Microparticles in Atherosclerosis: Biomarkers of Disease

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Abstract

Microparticles (MPs) are membrane vesicles released by various cell types (platelets, endothelial cells, monocytes) in circulation, which play inevitable role in thrombosis and vascular inflammation. Literatures so far suggested MPs as biomarkers of vascular injury and inflammation and also contribute to the initiation and development of atherosclerosis and its related manifestations. Atherosclerosis is the major underlying pathophysiology for the various cardiovascular diseases (CVDs). In addition, most recent data suggest a potential prognostic role of circulating MPs. Present article summarizes briefly about the different MPs and their importance as markers to check the vascular health in various CVDs.

Keywords: Atherosclerosis; Microparticles; Platelet microparticles; Endothelial microparticles

Introduction

Cardiovascular diseases (CVDs) such as coronary artery disease (CAD) and stroke are the largest causes of death in developing countries and are one of the main contributors to disease burden in a population. It has been predicted that between 1990 and 2020, these diseases to be increased by 120 percent for women and 137 percent for men in developing countries as compared with 30–60 percent in the developed countries [1-3]. Atherosclerosis is the main etiology of cardiovascular diseases. It is now widely accepted that the development of atherosclerotic lesions involves a chronic inflammatory response that includes both innate and adaptive immune mechanisms and is characterized by interactions among platelets, leukocytes, and endothelial cells [4-6]. This chronic inflammatory condition can be converted into an acute clinical event by plaque rupture and thrombosis. Most of the cardiovascular events occur as a result of plaque rupture, a later-stage complication seen in atherosclerosis. These plaques are characterized by large, necrotic, highly thrombogenic lipid cores, thin fibrous caps and increased numbers of macrophages, T-lymphocytes and platelets [4,7].

Endothelial cell (ECs) dysfunction is a precursor and common denominator of cardiovascular diseases and is an early event in the development and progression disease. Under physiological conditions, vascular endothelium represents a complex regulated surface maintaining an anti-thrombogenic potential. This pattern is shifted toward a prothrombotic state with the activation of endothelial cells. Activation can be due to various agents such as proinflammatory cytokines, infectious agents, or their components (e.g. LPS). Endothelial activation is associated with shedding fragments of their plasma membranes into the extracellular space. Such fragments, resulting from an exocytotic budding process, are colloquially known as endothelial microparticles (EMPs) that help in thrombosis. In various human studies measuring endothelial dysfunction offer prognostic information with respect to vascular events [7-13].

Platelets represent an important linkage between inflammation, thrombosis and atherogenesis. Platelets tend to adhere to the damaged or disrupted endothelial surfaces. Changes in intraplatelet calcium concentration, as a result of either calcium influx or mobilization of intracellular stores, are fundamental to process of platelet activation and precedes several activation responses such as aggregation, shape change, secretion of internal granules, shedding of microparticles, expression of P-selectin (CD62P) and procoagulant activity [14,15]. When activated, platelets release potent mitogenic factors such as platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β) and epidermal growth factor (EGF), which lead to smooth muscle cell proliferation and progression of atherosclerotic lesions. Although, platelets may not contribute directly to plaque formation, platelet activation is a feature of atherosclerotic vascular disease in humans. Cellular activation of platelets by physiological agonists results in membrane vesiculization followed by shedding of blebs or microparticles called platelet microparticles (PMPs) and are known to possess procoagulant activity. MPs have been shown to have many pathophysiologic effects, including effects on thrombosis, cell signaling, and angiogenesis [15-18].

In literature, microparticles (MPs) are defined as membrane vesicles released by various cell types (platelets, endothelial cells, monocytes) in circulation after cell activation or apoptosis [19,20]. For a long time MPs have been thought to be as inert debris. However, recent studies pointed out their importance in exchange of biological signals from the parent cells to various target cells by direct cell-to-cell contact or alternatively through secretion of soluble mediators and effectors [20,21]. MPs have been shown to have many pathophysiologic effects, including effects on thrombosis, cell signaling, and angiogenesis [22]. An increased concentration of tissue factor (TF), is believed to initiate and accelerate blood coagulation and fibrin formation. Up to two thirds of the plasma tissue factor activity is carried on by PMPs [23]. PMPs also have a role in the inhibition of fibrinolyis by expressing plasminogen activator inhibitor-1 on their surface [24]. Indeed, experimental evidence points to the role of PMPs in causing further platelet activation and endothelial dysfunction and in generating an inflammatory state [22,25]. Plasma MPs also constitute a phospholipase A2 (PLA2) substrate and lead to lysophosphatidic acid
Microparticles formation and Composition

Extracellular vesicles are a heterogeneous population of particles released from various cell types into the extracellular space under both normal and stressed conditions. On the basis of their size, content, and mechanism of formation, these particles are divided into 3 categories—exosomes, apoptotic bodies, and microparticles (MPs) [21,27,28]. Present article focuses majorly on the microparticles.

Microparticles (MPs) are released from the cell surface following cell activation. Activation can be triggered by chemical stimuli, such as cytokines, thrombin, and endotoxin, or physical stimuli, such as shear stress or hypoxia. MPs represent a heterogeneous population of vesicles that range from approximately 50-1000 nm which circulate in various biological fluids (plasma, peripheral blood, cord blood, urine, saliva and cerebrospinal fluid) [27,29]. MPs are phospholipid-enclosed vesicles that originate from endothelial cells, erythrocytes, leukocytes, megakaryocytes, or platelets. MPs retain certain antigens of their parent cells. MPs can contain nucleic acids—notably mRNA and micro RNA (miRNA)—suggesting that they could transfer genetic material to target cells [28]. An increase in the cytosolic calcium concentration is one of the factors that trigger the release of MPs. The origin of MPs is important because MPs with similar shapes and diameters though derived from different cell types possess unique functional capabilities. Current nomenclature of cell derived vesicles was discussed elsewhere [30,31].

MPs production is a tightly regulated and a selective process. Also, microparticles play important role as mediators of cell-to-cell communication. MP-associated intercellular communication can take place through different pathways. They can (i) directly interact with the ligands present on the surface of target cells and activate cascade signaling, and (ii) transfer proteins, mRNA, miRNA, and bioactive lipids by interacting with target cells by either fusion or internalization [27,32]. Through this latter mechanism, target cells can acquire new surface antigens and therefore new biological properties and activities. Details about the communication can be read at references [33,34].

Considering, parallelism between platelet (PMPs) and endothelial (EMPs) microparticles expression that supports a close interplay between platelets and ECs in the pathophysiology of CAD, present article focused on these two MPs.

Platelet Microparticles

Platelet-derived microparticles (PMPs) represent the most abundant microparticle subtype and their presence reflects platelet activity and the thrombotic state of a vascular system. Increase in cytosolic calcium induces a disruption of the membrane skeleton and a vesiculation of platelets. PMPs contain effector molecules such as thrombospondin, CXCR4, protease-activated receptor-1 (PAR-1), P-selectin (CD62P), GP5 (CD63), and alpha-granule derived factor Va [16,28]. The formation of PMPs is associated with the exposure of binding sites for factors Va, VIII, and X, which leads to procoagulant activity. Platelet microparticles express Gp Ib (CD42b), platelet endothelium adhesion molecule (PECAM-1; CD31), the integrin αIIbβ3 (GpIIb-IIIa) [35], P-selectin (CD62P) [36], CD63, CD41a and CD61 [37]. Abnormal PMP levels have been shown in patients with coronary artery disease (CAD) [17,38], diabetes [39], hypertension [40], peripheral vascular disease [12], severe thrombotic states such as acute myocardial infarction and stroke [41,42].

Biological role of PMPs extends beyond their participation in coagulation. MPs interact with endothelial and blood cells and are involved in the regulation of endothelial function. Stimulation of endothelial cells by platelet MPs in vitro results in the release of cytokines, Interleukin-6 (IL-6), and IL-8, and a rise in the expression of intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, which in turn have also been reported to be potential biomarkers in various vascular related diseases and their related complications [8,11,43-45].

Endothelial Microparticles

Like platelets, endothelial cells also shed fragments of their plasma membrane known as endothelial microparticles (EMP). The protein compositions of EMPs depend on the stimuli that trigger their release. EMPs carry endothelial proteins such as vascular endothelial cadherin, platelet endothelial cell adhesion molecule-1, intercellular cell adhesion molecule (ICAM-1), endoglin, E-selectin and integrins [41,46]. Endothelial NO synthase and vascular endothelial growth factor receptor (VEGFR-2), E-selectin (CD62E) are also expressed by activated endothelial cells. EMPs are a hallmark of endothelial cell activation and express CD31, CD54, CD62E and αVβ3 integrins [41,47].

EMP also help in endothelial cell survival. EMPs release from cells results in the diminished levels of caspase-3, thus EMPs contribute to the sorting of several proapoptotic factors preventing cell detachment and apoptosis [48]. With the help of plasmin, EMPs activate matrix metalloproteinases (MMPs), which in turn help in the extracellular matrix degradation and tissue remodeling [49].

Microparticles as Biomarkers in Atherosclerosis

Various reports have highlighted circulating MPs levels in association with different cardiovascular diseases, as a witness of ongoing pathophysiological processes such as thrombosis, inflammation, or apoptosis. Changes in circulating levels of MPs might provide important clinical information in healthy subjects and in patients with cardiovascular disorders. Several studies identify plasma levels of endothelial MPs as a surrogate marker of vascular function.

There is growing evidence that PMPs act as proinflammatory mediators and pathological factor. PMPs have been demonstrated to effect vessel walls as they adhere to both the sub-endothelium and activated endothelial cells through the surface GPIIbIIIa [50]. PMPs are generated from activated platelets and apart from causing further platelet activation by a positive feedback mechanism, they have also been shown to activate the coagulation cascade, inhibit fibrinolysis, cause endothelial dysfunction and generate an overall inflammatory state [51]. Katopodis et al. reported that mean PMP levels were nearly twice as high in the recent MI group and were significantly elevated in patients with unstable angina as compared to the healthy subjects [14].
Tan et al. in their study on 59 patients with peripheral artery disease (PAD) observed no significant correlation of PMPs with hsCRP (C-reactive protein) and severity of disease, though the PMP levels were significantly higher in the patient group as compared to the controls [16]. In type 1 diabetes, total, platelet- and endothelial-derived MPs, displaying enhanced pro-coagulant activity, are elevated and correlate with HbA1c (1c) levels [52]. Increased PMP concentrations were found to be positively correlated with body mass index in obese women without specific CVDs risk factors [53].

Elevated EMP (CD 31+/42+) levels were described in a study with varying severity of coronary artery disease [51]. These authors also observed a direct correlation between EMP levels and angiographic imaging and the levels also correlated well with the morphology and severity of stenosis. In a cross sectional study, Mallat et al. reported elevated EMPs in patients with acute MI and in patients with unstable angina [54]. EMP levels also correlated positively with the severity of the disease and with hsCRP levels [15]. Simak et al. found significant correlations between EMP levels, lesion volume, and clinical outcome in subjects with acute ischemic stroke [55]. In addition, in patients presenting a characterized endothelial dysfunction, levels of circulating EMP are inversely correlated with the amplitude of flow-mediated dilatation, independently of age and pressure in subjects with endothelial dysfunction [56]. Moreover, Amabile et al. reported EMP expressing E-selectin could predict the 1-year outcome of patients with pulmonary hypertension [57]. In subjects with high risk of CHD, EMP baseline levels were demonstrated to predict the outcome, independently of Framingham score and C-reactive protein and brain natriuretic peptide levels [58]. Similar results have been found in patients with chronic renal failure and high values of CD31-CD41-EMP that were independent predictors of death and major cardiovascular events [59]. Detailed analytic approach focusing on characterizing the cellular origin, number, size, and functional activity have been recently discussed somewhere else and beyond the scope of this article [25,31].

Based on the review of literature cited here undoubtedly demonstrate that detection and quantification of MPs is an interesting and valuable tool to appreciate CVDs risks. However, MPs cannot be applied for the routine diagnostic of CVDs yet and the clinical utility of these molecules remains to be established. With a multidisciplinary approach and the proper verification studies in relevant populations, microparticles may prove to be true biomarkers of disease state and progression in near future.

Microparticles and pharmacological interventions

Various studies have reported the effect of certain drugs, used to decrease CVDs risk, on MP concentrations, suggesting that the beneficial effects via a reduction of MP concentrations. However, the cellular mechanisms leading to MP formation and release are not completely elucidated and it is not yet possible to direct and precisely target them. Antiplatelet agents, such as thienopyridines (ticlopidine) or glycoprotein IIb-IIIa inhibitors (abciximab) can decrease platelet activation and the related platelet microparticle release [60,61].

Other antihypertensive agents (β-blockers, calcium channel inhibitors) also demonstrated an impact on platelet MP levels [62]. Statins are the drug of choice for CVDs as it has been reported to exhibit pleiotropic effects [63-66]. In view of the effects of MPs in atherosclerosis, it is of interest that HMG-CoA reductase inhibitor, atorvastatin, fluvastatin, parvastatin shown to have preventive effects [67,68]. Oxidative stress, cardinal feature of many pathological conditions, also triggers numerous deleterious processes in atherosclerosis and its related manifestations, leading to endothelial dysfunction and platelet activation [69]. Treatment with vitamin C (a known anti-oxidant) for 5 days has reported a decrease of endothelial and platelet MPs in diabetic and dyslipidaemic patients [70]. Peroxisome proliferator-activated receptors are ligand-activated nuclear receptors regulating the expression of genes implicated in lipid and glucose metabolism, and inflammation. PPAR-α and PPAR-γ agonists are used in clinical practice to improve dyslipidaemia and type 2 diabetes [71]. The PPAR agonist pioglitazone, bezafibrate reduced circulating endothelial MPs in patients [72,73]. Production of matrix-degrading proteases, particularly matrix metalloproteinases (MMPs), by endothelial cells and other vascular cells is a critical event during atherosclerosis [74-77]. MMPs are known to be highly regulated at the level of synthesis and activation [74,75]. Endothelial cells shed MMP-containing vesicles and this may be a mechanism for regulating localized proteolytic activity [78], which lead to plaque disruption and therefore can be explored in near future.

Conclusion

The studies discussed above substantiate PMPs and EMPs as promising markers of platelet and endothelial activation. In this review, we have attempted to highlight that increased PMPs and EMPs are both related to the severity of CAD. However, it is still not clear if this relationship a cause or effect of atherosclerosis. Therefore, routine and standardized measurement and critical characterization of circulating MPs in a large and multi-institutional study cohort will open up interesting prospects for identification of subjects at high cardiovascular risk and for assessment of therapeutic efficiency.

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