEEN INFLAMMATION AND ENDOTHELIAL DYSFUNCTION

Recent studies have suggested an association between infection and inflammation and between infection and risk factors of cardiovascular disease.<sup>12</sup> It is based on the exposure of endothelial cells to pro-inflammatory cytokines leads to expression of cell-surface adhesion molecules and impairs endothelium-dependent relaxation.<sup>13,14</sup> The experimental data suggest that the inflammatory response may provide a link between systemic inflammation and cardiovascular disease. There are some studies which demonstrate an inverse correlation between CRP (C reactive protein) and forearm blood flow responses to acetylcholine in males with documented coronary artery disease.<sup>15</sup> In addition, other studies have shown that CRP is an independent determinant of endothelium-dependent vascular function in both coronary heart disease patients and healthy subjects.<sup>16,17</sup> Results presented by Cleland et al show a relationship between low-grade inflammation and basal endothelial NO synthesis. It should be pointed out that not only observational but also experimental studies have been able to demonstrate an association between inflammation and endothelial dysfunction in humans. Indirect evidence of this link was found in type 1 diabetic patients. It has been observed an inverse relationship between CPR and endothelium derived proteins, such as von

Willebrand factor and adhesion molecules (ICAM-1).

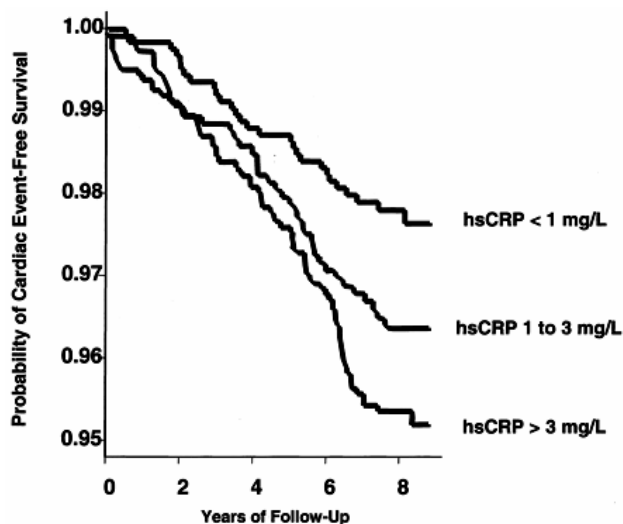
One of the novel risk factors, now available, the high-sensitivity C-reactive protein (hsCRP) - a marker of low-grade vascular inflammation, is the most promising. Prospective epidemiological studies consistently demonstrate that hsCRP adds independent prognostic information at all levels of LDL cholesterol and at all levels of the Framingham Risk Score.<sup>18</sup> The Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) published in January 2003 the first set of guidelines to endorse use of hsCRP as an adjunct to traditional risk factor screening.<sup>19</sup> (Figure 3)



**Figure 3.** Cardiovascular event-free survival according to baseline levels of CRP and LDL (adapted from the CDC/AHA Report).<sup>19</sup>

The CDC/AHA report also endorsed hsCRP as the only inflammatory biomarker currently available with adequate standardization and predictive value to justify use in outpatient clinical settings. On the basis of data from available investigations, levels of hsCRP <1, 1 to 3, and >3 mg/L have been defined as lower, moderate, and higher cardiovascular risk. (Figure 4)

Taking a conservative approach, the CDC/AHA report suggested that the best use of hsCRP was in patients at intermediate Framingham risk. Since the publication of the CDC/AHA report, abundant data have emerged not only confirming the ability of hsCRP to add prognostic information to the Framingham Risk Score but also linking hsCRP to metabolic syndrome and the development of incident type 2 diabetes. Moreover, accumulating data suggest that both very low and very high levels of hsCRP seem to provide independent prognostic information across a full spectrum of Framingham risk.



**Figure 4.** Clinical predictive value of hsCRP levels <1, 1 to 3, and >3 g/L among individuals already defined as having metabolic syndrome by ATP III criteria (adapted from the CDC/AHA report).<sup>19</sup>

### **FACTORS THAT INDUCE AND PROMOTE INFLAMMATION IN ENDOTHELIAL DYSFUNCTION IN METABOLIC SYNDROME**

Recent studies suggested that the endothelial dysfunction could be more than just a denudation and that is a chronic inflammatory process of an artery, every characteristic lesion of atherosclerosis representing in fact a different stage. Among the possible causes of endothelial dysfunction there are: elevated and modified levels of LDL, smoking which release free radicals, hypertension and diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations and infectious microorganisms such as herpes viruses or Chlamydia pneumoniae. A combination of these factors can be found also in the metabolic syndrome. The injury will increase the adhesiveness of the endothelium, especially for leukocytes and platelets. This will induce the procoagulant instead of anticoagulant properties of the endothelium and from vasoactive molecules, cytokines and growth factors. The inflammation will stimulate migration and proliferation of smooth muscle cells within the inflammation area. Also, the inflammation process will generate an increased number of macrophages and lymphocytes which will multiply within the lesion. Macrophages and lymphocytes will release hydrolytic enzymes, cytokines, chemokines and growth factors, which will induce lesions and sometimes focal necrosis. Then, a fibrous cap will cover the lesion, overlying a core of lipid and necrotic tissue, generating a complicated lesion.

### **Dyslipidemia**

In metabolic syndrome, dyslipidemia is characterized by increased levels of triglycerides and LDL cholesterol and reduced levels of HDL cholesterol.

Tumor necrosis factor, interleukin-1 macrophage and colony-stimulating factor, the mediators of inflammation, will increase the binding of LDL to endothelium and smooth muscle, and will increase the transcription of LDL-receptor gene. These lipids will maintain the inflammation, the mediators of inflammation will modify the lipoproteins which will maintain a further inflammation.

### **Hypertension**

In patients with hypertension, concentration of angiotensin II is often elevated. Angiotensin II had beside the vasoconstrictor effect, a role in stimulation of the growth of smooth muscle. Proinflammatory effect of hypertension will be shown by the increased formation of hydrogen peroxide and free radicals such as super oxide anion. The result will be reducing of nitric oxide formation by the endothelium, increasing leukocyte adhesion and peripheral resistance. It remains unclear the exact pathophysiological mechanism of the inflammation in hypertension. The observations that CRP plays an important role in induction of plasminogen activator inhibitor-1 (PAI-1), supports the hypothesis that it may be a link between CRP levels and the development of hypertension. PAI-1 is a potent marker of impaired fibrinolysis and atherosclerosis, and also over expressed by the endothelial cells of hypertensive patients.

### **Various infections cause endothelial dysfunction**

Recent studies suggest the implication of chronic Chlamydia pneumoniae infection in the development of atherosclerotic process in general population and in high risk patients. There are some authors who have shown that repeated Chlamydia pneumonia infections impair endothelial function. In a preliminary study Prasad et al. have shown that prior infection with *Cytomegalovirus*, hepatitis A virus, *herpes simplex* virus type 1, *C. pneumonia* and *Helicobacter pylori* are risk factors for coronary endothelial dysfunction.

## **CLINICAL RECOMMENDATIONS**

Some studies which consider the CRP level as a CHD risk factor have not suggest an upper limit of CRP level as an exclusion criterion.<sup>19,20</sup> In this consideration is difficult to interpret CRP levels unequivocally. In addition to being a marker of inflammation, CRP may have direct detrimental

effects on vascular tissues, which may partly explain the association of insulin resistance with inflammation and endothelial dysfunction.<sup>21</sup> Cross-sectional studies in other populations have shown relationships between chronic inflammation and body mass index, insulin resistance, diabetes, blood pressure and other metabolic syndrome components, as well as an inverse relationship with physical activity. The association of CRP (and sE-selectin) concentration with blood pressure was stronger in women. Furthermore, CRP level predicted six-year incidence of metabolic syndrome components among women in that study.<sup>22</sup>

A recommended approach in primary prevention is to measure CRP only among those at intermediate risk as defined by the Framingham Risk Score. For example, clinicians might conservatively choose to evaluate CRP only among those with a calculated 10-year Framingham risk between 5% and 20%. Although this strategy has epidemiological appeal, it is likely to be less efficient and perhaps less cost-effective. In secondary prevention, the potential utility of CRP is less certain, as aggressive therapies should already be instituted and LDL evaluation provides an excellent method to assess statin efficacy. In the setting of acute coronary ischemia and unstable angina, the role of CRP is rapidly evolving. Multiple studies demonstrate that CRP levels predict early and late mortality in acute coronary ischemia and add to the predictive value of cardiac troponin.<sup>23,24</sup>

## **CONCLUSIONS**

The endothelial function is disturbed by the characteristic changes found in the metabolic syndrome. Endothelial dysfunction is an early marker of ongoing atherosclerotic process. Furthermore, it has been recognized that endothelial dysfunction plays an important role in many conditions associated with a high prevalence of atherosclerotic cardiovascular disease. The identification of elevated CRP as a transient independent risk factor for endothelial dysfunction might provide an important clue to link a systemic marker of inflammation to progression of atherosclerotic disease.

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