Circulating microparticles: major mediators of the pathogenesis of cardiovascular complications in diabetes

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Keywords. Microparticles, diabetes, angiopathy.

Summary

Microparticles, small vesicles (0.1-1 μm) released from the plasma membrane of activated and/or apoptotic cells, are considered as biomarkers for various diseases as well as authentic effectors able of delivering biological messages to target cells determining the cell stimulation.

Accumulating evidence indicate that circulating microparticles are shed into body fluids at low levels under physiological conditions and at higher levels in a large number of pathological states including cardiovascular and metabolic disorders. The cellular origin and site of release are essential factors in determining the functional activities of microparticles on the recipient cells. With regard to the cardiovascular complications associated diabetes, the exact role of microparticles has not been enough investigated and discussed.

This review brings a better understanding of the importance of circulating microparticles in the pathogenesis of diabetes and emphasizes their increasing contribution in the development of cardiovascular complications in diabetes, in order to shed light on their role as predictive, diagnostic markers and targets for therapy in the major cardiovascular pathological situations.

Introduction

The recognition of the importance of diabetes in cardiovascular disease has greatly increased lately. Diabetes induces an extensive damage of the macro- and microvasculature disturbing the endogenous vascular repair mechanisms, thus causing cardiovascular complications. It has been already established that cardiovascular disease remains the leading cause of death in patients with diabetes.

The discovery of microparticles (MPs) has opened new perspectives capturing the attention of basic and clinical scientists for their potential to become new therapeutic targets and clinical biomarkers.

MPs known as small vesicles (between 0.1 and 1 μm in diameter) are distinguished from other groups of cell-derived vesicles (such as exosomes and apoptotic bodies), released into body fluids from various cell types including platelets, endothelial cells, and leucocytes upon apoptosis or activation. In their lifetime, the cells subjected to different stimuli as physiological agonists, shear stress, apoptotic stimulation, release MPs, but this phenomenon is aggravated under pathological conditions as inflammation or other cellular stresses, which enhance MP production. Changes in the circulating levels of MPs, resulting from the active balance between MP generation and clearance, can be detected in the plasma of healthy subjects and patients.
with cardiovascular disorders, providing important clinical information (Piccin et al., 2007). Levels of MPs are easily measurable in body fluids using different techniques such as protein concentration, ELISA assays, or flow cytometry associated with their pro-coagulant activity (Georgescu et al., 2009, Badila et al., 2014, Andrei et al., 2014).

Elevated levels of circulating MPs are associated with a number of cardiovascular and inflammatory pathologies (e.g. atherosclerosis, heart failure, thrombosis, acute myocardial infarction, diabetes, hypertension, and metabolic syndrome) making them useful biomarkers for disease activity (Feng et al., 2010, Amabile et al., 2010, Georgescu et al., 2012, 2013, Baron et al., 2012). In patients with diabetes mellitus the elevated circulating levels of various MPs predict cardiovascular outcome (Tripodi et al., 2011, Feng et al., 2010, Tsimerman et al., 2011, Sinning et al., 2011). Once MPs are released into the circulation, they bind and fuse with their target cells through receptor–ligand interaction and act as biological vectors, which modulate inflammatory, angiogenic and coagulation reactions, essential in the development of diabetic complication (Diamant et al., 2004). Thus, MPs represent an intercellular communication and delivery mechanism for the efficient and effective transfer of biological information. These cargo vectors contain packages of material selectively assimilated from their parental cell, which includes bioactive lipids, integrins, cytokines, enzymes, mRNA and micro-RNAs (miRNAs) that can reprogram recipient cells (Norling and Dalli, 2013).

MPs from patients with type 2 diabetes were shown to increase the coagulation activity in endothelial cells (ECs), and to have a key role in angiogenesis and skin wound healing process (Tsimerman et al., 2011). Ettelaie and collaborators (2008) showed that the TF-containing MPs released from AGEs or glucose-treated renal mesangial cells induce the capillary formation with human dermal microvascular ECs in vitro (Ettelaie et al., 2008). Moreover, the analyses of MPs from those patients compared with healthy controls, revealed elevated numbers of TF-bearing MPs, more specifically from T-helper cells, platelets, and granulocytes. These correlated with parameters of the metabolic syndrome (Diamant et al., 2002) suggest a role for MPs in the genesis of prothrombotic profile in diabetes (Sinning et al., 2011). Interestingly, the elevated endothelial-derived microparticle (EMP) levels are predictive in identifying a subpopulation of diabetic patients without typical anginal symptoms who have angiographic evidence of coronary artery disease (CAD) (Nomura et al., 2009).

The differential risk of MPs on macroangiopathy (cerebrovascular disease, coronary artery disease, peripheral artery disease) and microangiopathy (retinopathy, nephropathy, peripheral neuropathy) in patients with diabetes has been evaluated in a lot of scientific studies. The Figure 1 indicates the pathological role of MPs in the development of cardiovascular complications in diabetes.

![Fig. 1](image_url) The schematic diagram showing the contribution of MPs to advance of cardiovascular complications in diabetes with main on macro-, microangiopathy.

**Materials and methods**

**MPs and macroangiopathy**

In type 2 diabetic patients with macroangiopathy, including coronary, peripheral and cerebrovascular disease the increased levels of circulating MPs were reported, such as platelet-derived-MPs (PMPs) (Tan et al., 2005), CD31+/annexin V+ EMPs (Sinning et al., 2011, Werner et al., 2006, Jung et al., 2011), CD31+/CD42b+ EMPs (Jung et al., 2011), and CD144+ EMPs.
CRP monomers in vascular disease (Habersberger et al., 2012). Therefore, elevated levels of circulating MPs may be an indicator and a useful risk stratification tool for diabetic macrovascular complications. Moreover, circulating MPs may be potential pathogenic factors that impair endothelial cells and atherosclerotic plaque instability (Wang et al., 2014).

**MPs and microangiopathy**

**MPs and diabetic retinopathy**

The levels of PMPs and monocyte-derived MPs have been shown to correlate with diabetic complications, gradually increasing with the progression of diabetic retinopathy, from the non-proliferative stage to the proliferative stage, and are significantly higher in diabetic retinopathy with areas of capillary occlusion than in patients without areas of capillary occlusion (Ogata et al., 2005; 2006). The levels of monocyte-derived MPs have been positively correlated with PMPs, activated platelets, and adhesion molecules in diabetic patients and could be a prognostic factor for diabetic retinopathy progression (Ogata et al., 2006). The high level of PMPs may stimulate the coagulation cascade and increase the adhesion of leukocyte and ECs (Ogata et al., 2005). In contrast, another study reported that MPs from diabetic retinopathy cohorts are less procoagulant than those from type 2 diabetic patients with CAD and diabetic foot ulcers (Tsimerman et al., 2011). Thus, it was suggested that type 2 diabetic patients with retinopathy have high levels of TF but a low TF/TF pathway inhibitor ratio, suggesting a low procoagulant state (Tsimerman et al., 2011).

Another study found that MPs of endothelial, platelet, photoreceptor, and microglial origin can be identified in vitreous samples, from diabetic patients, and EMPs are the most abundant MP subpopulation (Chahe et al., 2010). Vitreous MPs stimulate endothelial proliferation in vitro and new vessel formation in a matrigel plug model in vivo, which suggests the vitreous MPs may contribute to the progression of diabetic retinopathy. Moreover, the proliferative...
diabetic retinopathy is associated with a specific increase in the local shedding of EMPs originating from new vessels (Chahed et al., 2010). Also, abnormal expression of miRNA in MPs may be involved in neoangiogenesis (Stepien et al., 2012). However, the branched tube networks induced by MPs in diabetic retinopathy were unstable and collapsed over time (Tsimerman et al., 2011). Thus, the underlying role of circulating MPs in diabetic retinopathy pathogenesis may be based on their ability to convey angiogenic and inflammatory signals.

**MPs and diabetic nephropathy**
The presence of intra-glomerular extracellular MPs was observed with microspherical and thread-like structures under an electron microscope in renal biopsy tissue from patients with various renal diseases, including diabetic nephropathy (Nakajima et al., 1991). A few studies have indicated the increased levels of monocyte-derived MPs (Omoto et al., 2002, Nomura et al., 2004a), EMPs (Nomura et al., 2004b), and PMPs (Shouzu et al., 2000, Kobayashi et al., 2008, Omoto et al., 1999) in patients with diabetic nephropathy. The increase in monocyte-derived MPs is most significant in patients with diabetic nephropathy among the type 2 diabetic patients with diabetic microangiopathy, ie, nephropathy, retinopathy, or neuropathy (Omoto et al., 2002). Thus, the elevated levels of EMPs and monocyte-derived MPs may serve as biomarkers for nephropathy progression in the type two diabetes (Omoto et al., 2002, Nomura et al. 2004a, 2004b).

It is known that glomerular endothelial dysfunction and microalbuminuria in the early stages of diabetic nephropathy are caused by hyperglycemia, AGE and ROS/NO imbalance. The circulating PMPs (Shouzu et al., 2000, Kobayashi et al., 2008, Omoto et al., 1999), monocyte-derived MPs (Omoto et al., 2002, Nomura et al., 2004a), EMPs (Nomura et al., 2004b), and MPs derived from renal mesangial cells (Etelaei et al., 2008) may act as mediators and influence the endothelial function by stimulating the release of cytokines and the expression of various adhesion molecules by ECs, inducing the morphological changes that lead to angiogenesis induction in microvascular ECs.

**MPs and diabetic neuropathy**
Neuropathy in both type 1 and 2 diabetes has shown to be associated with the increased levels of circulating MPs in a few studies. Type 2 diabetic patients with diabetic neuropathy have increased blood concentrations of monocyte-derived MPs (Omoto et al., 2002), while type 1 diabetic patients suffering from one or more microvascular complications, including neuropathy, display higher levels of EMPs, compared to those without diabetic complications (Sabatier et al., 2002). Therefore, the elevated circulating MPs may play a pathological role in the progression of microvascular complications in type 2 diabetes, by stimulating the coagulation, endothelial inflammation and dysfunction, as well as angiogenesis (Wang et al., 2014). Accordingly, MPs might be novel therapeutic targets or biomarkers to monitor the progression of macro-, micro-vascular complications, and also the therapeutic response to their treatments.

**Regulatory roles of microparticle associated microRNAs in the cardiovascular complications in diabetes**
MicroRNAs (miRNAs) are a newly identified class of small non-coding RNAs (21 to 24nt) emerging as key players in the pathogenesis of hyperglycemia-induced vascular damage (Shantikumar et al., 2012, Zampetaki et al., 2012). These small non-coding RNAs orchestrate different aspects of diabetic vascular disease by regulating gene expression at the post-transcriptional level. Microarray studies have shown an altered profile of miRNAs expression in subjects with type 2 diabetes (Zampetaki et al., 2010, Karolina et al., 2011, Dehwah et al., 2012). Diabetic patients display a significant deregulation of miRNAs involved in angiogenesis, vascular repair, and endothelial homeostasis (Zampetaki et al., 2010).

miRNAs can be released by cells and taken up by vascular cells, modulating their cellular biology and there are studies revealing that miRNAs serve as messengers between cells (Hergenreider et al., 2012, Zhang et al., 2010,
Zernecke et al., 2009). miRNAs exit from the cells can be done by two ways: (1) by passive leakage from necrotic or apoptotic cells (Hoofnagle et al., 2004); (2) by active secretion from living cells within microvesicles (that are exosomes, microparticles, and apoptotic bodies) or in RNA-lipid/protein complexes (Ramachandran and Palanisamy 2012). Naked extracellular miRNAs are immediately degraded by ribonuclease (Mitchell et al., 2008), but encapsulation into microvesicles protect them from degradation and hence make them stable in circulation (Busch and Zernecke, 2012, Urbich et al., 2008).

The communication between cells by microparticle associated microRNAs

The presence of miRNAs in microparticles (MPs) has led to the intriguing idea that circulating miRNAs could have a function in cell-to-cell communication. This may suggest that miRNAs are selectively targeted for secretion in cell and taken up by a distant, target cell, possibly to regulate their gene expression. Currently, this is an intense area of investigation, and there are studies revealing that miRNAs may indeed function as mediators of cell-to-cell communication linking disparate cell types, diverse biological mechanisms, and homeostatic pathways (Zernecke et al., 2009, Zhang et al., 2010, Boon and Vickers, 2013). Furthermore, some miRNAs were found to be selectively accumulated inside the released MPs suggesting an organized package of miRNAs derived from their parental cells. Thus, with the development of epigenetics, MPs have been drawing increasing attention.

miRNAs from MPs were transferred and accumulated into recipient cells, where they may downregulate specific targets (Collino et al., 2010). The miRNA profiles of MPs differ significantly between patients with stable and unstable CAD and between stimulated and non-stimulated cultured cells in vitro (Diehl et al., 2012).

In the present only one miRNA, microRNA-126 (miR-126), present in MPs was reported to be involved in diabetes (Zampetaki et al., 2010). Recently it has been shown that EMPs released from apoptotic ECs promote vascular endothelial cell repair by transferring functional miR-126 to target ECs (Jansen 2013). In pathological hyperglycemic conditions, EMPs show reduced regenerative capacity, suggesting that hyperglycemia not only directly harms the endothelium, but also indirectly promotes vascular damage by altering endogenous vascular regeneration mechanisms. Moreover, analysis of miR-126 level in patients with stable coronary artery disease confirmed that diabetes mellitus reduces miR-126 expression in circulating MPs (Jansen 2013). The endothelial cell–derived miR-126 was most consistently associated with diabetes mellitus, which is interesting because miR-126 was also one of the identified downregulated miRNAs in atherosclerotic CAD (Fichtlscherer et al., 2010, Tijssen et al., 2010). It has been shown that miR-126 plays an important role in maintaining endothelial cell homeostasis and vascular integrity by facilitating vascular endothelial growth factor signaling (Wang et al., 2008, Fish et al., 2008). Besides, there are evidences suggesting that reduced miR-126 expression levels are partially responsible for impaired vascular repair capacities in diabetes (Meng et al., 2012, Wang et al., 2009). Moreover, a reduction in the level of miR-126, as well miR-15a, and miR-223 was already detectable years before the manifestation of diabetes, and therefore they could possibly be useful for risk prediction (Creemers et al., 2012, Tijssen et al., 2012). These results demonstrate that MPs can deliver miRNAs into recipient cells, where the exogenous miRNAs can regulate target gene expression and the functions of recipient cells. Instead of one single type of message, MPs may manage to deliver multiple messengers, including miRNA, specific subsets of the transcripts, miRNAs, and proteins, at one time. MPs may regulate the expression of functionally related genes and the activity of complex, hierarchical signaling and metabolic pathways between neighboring cells in a concerted and coordinated fashion (Wang et al., 2014).

Microparticle associated microRNAs as modulators and diagnostic biomarkers

Because of their high stability in the circulation, the ease by which miRNAs can be detected in a quantitative manner by methods
(such as real-time PCR and microarrays) and reproducibility of the results along with consistency among individuals of same species, miRNAs are gaining a lot of interest as the diagnostic biomarkers of several chronic diseases such as diabetes, and cardiovascular diseases (Jansen et al., 2012, Tijsen et al., 2012, Creemers et al., 2012). An ideal biomarker fulfills a number of criteria, such as: accessibility through noninvasive methods; a high degree of specificity and sensitivity; the ability to differentiate pathologies, allowing early detection; sensitivity to relevant changes in the disease; a long half-life within the sample; and the capability for rapid and accurate detection. Circulating miRNAs are able to fulfill a number of these criteria (Etheridge et al., 2011). There is increasing evidence for the potential use of specific EMP-associated miRNA signatures in body fluids or particularly in peripheral blood as biomarkers to predict metabolic diseases (Muller, 2012).

**Microparticle associated microRNAs as preventive and therapeutic strategies**

The deregulation of miRNA function has been linked to diabetes, although it is not yet fully certain whether this is a cause or effect of the pathology. If miRNAs are indeed active in the pathogenesis of diabetes and its related complications, the restoration of normal function by modifying the expression of specific miRNAs may be a therapeutic target for managing this disease. Chemically modified siRNA-like oligonucleotides have been used to decrease miRNA expression (antagomirs) in vivo (Kolfschoten et al., 2009, Krutzfeldt et al., 2005). However, due to the hypothetical transient nature of their effects, it is likely that frequent doses may be required to sustain benefit. Given the chronic nature of diabetes, this would require the need for repeated injections with their associated costs. Adeno-associated virus (AAV) vectors containing miRNA mimics have been found to promote miRNA expression in vivo (Snove and Rossi, 2006). However, for their short transgene expression, adenovirus may not be the best approach to treat diabetes and its chronic complications in the clinical arena. Another therapeutic strategy involves ‘miRNA sponges’. These artificial miRNA decoys bind native miRNA to create a loss of function of a particular miRNA. These sponges contain multiple binding sites directed against a particular miRNA or against a miRNA seed sequence family (Ebert et al., 2007). The use of miRNA sponges in an AAV vector delivery system may be a potential novel strategy for miRNA therapeutics. While the first reports on miRNA therapeutics are encouraging, the fact that a typical miRNA targets several genes suggests that clinical intervention may be very complex. Moreover, the functional delivery of miRNAs to distant cells also may make MPs ideal candidates as vehicles for such therapies.

**Conclusions**

Future directions and conclusions, although the field of cardiovascular complications in diabetes research has advanced considerably in the last time, this research area is still fraught with a number of challenges. Many of the challenges are to find out the mechanisms linking between diabetes and cardiovascular disease, new mediator, biomarkers to generate new management strategies for prevention and therapy. There is now accumulating evidence on the multiple faces of MPs as conveyors of cell information with major role in inflammation, thrombosis and angiogenesis. They can exert functional effects on target cells through a number of currently known mechanisms. In addition, miRNA content within MPs elicited many questions about their pathological effects and made to ask whether they are friends or foes. It is hoped that addressing MPs as targets for therapy in diabetes will favorably modify the risk for cardiovascular complications and survival.

In conclusion, new avenues and targets for therapeutic control may be realized through a better understanding of the role of MPs and their associated miRNAs in the pathogenesis of cardiovascular complications in diabetes.

This review will undoubtedly uncover new research directions and provide novel insights.
into the world of MPs with role in the intracellular communication and modulation of vascular disorders in cardiovascular complications in diabetes.

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