

# The Endothelial Progenitor Cell Dysfunction in Type 2 Diabetes Mellitus: the Link with Heart Failure Developing

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## Abstract

Diabetes mellitus (DM) and pre-diabetes are established risk factors of premature cardiovascular (CV) disease and events including heart failure (HF). Developing type 2 diabetes mellitus (T2DM) associates with decreased number and weak function of EPCs that corresponds to impaired vascular repair and endothelial dysfunction. The circulating number of endothelial progenitor cells (EPCs) decrease in patients with established heart failure (HF) depending the severity of the disease and may reflect poor prognosis, but the role of EPC dysfunction in T2DM-induced HF is not fully investigated. The Editorial is depicted a role of decreased circulating number and lowered function of EPCs in T2DM patients as a predictive biological marker of HF manifestation. It has been suggested that the potential use of EPCs as a novel personified indicator of cardiac dysfunction in diabetics is challenging and requires being under scrutinizes in future.

**Keywords:** diabetes mellitus, endothelial progenitor cells, heart failure, biomarkers

## Introduction

Diabetes mellitus (DM) and pre-diabetes are established risk factors of premature cardiovascular (CV) disease and events including heart failure (HF) [1, 2]. There are numerous innate molecular mechanisms that are involved in the pathogenesis

of cardiac dysfunction in type 2 DM (T2DM), majority all of them are typically attributed to poor hyperglycemia control, metabolic memory phenomenon, dyslipidemia, oxidative stress, low-grade systemic and microvascular inflammation, accelerating atherosclerosis, vasculopathy and ischemia [3]. Therefore, complexed contribution of several co-morbidities, such as hypertension, atherogenic hyperlipidemia, abdominal obesity, renal insufficiency, can be seized upon the triggers of different HF phenotypes in T2DM [4]. Although altered insulin-related signaling pathways and imbalance in ERK1/2 and PKC $\alpha$  activity in T2DM are considered a leading causes that modifying cardiac contractile and structure proteins (titin, SERCA, troponins) through mediate cardiomyocyte tension / injury and biochemical stress and thereby contributing to diastolic / systolic dysfunction [5, 6], impaired tissue reparation remains large unknown factor corresponding to modification of genome circulating progenitors and residence cells [7].

Endothelial progenitor cells (EPCs) are defined as CD45(-) adherent cells derived from peripheral blood- or bone marrow-derived mononuclear cells that co-expressing endothelial cell antigens (CD34, CD133, CD309) and demonstrating isolectin-binding capacity and ability to appear in fibronectin coated dish [8]. Some populations of EPCs may lose CD133 antigen within differentiation period and may express on their surface other antigens, i.e. CD31, CD144, endothelial NO synthase and von Willebrand factor [9]. All EPCs were divided into early outgrowth EPCs (5-7 days after fibronectin plating) or late outgrowth EPCs (7-10 days after fibronectin plating) [10]. Depending on presentation on the cell surface CD34 antigen all late outgrowth EPCs are divided into two populations. The population of EPCs with immune phenotypes CD34(+)CD31(+), CD34(+)CD31(+)CD146(+), CD34(+)CD31(+), CD105(+), and CD34(+)CD31(+)CD309(+) demonstrated higher proliferative potency to CD34(-) EPCs co-expressing CD31, CD309, CD105 and CD146 antigens. Therefore, CD34(+) EPCs had reproduced tubes and colony shaping in the single-cell colony-formation investigation as well as they responded to angiogenic growth factors [11].

T2DM can modify EPC numbers and function by various means acting as epigenetic regulator, while at early stage of T2DM in young patients the number of EPCs may even temporary increase [12]. Combined influences of oxidative stress components, oxidized lipids, inflammatory cytokines, and hyperglycemia lead to mitochondrial dysfunction, altered nucleotide metabolism and impaired chromatin in the EPCs thereby worsening their ability to differentiation, proliferation, moving, and survival [13]. As a result, modified EPCs cannot (trans)-differentiate into mature endothelial cells and restore integrity of endothelium and vascular function [14]. On the other hand, modified EPCs frequently synthase and realize micro vesicles with micro RNAs, modified DNAs and active molecules that directly injury structure and function of target cells, such as immature hemoangioblasts and tissue resident cells [15]. Therefore, losing ability of modified EPCs to secrete angiogenic growth factors lead to impaired cell-to-cell cooperation and mediate altered vascular reparation particularly limiting

trans-differentiation of adventitial cells / immature endothelial progenitors into smooth muscle cells and EPCs into mature endothelial cells [16, 17]. In fact, neovascularization and angiogenesis supporting by EPCs are sufficiently decrease in T2DM and they can be a pivotal factors contributing to CV complications and HF. Indeed, the number of circulating EPCs inversely associates with the number of CV risk factors [18] and it is reduced in CV disease including HF and T2DM [19, 20]. There is evidence that not just decreased number of EPCs, but weak function of circulating EPCs may be an additional risk factor with independent ability to predict CV mortality rate, a risk of urgent hospital admission due to HF and newly diagnosed HF in patients with pre-diabetes and established T2DM [21]. Interesting, the lowered function of EPCs appeared prior to dramatically decreased number of EPCs in young patients with T2DM without established CV disease and HF, while in T2DM-induced HF there was significantly lowered number and weak function of circulating EPCs [21]. Whether this fact would be useful to differentiate diabetics at risk of HF manifestation is not fully clear and requires to be investigated in large clinical studies. In fact, the measurement of circulating number and assay function of EPCs may serve as a surrogate biological marker for T2DM patients at higher risk HF and HF-related complications [22].

In conclusion, there are multiple factors that affect number and function of circulating EPCs in T2DM and T2DM-induced HF. However, the potential use of EPCs as a novel personified biological marker of cardiac dysfunction in diabetics is challenging and requires being under scrutinizes in future.

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