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Circulating Endothelial-Derived Apoptotic Microparticles as Novel Perspective Biomarker for Diabetes

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Abstract

Diabetes mellitus is major independent risk factor for cardiovascular morbidity and mortality worldwide. The endothelium is crucial for preserving endothelial integrity and preventing the development of DM-related vascular injury and is considered an important targeting for traditional risk factors. The Endothelial-derived apoptotic MicroParticles (EMPs) are novel biological marker of endothelium injury and vasomotion disorders that are involved in pathogenesis of DM, cardiovascular, and inflammatory diseases. The controversial opinions regarding impact of circulating EMPs in major cardiovascular and metabolic diseases and summary of the perspective regarding implementation of the EMPsas component of the risk stratification model are discussed.

Keywords: Diabetes Mellitus; Cardiovascular risk; Apoptotic Microparticles; Stratification

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Diabetes mellitus is became a powerful independent risk factor for cardiovascular morbidity and mortality worldwide [1]. There is a steadily trend toward increased proportion of the patients with exiting DM and cardiovascular diseases [2, 3]. As known, the reparation of the endothelium is crucial for preserving endothelial integrity and preventing the development of DM-related vascular injury including atherosclerosis [4, 5]. Overall, the endothelium is considered an important targeting for traditional risk factors because the endothelial dysfunction remains to be independently associated with cardiovascular mortality [6]. Thus, biomarkers of endothelial dysfunction and endothelial cell injury are determined as perspective tool for risk stratification of the DM patients. MicroParticles (MPs) are heterogeneous in size (0.1-1 μm), small membrane vesicles that produced as result in activation, injury or apoptosis of cells originated form difference sources [7]. Because MPs are small fragments of biological membranes and cytoplasm of different precursors they contain membrane, cytoplasmic, and nuclear constituents,such as enzymes, receptors, active molecules, regulated peptides, miRNAs, etc. and may contribute multifunctional and sometimes bidirectional effects in terms of inflammation, coagulation, information cross-talk between cells, angiogenesis, neovascularization [8]. The exact biological role of MPs depending of their origin is currently being investigated. Recent studies have been shown that circulating Endothelial-derived apoptotic MicroParticles (EMPs) released by activated or apoptotic endothelialcells increase in subjects with DM when compared with healthy individuals and may contribute to endothelial function, thrombotic effects, vascular integrity, low-intense inflammation that are suitable for DM-related complications [9, 10]. Despite EMPs are precursor of inflammatory responses that may contribute in vascular wall injury, EMPsreleased from apoptotic endothelial cells may influence endothelial cells restore and contribute angiogenesis [11].Taken together such data allow suggesting the paradoxical

biological effects of circulating EMPs may probably depend on origin of the EMPs and the environment surrounding microparticles-releasing endothelial cells [12, 13]. Tramontano et al. [13] found that circulating EMPs from type 2diabetes mellituspatientspredominately expressed constitutive markers (CD31 andCD105) as opposed to inducible markers and that circulating $CD31^+$, $CD105^+$, and $CD106^+$ EMPs are significantly elevated in patients with DM when compared with healthy subjects.Circulating EMPs from type 1 diabetic patients may induce platelet/endothelial cell interaction under flow and they intensity correlate with the severity of the DM-related vasculopathy [14].Werner et al. [15] reported that endothelial-dependent vasodilatation closely relies on the degree of endothelial cell apoptosis, which is readily measurable by circulating $CD31^+$/annexin V^+apoptotic EMPs. It is well known that procoagulant potential of the blood in the DM patient's associates with the level of glycemic control [16]. In this context, elevated circulating $CD31^+$/annexin V^+EMPsin diabeticsmight contributes realizing and activation of tissue factor from it [17]. This process is considered a crucial for cross road for atherosclerosis, endothelial dysfunction and thrombosis. In addition, the measurement of EMPswould probably is helpful to determine DM-related vascular complications. Unfortunately, no strongly evidences that apoptotic EPCs might be improve the contemporary risk score models in DM subjects. Therefore, no consensual position regarding phenotype of the MPs is required identification in circulation. However, the results of recent investigations allow expecting this concept is long-life and that we will have a powerful tool for risk stratification in DM patient population. Based on the mentioned above data it has been suggested that EMPs may use in risk stratification of DM subjects. This concept is novel and is appeared to be controversial, while circulating EMP assay promises to be powerful prognostic tool irrespective age, sex, ethnic, creatinine clearance and kidney function.

Conclusion: The controversial opinions regarding impact of circulating EMPs in DM and major cardiovascular diseases as well as limited data for predictive value of MPs in DM are required new investigations, while the perspective of implementation of the EMPs as risk stratification model is very attractive.

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