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Progenitor Endothelial Cell Dysfunction in Obese Patients: Possibilities for Cardiovascular Risk Prediction

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Abstract

Obesity is recognized a leading factor contributing in diabetes and cardiovascular (CV) disease development worldwide. Among obese individuals at least two phenotypes are determined, i.e. metabolically healthy obese and metabolically non-healthy obese. Subjects with one or other phenotype appear to be distinguished in CV risk and diabetes. Although lack of strong definition of metabolically healthy obese as a transient age- and ethnic-related phenotype accompanied to some behavioral and environmental factors, the role of co-existing metabolic abnormalities in translation of metabolically healthy obese to metabolically non-healthy obese is under debates. Outgrowth endothelial progenitor cells (EPCs) have protective abilities to vasculature and they are posed as a central key of endogenous repair system. In this context, weak functionality and reduced number of circulating EPCs determined as EPC dysfunction might link phenotypes of obese and CV risk. The editorial is considered a role of EPC dysfunction as a predictive biomarker in CV diseases and events in patients with different phenotypes of obese.

Keywords: Obese; Metabolically healthy obese; Cardiovascular risk; Stratification; Endothelial dysfunction; Endothelial progenitor cells

Introduction

Amongst general population individuals obesity has been remained as a leading factor contributing in metabolic and cardiovascular (CV) complications, including asymptomatic atherosclerosis, vascular calcification, coronary artery disease, peripheral artery disease, hypertension, and stroke [1]. Although obesity and in particular increased body mass index (BMI) have dramatically increased worldwide [2], the impact of various body-size phenotypes in CV risk and CV outcomes is under discussion [3,4].

Based on the Adult Treatment Panel-III (ATP-III) criteria, there is a concept accordingly of which the levels of BMI and other anthropometric parameters, i.e. height, and waist and hip circumferences, might identify plenty accurate overweight/obesity [5]. Consequently, subjects with established obesity and co-existing metabolic abnormalities including dyslipidemia, insulin resistance (IR), increased fasting glucose and impaired glucose tolerance, are referred metabolically non-healthy, whereas obese individuals without these abnormalities might be defined as metabolically healthy [6,7]. Interestingly, there is not strong definition of metabolically healthy obese as a transient age- and ethnic-related phenotype accompanied to some behavioral and environmental factors [8]. However, accordingly the contemporary "fit but fat" concept an absence of follow sings, such as abdominal type of obesity, insulin sensitivity, impaired glucose tolerance, and low level of cardiorespiratory fitness, is considered an acceptable criteria of metabolically healthy obese [9]. In fact, normal weight individuals exhibit a 60% lower risk of CV disease and events compared with both obese patients' cohorts including metabolically healthy and metabolically non-healthy obese [10]. In fact, individuals with different obesity phenotypes appear to be distinguished from healthy volunteers in CV risk, while patients with metabolically non-healthy obese might exhibit higher CV risk and diabetes accompanied with exaggerated frequency of unfavorable clinical outcomes including atherosclerosis-related events and stroke when compared with those who refer as metabolically healthy [11]. On the other hand, there is limited evidence regarding that the ischemic stroke rate is probably accompanied to poor metabolic health rather than with overweight or obesity [4]. Whether metabolomics abnormalities would be powerful tool to stratify the patients with different obese phenotypes is not clear [12]. The contemporary "fat-but-fit" hypothesis has issued from that the metabolically healthy obese is a transient state, which may translate into a metabolically active state over time affecting endogenous reparative response especially in the endothelium [13,14]. In this context, progenitor endothelial cell (EPC) dysfunction may play a pivotal role in target organ damage at the different stages of obese and its transformation in various phenotypes and at diabetes development [15]. Probably, clinically use of biomarkers of altered endothelial function for prediction of and risk stratification of obese patients appears to be promised [16].

By now, EPCs have defined as cells, which are positively labeled with both hematopoietic stem cells (CD34) and endothelial cell markers, i.e. predominantly vascular endothelial growth factor receptor-2 (VEGFR2), CD31 cumulatively [17]. Outgrowth endothelial progenitors as a subpopulation of EPCs exhibit a protective impact on the endothelium mediating proliferation and having the ability to promote angiogenesis and collateral vessel growth [18]. These processes are under closely paracrine and epigenetic regulation affected in particularly migration, proliferation, and mobilization of EPCs from bone marrow and peripheral tissues [19,20]. The reduced ability of EPCs to realize their potency in proliferation, differentiation, adhesion, migration, incorporation into tubular structures, and survival defined as progenitor cell dysfunction [21]. Therefore, wear EPCs functionality may associate with lowering EPCs' count in the

peripheral blood that is considered an initiation of endothelial dysfunction and any cause-related vasculopaty linked etiological factors, co-morbidities, aging and CV events [22,23]. Nevertheless, EPCs dysfunction well predicts CV risk in general population and in subjects with established CV and metabolic disease [24-26].

The primary reason of metabolic states-related deficit of circulating EPCs which has been particularly attributed to their defective mobilization, proliferation and shortened survival is not fully clear. In fact, glucose toxicity, lipid toxicity, inflammation and reactive oxidative species are now recognized as mainly factors contributing in EPC dysfunction in diabetes. They act through decreased expression of protein kinase A regulatory subunit 1β (PRKAR1β), activation of protein kinase A (PKA), matrix metalloproteinase-9, and phosphorylation of α4 integrin on serine 988 [27]. However, alteration of structure/function and reduced number of circulating EPCs has now identified in prediabetes [23,28]. In contrast, controversial results regarding being of progenitor dysfunction in obese individuals beyond diabetes were found within last decade [29,30]. The first controversial affects the obese children and adolescents, in which circulating EPC count is elevated accompanying to body mass index and evidence of endothelial activation [30]. The next controversial relates to an evidence regarding that the adult obese individuals may present an exaggerated number of endothelial cell-originated microparticles, a low number of EPCs, and high levels of adipokines in peripheral blood beyond inflammatory condition [31]. Moreover, in adult obese individuals circulating EPC number may decrease along with elevated serum level of visfatin, insulin resistance and accumulation of oxidative stress product [32].

Because of recent studies have found that the deficiency of EPC and their functional alterations tightly associated with the development and progression of CV disease [33-35], dysfunction of EPC might be first early and probably potentially reversible sign of exhaustion of endogenous endothelial reparation mechanisms leading to the development of endothelial dysfunction and asymptomatic vascular damage in obese individuals of various aging. It might be speculated that the different obese phenotypes appears to be distinguished in endothelial activation and that metabolically non-healthy obesity is accompanied to weak EPC functionality and lowering EPC count. Whether EPC dysfunction would be early biomarker to determination of asymptomatic vasculopathy in obese to risk stratification is not completely understood, while this suggestion is obviously promised. Large clinical investigations are required to explain in detail whether progenitor dysfunction is not only whiteness of nature evolution of the obese, but it is factor contributing in transformation of healthy obese to metabolically non-healthy phenotype.

In conclusion, EPC dysfunction is probably powerful factor linking obese, CV events with age by impairing angiogenesis and vascular reparation. The role of the EPC dysfunction as a predictor of CV disease and events in obese individuals requires more investigations in the future.

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