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Journal of Cardiovascular Emergencies 2022;8(3):59-63
DOI: 10.2478/jce-2022-0009

CLINICAL UPDATE

Adhesion Molecules and Vulnerable Plaques – Promoters of Acute Coronary Syndromes

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ABSTRACT

Biological factors that characterize extrinsic plaque vulnerability include various pro- and anti-inflammatory cytokines that contribute to the development and progression of atherosclerosis. Adhesion molecules are among the initiators of the atherosclerotic process, by mediation of endothelial inflammation. The soluble forms of these adhesion molecules have been identified in the circulatory blood, with an increased level in case of subjects with atherosclerotic lesions and higher levels in patients with acute coronary syndromes or vulnerable plaques. In addition, several authors have found a significant predictive capacity of these molecules in case of patients presenting with acute coronary and cerebrovascular events. The aim of this manuscript is to provide a short description of the role of adhesion molecules in the development and progression of atherosclerotic lesions towards acute coronary syndromes, as well as their capacity for predicting major adverse cardiovascular events in vulnerable cardiovascular patients.

Keywords: adhesion molecules, endothelial inflammation, vulnerable plaques, major adverse cardiovascular events

ARTICLE HISTORY

Received: July 17, 2022
Accepted: August 1, 2022

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INTRODUCTION

Acute coronary syndromes, the most severe consequence of coronary atherosclerosis, are most frequently caused by the erosion and rupture of an atheromatous plaque that becomes unstable under certain conditions. Coronary plaque rupture is the pathophysiological substrate in over 75% of acute myocardial infarction (AMI) cases.[1] Nevertheless, in 25–40% of patients with ST-elevation myocardial infarction (STEMI), the acute coronary event is triggered by lesions with an intact thin fibrous cap and a large necrotic, lipid-rich core.[2,3] The vulnerabilization of coronary plaques is a complex biomechanical process that requires interaction between coronary shear stress and the structural characteristics of atheromatous lesions, but also the local and systemic biological reactions of the immune system. Plaque architectonics (thickness of the fibrous cap, size of the necrotic core, various degrees and forms of calcification), in combination with external factors (coronary flow hemodynamics, systemic and local hemorheologic properties), provide a complementary role in the natural evolution of atheromatous plaques, either towards stabilization, or towards vulnerabilization, erosion, and rupture. [4,5–8]

Biological factors that characterize extrinsic plaque vulnerability include various pro- and anti-inflammatory cytokines that contribute to the development and progression of atherosclerosis. Vascular inflammation modulates the process of remodeling, plaque healing, and also erosion, rupture, and evolution towards acute coronary

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events that can be potentially fatal. A vulnerable plaque with increased propensity to rupture has a thin fibrous cap, with increased inflammatory activity and an excessive production of proteolytic enzymes.[3,9,10] Therefore, local inflammation triggers the activation of macrophages and T lymphocytes, which release a series of inflammatory cytokines and proteases that inhibit fibrous cap formation by increasing extracellular matrix degradation.

Adhesion molecules are among the initiators of the atherosclerotic process, by mediation of endothelial inflammation. Their action includes the regulation of leukocyte transmigration across the endothelial membrane via a signaling pathway that is triggered by increased oxidative stress and coronary shear stress variability. In essence, adhesion molecules that are expressed on the surface of endothelial cells and leukocytes mediate the recruitment of inflammatory cells in the initial phase of atherosclerosis as a response to various stimuli. Selectin E, P, and L contribute to leukocyte rolling and adhesion on the endothelial surface, while intercellular (I-CAM) and vascular (V-CAM) adhesion molecules, and certain integrins induce inflammatory cell arrest and adhesion on the vascular surface.[11] The soluble forms of these adhesion molecules have been identified in the circulatory blood, with an increased level in case of subjects with atherosclerotic lesions and higher levels in patients with acute coronary syndromes or vulnerable plaques. In addition, several authors have found a significant predictive capacity of these molecules in case of patients presenting with acute coronary and cerebrovascular events.[12–15]

The aim of this manuscript is to provide a short description of the role of adhesion molecules in the development and progression of atherosclerotic lesion towards acute coronary syndromes, as well as their capacity for predicting major adverse cardiovascular events (MACE) in vulnerable cardiovascular patients.

ADHESION MOLECULES – GENERAL CONSIDERATIONS

Cell-adhesion molecules (CAM) are proteins expressed on the surface of cells, which mediate their bond either to the surface of other cells or to the components of the extracellular matrix. These molecules are involved in a number of vital biological processes, from embryogenesis and cell growth to inflammatory processes. The vascular endothelium is a dynamic system with natural anti-adhesive and anticoagulant properties, but in case of injury, its response consists in the activation of procoagulant mechanisms and adhesion, followed by the transmigration of inflammatory cells at a subintimal level. This process is crucial for the initiation of the pathophysiological process of atherosclerosis, but also for the occurrence of acute coronary syndromes.[11] There are multiple types of adhesion molecules that are grouped into four large families: (1) immunoglobulin-like molecules (I-CAM, V-CAM, PE-CAM); (2) selectins (P-selectin, E-selectin, L-selectin); (3) integrins; (4) cadherins.[16,17] The role of these adhesion molecules, in association with pro-inflammatory cytokines, is to recruit inflammatory cells to the endothelial surface, thus determining the atherosclerotic process.

THE ROLE OF ADHESION MOLECULES IN THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Lipid striae, the earliest atherosclerotic lesions, are composed almost entirely of monocyte-derived macrophages. Monocyte recruitment is initiated by the attachment of activated monocytes at the endothelial level through the expression of CAM, such as intercellular CAM (I-CAM) and vascular CAM (V-CAM). In response to various inflammatory cytokines, these molecules are expressed on the endothelial surface and allow the adhesion and transmigration of circulating leukocytes. Leukocyte transmigration at the subendothelial level occurs under the influence of pro-inflammatory stimuli. Endothelial cells are exposed to a series of insults that promote the expression of adhesion molecules. One of the insults is intravascular shear stress, more specifically coronary flow variations, and the alternation between laminar and turbulent flow at the endothelial surface, which will cause the hyperexpression of I-CAM, V-CAM and endothelial selectin (E-selectin). The hyperexpression of adhesion molecules, in association with the activation of the inflammatory cascade, will determine leukocyte transmigration at the endothelial level, with the formation of foam cells, in the presence of associated insults (inflammation, cardiovascular risk factors).[18]

Selectins are part of a family with three members that have a similar biomolecular structure, being named according to the main site of expression, namely: L-selectin – at leukocyte level; E-selectin – at the endothelial level; P-selectin – at the platelet level, but they are also found on the endothelial surface. L-selectin is present on the surface of all leukocytes and some lymphocytes, P-selectin is stored inside platelets, being expressed on the cell surface in the context of inflammatory activation, and E-selectin is absent in resting conditions, its expression being transcriptionally induced by a series of pro-inflammatory cytokines. The hyperexpression of selectins deter-

mines the maintenance of the inflammatory process and the alteration of endothelial integrity, being part of the leukocyte recruitment process at the endothelial level.[18]

Immunoglobulin-like adhesion molecules are part of a superfamily with over 765 members, which structurally includes major histocompatibility complex I and II molecules, T lymphocyte receptor complex proteins, and surface glycoproteins.[19] Representatives of this class (I-CAM, V-CAM, PE-CAM) play a central role in cell adhesion, including inflammation, neoplasia with secondary determinations, neurodegenerative pathologies etc.[20] The hyperexpression of adhesion molecules at the level of the activated endothelium is a key element in the atherosclerotic pathophysiological process.

V-CAM is expressed at the endothelial level, interferes with a series of specific integrins at the platelet and leukocyte level, and determines the rolling process and firm leukocyte adhesion in the presence of inflammation and risk factors for atherosclerosis. V-CAM is not present at the endothelial level under physiological conditions, but its expression is rapidly induced by pro-atherosclerotic conditions. In addition to its role in the formation of atherosclerotic lesions, V-CAM has an important role in the process of neointimal formation that occurs after endothelial injury, and thus in the process of restenosis post-implantation of endoluminal stents.[21,22]

I-CAM-1 is part of the immunoglobulin-like CAM superfamily, with a role in cell adhesion, which modulates the integrity of endothelial junctions. It is expressed basally, but also through stimulation by pro-inflammatory cytokines, on the surface of endothelial cells and leukocytes. I-CAM expression is increased in areas of increased inflammation, at the level of atherosclerotic plaques, and more so in areas with significant leukocyte infiltration, thus indicating its critical role in maintaining the inflammatory cascade in the atherosclerotic process.[11]

The platelet endothelial cellular adhesion molecule (PE-CAM) is present on the surface of leukocytes, platelets, and endothelial cells, having the highest density at the junctions between endothelial cells. Through its affinity for a series of specific integrins, it causes disintegration of the endothelium and thus inflammatory cell extravasation from the endoluminal level to the intimal and subintimal levels.[23]

Integrins represent a family of transmembrane glycoproteins that are non-adhesive in the case of dormant cells, are present on the cell surface, and are activated by a series of pro-inflammatory signals that cause a change in their conformation, with increased affinity for specific ligands. In atherosclerosis, specific ligands include specific proteins of the extracellular matrix, including laminins, collagen, fibronectin. Additionally, there are a series of specific integrins for interaction with I-CAM and V-CAM, but also with smooth muscle fibers, leukocytes, and platelets, which determine both the incarceration of inflammatory cells at an endothelial and subendothelial level, and platelet activation. The role of integrins presenting increased affinity for components of the extracellular matrix is to anchor inflammatory cells at this level, while of those with affinity for platelets is thrombocyte activation, thus maintaining the inflammatory cascade responsible for the initiation and progression of atherosclerosis, and also for the increased predisposition to thrombosis.[11,24–26] Figure 1 illustrates the role of adhesion molecules in the leukocyte recruitment process that occurs in the pathophysiology of atherosclerosis.

THE PREDICTIVE CAPACITY OF ADHESION MOLECULES IN VULNERABLE CARDIOVASCULAR PATIENTS

Serum levels of soluble adhesion molecules have been assessed by numerous authors as having a predictive effect for the development of atherosclerotic coronary artery disease, but also for adverse cardiovascular events, acute coronary syndrome, and heart failure.

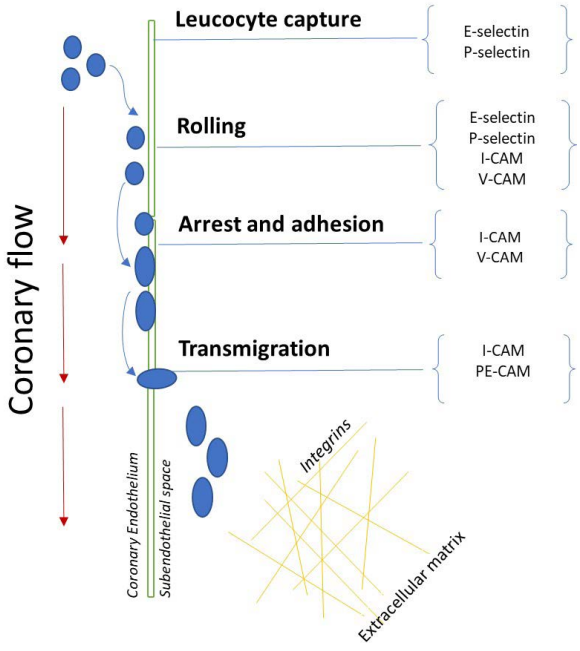

FIGURE 1. Schematic representation of the role of adhesion molecules in the leukocyte recruitment process that occurs in the pathophysiology of atherosclerosis

A prospective study conducted more than two decades ago showed a positive correlation between the level of soluble I-CAM-1 and the risk of AMI in previously healthy men.[27] Similarly, a study in laboratory animals showed that inhibition of monocyte adhesion to the endothelium, by reduced expression of V-CAM, was associated with a 40% reduction in atherosclerotic lesions.[28]

In patients with previously documented coronary artery disease, baseline levels of V-CAM and I-CAM were significantly higher in those who died of cardiovascular causes.[29] Serum P-selectin level was associated with an increased risk of AMI, stroke, coronary revascularization, and cardiovascular death at 3.5 years of follow-up in 345 apparently healthy female subjects, independent of age or other cardiovascular risk factors.[30] Moreover, in a cohort of young adult patients, circulating levels of E-selectin and I-CAM-1, but also the increase of I-CAM-1 over time, were associated with an alteration of left ventricular systolic function assessed at age medium, at 7, 15, and 30 years, respectively.[31] Additionally, the serum concentration of soluble variants of I-CAM and V-CAM were also significantly higher in patients with AMI, unstable and stable angina, compared to controls without coronary atherosclerosis. However, this difference was not maintained in the case of E-selectin levels.[32] Elevated V-CAM levels were also associated with increased severity of coronary plaques assessed by invasive coronary angiography, and all subjects with a V-CAM level above 876 ng/L presented severe coronary atherosclerotic lesions.[33]

The serum concentration of V-CAM, I-CAM, and E-selectin was also significantly higher in patients with angiographically documented ischemic coronary disease who experienced MACE at 4.1 years compared to those who did not have MACE. In the same study, the predictive ability of V-CAM was significant even after adjustment for hs-CRP level, with a 2.8-fold increase in the risk of MACE ($p = 0.003$) independent of the level of systemic inflammation.[29] Serum levels of I-CAM-1 were significantly higher in patients who developed MACE at one year, in patients with revascularized STEMI and NSTEMI.[34]

The circulating level of V-CAM-1 was significantly associated with the risk of heart failure over a long follow-up period of up to 14.4 years (HR 1.94, 95% CI 1.17 to 3.23, $p = 0.01$) in a cohort of 2,297 participants from the MESA (The Multi-Ethnic Study of Atherosclerosis) study.35 Patients developing post-infarction heart failure had significantly higher values of I-CAM (1,594.20 ng/mL vs. 1,158.74 ng/mL, $p < 0.001$) and V-CAM (1,719.58 ng/mL vs. 1,304.34 ng/mL, $p = 0.001$), demonstrating a significant predictive capacity (I-CAM: AUC 0.825, $p < 0.0001$; V-CAM: AUC 0.797, $p = 0.001$).[14]

CONCLUSIONS

Adhesion molecules are among the initiators of the atherosclerotic process by mediating the recruitment of inflammatory cells in the initial phase of atherosclerosis, with endothelial inflammation, as a response to various stimuli. The soluble forms of these adhesion molecules have been identified in the circulatory blood, with an increased level in case of subjects with atherosclerotic lesions and higher levels in patients with acute coronary syndromes or vulnerable plaques. In addition, soluble levels of adhesion molecules have shown predictive capacity in case of patients presenting with acute coronary and cerebrovascular events, as well as heart failure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT/FUNDING

This work was supported by the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș Research Grant number 510/13/17.01.2022.

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