Journal of Clinical & Experimental Cardiology

Mahajan, J Clin Exp Cardiolog 2015, 6:1
DOI: 10.4172/2155-9880.1000356

Review Article Open Access

Microparticles in Atherosclerosis: Biomarkers of Disease

Kunal Mahajan*

Department of Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

***Corresponding author:** Kunal Mahajan, Department of Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India-171001, Tel- +91 8628864820; E-mail: kunalmahajan2014@yahoo.com

Received date: November 29, 2014; **Accepted date:** January 2, 2015; **Published date:** January 10, 2015

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 cardio vascular 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 fibrinolysis 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

production, a strong platelet agonist. MPs, produced in the atherosclerotic plaques, contribute to lesion progression by stimulating its neovascularization. In addition, MPs impairs the release of nitric oxide from the vascular endothelial cells and therefore affect normal vasculature [26].

A number of studies have demonstrated their direct association with the severity of various vascular diseases and hence their clinical importance. This review summarizes current knowledge about the MPs and their implication as disease markers in reference to CVDs.

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 ranges from approximately 50-1000nm 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-activatedreceptor-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 GpIb (CD42b), platelet endothelium adhesion molecule (PECAM-1; CD31), the integrin aIIb β3 (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 (EMPs). 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 (VEGF-R2), 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].

EMPs 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 proapototic 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 HbA (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-selctin 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. Antiplatelets 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 platelets 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.

References

1. Gupta R, Joshi P, Mohan V, Reddy KS, Yusuf S (2008) Epidemiology and causation of coronary heart disease and stroke in India. Heart 94: 16-26.
2. Mahajan N, Malik N, Bahl A, Sharma Y, Dhawan V (2009) Correlation among soluble markers and severity of disease in non-diabetic subjects with pre-mature coronary artery disease. Mol Cell Biochem 330: 201-209.
3. Hanson MA, Fareed MT, Argenio SL, Agunwamba AO, Hanson TR (2013) Coronary artery disease. Prim Care 40: 1-16.
4. Libby P (2012) Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 32: 2045-2051.
5. Mahajan N, Dhawan V (2013) Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases. Int J Cardiol 168: 1788-1794.
6. Rosenfeld ME (2013) Inflammation and atherosclerosis: direct versus indirect mechanisms. Curr Opin Pharmacol 13: 154-160.
7. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H (2014) Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med 5: 927-946.
8. Dhawan V, Mahajan N, Jain S (2006) Role of C-C chemokines in Takayasu's arteritis disease. Int J Cardiol 112: 105-111.
9. Hollander JE, Muttreja MR, Dalesandro MR, Shofer FS (1999) Risk stratification of emergency department patients with acute coronary syndromes using P-selectin. J Am Coll Cardiol 34: 95-105.
10. Mahajan N, Dhawan V, Malik S, Jain S (2010) Implication of oxidative stress and its correlation with activity of matrix metalloproteinases in patients with Takayasu's arteritis disease. Int J Cardiol 145: 286-288.
11. Mahajan N, Dhawan V, Sharma G, Jain S, Kaul D (2008) 'Induction of inflammatory gene expression by THP-1 macrophages cultured in normocholesterolaemic hypertensive sera and modulatory effects of green tea polyphenols'. J Hum Hypertens 22: 141-143.

12. Zeiger F, Stephan S, Hoheisel G, Pfeiffer D, Ruehlmann C, et al. (2000) P-Selectin expression, platelet aggregates, and platelet-derived microparticle formation are increased in peripheral arterial disease. Blood Coagul Fibrinolysis 11: 723-728.
13. Polovina MM, Potpara TS (2014) Endothelial dysfunction in metabolic and vascular disorders. Postgrad Med 126: 38-53.
14. Katopodis JN, Kolodny L, Jy W, Horstman LL, De Marchena EJ, et al. (1997) Platelet microparticles and calcium homeostasis in acute coronary ischemias. Am J Hematol 54: 95-101.
15. Malik N, Dhawan V, Bahl A, Kaul D (2009) Inhibitory effects of Terminalia arjuna on platelet activation in vitro in healthy subjects and patients with coronary artery disease. Platelets 20: 183-190.
16. Tan KT, Tayebjee MH, Lynd C, Blann AD, Lip GY (2005) Platelet microparticles and soluble P selectin in peripheral artery disease: relationship to extent of disease and platelet activation markers. Ann Med 37: 61-66.
17. Tan KT, Tayebjee MH, Macfadyen RJ, Lip GY, Blann AD (2005) Elevated platelet microparticles in stable coronary artery disease are unrelated to disease severity or to indices of inflammation. Platelets 16: 368-371.
18. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP (2003) Platelets as predictors of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost 9: 177-190.
19. Rautou PE, Leroyer AS, Ramkhelawon B, Devue C, Duflaut D, et al. (2011) Microparticles from human atherosclerotic plaques promote endothelial ICAM-1-dependent monocyte adhesion and transendothelial migration. Circ Res 108: 335-343.
20. Sabatier F, Lacroix R, Camoin-Jau L, Anfosso F, Sampol J, et al. (2011) [Circulating endothelial cells, microparticles and progenitors: towards the definition of vascular competence]. Rev Med Interne 32: 54-63.
21. Rautou PE, Vion AC, Amabile N, Chironi G, Simon A, et al. (2011) Microparticles, vascular function, and atherothrombosis. Circ Res 109: 593-606.
22. Leroyer AS, Tedgui A, Boulanger CM (2008) Role of microparticles in atherothrombosis. J Intern Med 263: 528-537.
23. Muller I, Klocke A, Alex M, Kotzsch M, Luther T, et al. (2003) Intravascular tissue factor initiates coagulation via circulating microvesicles and platelets. FASEB J 17: 476-478.
24. Podor TJ, Singh D, Chindemi P, Foulon DM, McKelvie R, et al. (2002) Vimentin exposed on activated platelets and platelet microparticles localizes vitronectin and plasminogen activator inhibitor complexes on their surface. J Biol Chem 277: 7529-7539.
25. Burnouf T, Goubran HA, Chou ML, Devos D, Radosevic M (2014) Platelet microparticles: detection and assessment of their paradoxical functional roles in disease and regenerative medicine. Blood Rev 28: 155-166.
26. Amabile N, Guerin AP, Leroyer A, Mallat Z, Nguyen C, et al. (2005) Circulating endothelial microparticles are associated with vascular dysfunction in patients with end-stage renal failure. J Am Soc Nephrol 3381-3388.
27. Barteneva NS, Fasler-Kan E, Bernimoulin M, Stern JN, Ponomarev ED, et al. (2013) Circulating microparticles: square the circle. BMC Cell Biol 14: 23.
28. Piccin A, Murphy WG, Smith OP (2007) Circulating microparticles: pathophysiology and clinical implications. Blood Rev 21: 157-171.
29. Smalley DM, Ley K (2008) Plasma-derived microparticles for biomarker discovery. Clin Lab 54: 67-79.
30. van der Pol E, Böing AN, Harrison P, Sturk A, Nieuwland R (2012) Classification, functions, and clinical relevance of extracellular vesicles. Pharmacol Rev 64: 676-705.
31. Baron M, Boulanger CM, Staels B, Tailleux A (2012) Cell-derived microparticles in atherosclerosis: biomarkers and targets for pharmacological modulation? J Cell Mol Med 16: 1365-1376.
32. Mezouar S, Mege D, Darbousset R, Farge D, Debourdeau P, et al. (2014) Involvement of platelet-derived microparticles in tumor progression and thrombosis. Semin Oncol 41: 346-358.
33. Martinez MC, Tual-Chalot S, Leonetti D, Andriantsitohaina R (2011) Microparticles: targets and tools in cardiovascular disease. Trends Pharmacol Sci 32: 659-665.
34. Martinez MC, Andriantsitohaina R (2011) Microparticles in angiogenesis: therapeutic potential. Circ Res 109: 110-119.
35. Schwarz M, Katagiri Y, Kotani M, Bassler N, Loeffler C, et al. (2004) Reversibility versus persistence of GPIIb/IIIa blocker-induced conformational change of GPIIb/IIIa (alphaIIbbeta3, CD41/CD61). J Pharmacol Exp Ther 308: 1002-1011.
36. George JN, Pickett EB, Saucerman S, McEver RP, Kunicki TJ, et al. (1979) Platelet surface glycoproteins. Studies on resting and activated platelets and platelet membrane microparticles in normal subjects, and observations in patients during adult respiratory distress syndrome and cardiac surgery. J Soc Occup Med 78: 340-348.
37. von Ahsen N, Ehrlich B, Scott CS, Riggert J, Oellerich M (2001) Cryoglobulins interfere with platelet counts by optical and impedance methods but not with the CD61 immunoplatelet count. Clin Chem 47: 1858-1860.
38. Bernal-Mizrachi L, Jy W, Jimenez JJ, Pastor J, Mauro LM, et al. (2003) High levels of circulating endothelial microparticles in patients with acute coronary syndromes. Am Heart J 145: 962-970.
39. Shouzu A, Nomura S, Omoto S, Hayakawa T, Nishikawa M, et al. (2004) Effect of ticlopidine on monocyte-derived microparticles and activated platelet markers in diabetes mellitus. Clinical and applied thrombosis/hemostasis : official journal of the International Clin Appl Thromb Hemost 10: 167-173.
40. Preston RA, Jy W, Jimenez JJ, Mauro LM, Horstman LL, et al. (2003) Effects of severe hypertension on endothelial and platelet microparticles. Hypertension 41: 211-217.
41. Dignat-George F, Boulanger CM (2011) The many faces of endothelial microparticles. Arterioscler Thromb Vasc Biol 31: 27-33.
42. Helal O, Defoort C, Robert S, Marin C, Lesavre N, et al. (2011) Increased levels of microparticles originating from endothelial cells, platelets and erythrocytes in subjects with metabolic syndrome: relationship with oxidative stress. Nutr Metab Cardiovasc Dis 21: 665-671.
43. Mahajan N, Bisht D, Dhawan V, Singh S, Minz RW (2010) Transcriptional expression and gelatinolytic activity of matrix metalloproteinases in Henoch-Schonlein purpura. Acta Paediatr 99: 1248-1252.
44. Mahajan N, Dhawan V, Malik S, Jain S (2010) Serum levels of soluble receptor for advanced glycation end products (sRAGE) in Takayasu's arteritis. Int J Cardiol 145: 589-591.
45. Mahajan N, Kapoor D, Bisht D, Singh S, Minz RW, et al. (2013) Levels of interleukin-18 and endothelin-1 in children with Henoch-Schönlein purpura: a study from northern India. Pediatr Dermatol 30: 695-699.
46. Tushuizen ME, Diamant M, Sturk A, Nieuwland R (2011) Cell-derived microparticles in the pathogenesis of cardiovascular disease: friend or foe? Arterioscler Thromb Vasc Biol 31: 4-9.
47. Ardoin SP, Shanahan JC, Pisetsky DS (2007) The role of microparticles in inflammation and thrombosis. Scand J Immunol 66: 159-165.
48. Abid Hussein MN, Böing AN, Biró E, Hoek FJ, Vogel GM, et al. (2008) Phospholipid composition of in vitro endothelial microparticles and their in vivo thrombogenic properties. Thromb Res 121: 865-871.
49. Lacroix R, Sabatier F, Mialhe A, Basire A, Pannell R, Borghi H, et al. Activation of plasminogen into plasmin at the surface of endothelial microparticles: a mechanism that modulates angiogenic properties of endothelial progenitor cells in vitro. Br J Haematol 110: 2432-2439.
50. Gawaz M, Neumann FJ, Dickfeld T, Reininger A, Adelsberger H, et al. (1997) Vitronectin receptor (alpha(v)beta3) mediates platelet adhesion to the luminal aspect of endothelial cells: implications for reperfusion in acute myocardial infarction. Circulation 96: 1809-1818.
51. Choudhury A, Chung I, Blann AD, Lip GY (2007) Elevated platelet microparticle levels in nonvalvular atrial fibrillation: relationship to p-selectin and antithrombotic therapy. Chest 131: 809-815.

52. Sabatier F, Darmon P, Hugel B, Combes V, Sanmarco M, et al. (2002) Type 1 and type 2 diabetic patients display different patterns of cellular microparticles. Diabetes 51: 2840-2845.

53. Goichot B, Grunebaum L, Desprez D, Vinzio S, Meyer L, et al. (2006) Circulating procoagulant microparticles in obesity. Diabetes Metab 32: 82-85.

54. Mallat Z, Benamer H, Hugel B, Benessiano J, Steg PG, et al. (2000) Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. Circulation 101: 841-843.

55. Simak J, Holada K, Risitano AM, Zivny JH, Young NS, et al. (2004) Elevated circulating endothelial membrane microparticles in paroxysmal nocturnal haemoglobinuria. Br J Haematol 125: 804-813.

56. Werner N, Wassmann S, Ahlers P, Kosiol S, Nickenig G (2006) Circulating CD31+/annexin V+ apoptotic microparticles correlate with coronary endothelial function in patients with coronary artery disease. Arterioscler Thromb Vasc Biol 26: 112-116.

57. Amabile N, Heiss C, Chang V, Angeli FS, Damon L, et al. (2009) Increased CD62e(+) endothelial microparticle levels predict poor outcome in pulmonary hypertension patients. J Heart Lung Transplant 28: 1081-1086.

58. Nozaki T, Sugiyama S, Koga H, Sugamura K, Ohba K, et al. (2009) Significance of a multiple biomarkers strategy including endothelial dysfunction to improve risk stratification for cardiovascular events in patients at high risk for coronary heart disease. J Am Coll Cardiol 54: 601-608.

59. Amabile N, Rautou PE, Tedgui A, Boulanger CM (2010) Microparticles: key protagonists in cardiovascular disorders. Semin Thromb Hemost 36: 907-916.

60. Morel O, Hugel B, Jesel L, Mallat Z, Lanza F, Douchet MP, et al. (2004) Circulating procoagulant microparticles and soluble GPV in myocardial infarction treated by primary percutaneous transluminal coronary angioplasty. A possible role for GPIIb-IIIa antagonists. J Thromb Haemost 2: 1118-1126.

61. Nomura S, Shouzu A, Omoto S, Nishikawa M, Iwasaka T (2005) Benidipine improves oxidized LDL-dependent monocyte and endothelial dysfunction in hypertensive patients with type 2 diabetes mellitus. J Hum Hypertens 19: 551-557.

62. Briel M, Vale N, Schwartz GG, de Lemos JA, Colivicchi F, et al. (2012) Updated evidence on early statin therapy for acute coronary syndromes: meta-analysis of 18 randomized trials involving over 14,000 patients. Int J Cardiol 158: 93-100.

63. Mahajan N, Bahl A, Dhawan V (2010) C-reactive protein (CRP) up-regulates expression of receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in THP-1 cells: inhibitory effects of atorvastatin. Int J Cardiol 142: 273-278.

64. Sharma I, Dhawan V, Mahajan N, Saha SC, Dhaliwal LK (2010) In vitro effects of atorvastatin on lipopolysaccharide-induced gene expression in endometriotic stromal cells. Fertil Steril 94: 1639-1646.

65. Mahajan N, Malik N, Bahl A, Dhawan V (2009) Receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in non-diabetic subjects with pre-mature coronary artery disease. Atherosclerosis 207: 597-602.

66. Tramontano AF, O'Leary J, Black AD, Muniyappa R, Cutaia MV, et al. (2004) Statin decreases endothelial microparticle release from human coronary artery endothelial cells: implication for the Rho-kinase pathway. Biochem Biophys Res Commun 320: 34-38.

67. Tehrani S, Mobarrez F, Antovic A, Santesson P, Lins PE, et al. (2010) Atorvastatin has antithrombotic effects in patients with type 1 diabetes and dyslipidemia. Thromb Res 126: e225-231.

68. Pashkow FJ (2011) Oxidative Stress and Inflammation in Heart Disease: Do Antioxidants Have a Role in Treatment and/or Prevention? Int J Inflam 2011: 514623.

69. Morel O, Jesel L, Hugel B, Douchet MP, Zupan M, et al. (2003) Protective effects of vitamin C on endothelium damage and platelet activation during myocardial infarction in patients with sustained generation of circulating microparticles. Journal of thrombosis and haemostasis 1: 171-177.

70. Mahajan N, Dhawan V (2010) In vitro modulation of peroxisome proliferator-activated receptor-gamma and its genes by C-reactive protein. Role of atorvastatin. Arch Med Res 41: 154-161.

71. Esposito K, Ciotola M, Giugliano D (2006) Pioglitazone reduces endothelial microparticles in the metabolic syndrome. Arterioscler Thromb Vasc Biol 26: 1926.

72. Baron M, Leroyer AS, Majd Z, Lalloyer F, Vallez E, Bantubungi K, et al. (2011) PPARalpha activation differently affects microparticle content in atherosclerotic lesions and liver of a mouse model of atherosclerosis and NASH. Atherosclerosis 218: 69-76.

73. Newby AC (2012) Matrix metalloproteinase inhibition therapy for vascular diseases. Vascul Pharmacol 56: 232-244.

74. Wu G, Mahajan N, Dhawan V (2014) Acknowledged signatures of matrix metalloproteinases in Takayasu's arteritis. Biomed Res Int 2014: 827105.

75. Mahajan N, Dhawan V, Mahmood S, Malik S, Jain S (2012) Extracellular matrix remodeling in Takayasu's arteritis: role of matrix metalloproteinases and adventitial inflammation. Arch Med Res 43: 406-410.

76. Mahajan N, Dhawan V (2010) Inhibition of C-reactive protein induced expression of matrix metalloproteinases by atorvastatin in THP-1 cells. Mol Cell Biochem 338: 77-86.

77. Taraboletti G, D'Ascenzo S, Borsotti P, Giavazzi R, Pavan A, Dolo V. Shedding of the matrix metalloproteinases MMP-2, MMP-9, and MT1-MMP as membrane vesicle-associated components by endothelial cells. Am J Pathol 160: 673-680.