

Biosensing of circulating apoptotic endothelial cell micro particles: the impact in risk stratification of obesity

Abstract

Obesity is considered a main factor mediating a risk of diabetes mellitus development and a predictor of CV disease and events. Contemporary criteria of Adult Treatment Panel-III allow determining subjects with established obesity and various metabolic abnormalities, i.e. increased fasting glucose, impaired glucose tolerance dyslipidemia and insulin resistance (IR), are referred metabolically unhealthy obesity (Met-UHO), whereas individuals without these findings could be defined as those who have metabolically healthy obesity (Met-HO). The mechanisms underlying the change in phenotype from Met-HO to Met-UHO are yet not understood. It has been postulated that apoptotic endothelial cell-derived micro particles (EMPs) could be a trigger of endothelial cell dysfunction and as well as a mediator on vascular repair. Moreover, the imbalance in circulating number of various type of EMPs may influence the risk of transformation of Met-HO into Met-UHO. The short communication is depicted the role of apoptotic EMPs in obesity phenotype modification.

Keywords: dyslipidemia, panel-III, hypertension, prediabetes, vesiculation, microRNAs, microvascular, annexin V+, mononuclears

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Abbreviations: Met-UHO, metabolically unhealthy obesity; EMPs, endothelial cell-derived micro particles; CV, cardiovascular; T2DM, type 2 diabetes mellitus; Met-HO, metabolically healthy obesity; MPs, micro particles; MetS, metabolic syndrome; VAT, visceral adiposity tissue; BMI, body mass index

Introduction

The prevalence of abdominal obesity has been raised worldwide achieving epidemic level.¹ Recent observation and clinical studies have clearly established that abdominal obesity especially morbid obesity (body mass index [BMI] more than 40kg/m²) related strongly to all cause and cardiovascular (CV) morbidity and mortality, as well as closely associated with a risk of type 2 diabetes mellitus (T2DM).² However, there is evidence regarding progressive annually increase of prediabetes/T2DM prevalence irrespectively BMI.^{3,4} Additionally, obese individuals with similar BMI may be protected or opposite predisposed to obesity-related complications (i.e. T2DM, dyslipidemia, hypertension) and CV disease.⁵ The speculations around so called a protective role of obesity in CV disease led to appearance of a term "obesity paradox", which is referred as shaping U-curve type relation between BMI values and CV mortality rate.⁶ It is suggested that "obesity paradox" might be a mismatch between different definitions of obesity in particularly based on BMI measurement. Therefore, the heterogeneity of obesity induced the concept of emerging metabolic phenotypes associated with obesity e.g. metabolically unhealthy obesity (Met-UHO) and metabolically healthy obesity (Met-HO) distinguished from each other for CV risk.⁷ Contemporary criteria of Adult Treatment Panel-III allow determining subjects with established obesity and various metabolic abnormalities, i.e. increased fasting glucose, impaired glucose tolerance dyslipidemia and insulin resistance (IR), are referred metabolically unhealthy obesity (Met-UHO), whereas individuals without these findings could

be defined as those who have metabolically healthy obesity (Met-HO). The innate mechanisms underlying the transformation in phenotype from Met-HO to Met-UHO are still not fully clear. Whether Met-HO is an early stage and transient state in the pathway to Met-UHO and T2DM is not understood.⁸

Micro particles (MPs) are defined a huge heterogeneous (diameter average from 100 to 1000nm) sub-population of extracellular released vesicles. MPs are originated from plasma membranes of various cells and secreted with specific process called "Vesiculation."⁹ As a derivate of cellular membrane MPs are discussed powerful autocrine and paracrine transducer of structure and functions of the target cells. MP released by apoptotic endothelial cells posse a wide spectrum of biological effects on cell-to-cell communication by transferring a wide spectrum of active molecules (proteins, peptides, hormones, growth factors, microRNAs) exhibiting coagulation activity, mediating cell growth and tissue differentiation.¹⁰ Additionally, apoptotic endothelial cell-derived MPs (EMPs) may directly injury an endothelial wall integrity and vascular function playing a central role in development of microvascular inflammation and IR.¹¹ Recent clinical studies have shown that the circulating levels of apoptotic EMPs were significantly increased in T2DM patients as compared with healthy volunteers¹² and they mediated CV risk in patients with established metabolic syndrome (MetS) and T2DM.¹³⁻¹⁵ Probably apoptotic EMPs may involve in the transformation of Met-HO into Met-UHO determining the risk of T2DM and CV disease. Indeed, the increased number of circulating CD31⁺/Annexin V⁺ and CD144⁺/Annexin V⁺ EMPs much more pretty accurate predicted Met-UHO and closely positively associated with IR.¹⁶ Thus, the most important factor that affects metabolic dysregulation in obesity is IR, which probably appears to be predominantly at early stage of the Met-HO.

There is evidence that an accumulation of visceral adiposity tissue

(VAT) might associate with over-production of pro-inflammatory cytokines including hs-CRP, leptin, resistin and vistafin and induce IR.¹⁷ Therefore, a sub-intimal vascular infiltration by LDL cholesterol strove for exaggerated production of free radicals by mononuclears/macrophages, which are able to oxidate some proteins incorporated into cytoskeleton and membranes of endothelial cells. Finally, membrane vesiculation of endothelial cells as a crucial component of EMP secretion is enhanced by inflammatory cytokines in conveying of VAT accumulation. Interestingly, the number of circulating apoptotic EMPs has positively associated with conventionally obesity biomarkers (adiponectin, leptin, vistafin) in Met-UHO patients, but did not relate to in Met-HO individuals. Additionally, we did not find severe metabolic abnormalities apart from leptin elevation in Met-HO patients compared with Met-UHO. In contrast, we have shown that IR was common finding for both Met-UHO and Met-HO individuals without sufficient difference in BMI.

The increased amount of VAT together with a chronic low-grading inflammation and IR predisposes to the development of endothelial dysfunction through attenuation synthesis and secretion of apoptotic EMPs. Indeed, pro-inflammatory cytokines, i.e. interleukin-6, tumor factor necrosis-alpha, leptin and vistafin, may directly influence a structure of maternal endothelial cells, induce apoptosis and trigger a secretion of EMPs by apoptotic endothelial cells.^{18–20} The main biological function of this process is an attenuation of endothelial cell repair and recovery of vascular function.²¹ Unfortunately, co-existing IR affects a secretome of endothelial progenitor cells and they are not able to differentiate into functionally mature endothelial cells even after stimulation by apoptotic EMPs.²² As a result, shaping of both apoptotic EMP-induced endothelial dysfunction and IR may become as maximum an early predictor of transformation of Met-HO into Met-UHO or as minimum a trigger of Met-UHO. Recently it has reported that circulating number of small apoptotic EMPs may independently predict asymptomatic atherosclerosis and CV disease in T2DM patients,²³ while their role in individuals with different phenotypes of obesity has remained controversial. First, it is not clear whether increased number of apoptotic EMPs that is actively secreted by apoptotically modified mature endothelial cells is adaptive innate mechanism of vascular repair or pathogenetic factor of shaping endothelial injury. Indeed, circulating EMPs, which are got maintenance in a large number of metabolic disorders including abdominal obesity, associated with IR and this has been tied to deleterious impact on endothelial cells.^{24,25} At the same time, apoptotic EMPs are known powerful factor, which is contributing in mobbing and differentiation of bone-derived and peripheral endothelial progenitor cells. Secondary, it is not fully understand the innate molecular mechanisms, which correspond to triggers of secretion of these apoptotic MPs.

Apoptotic MPs as cargo micro-vesicles consist of a variety of bio molecules including regulated proteins, active molecules, coagulative factors, DNAs, RNAs, miRNAs and non-coding RNAs.²³ The proportion of these components as well as an entire secretome is under a tight control of autocrine/paracrine mechanisms and inflammatory factors (i.e. tumor necrosis factor-alpha, interleukin-2,-6), which induces EMP formation in a time-dependent manner.^{9,10,25} Consequently, the final reply of the recipient cells, such as endothelial progenitor cells, is depends on epigenetic regulation of secretome secretion and primary trigger, which affects vesiculation of target cells.¹⁰ Obviously, an ability of apoptotic EMPs to enhance and modulate several immune

and inflammatory processes, coagulation and vascular function, angiogenesis and vascular injury, neovascularization and endothelial reparation may interact with other regulatory mechanisms the role of which in the pathogenesis of abdominal obesity requires still being determined more pretty accurate. Nowadays it is no excluded that release of apoptotic EMPs might act as a direct endogenous survival signal for target cells the role of which would investigate in detail in future.

Conclusion

Single and probably serial measurement of circulating number of apoptotic EMPs would be useful tool for stratification amongst established abdominal obesity individuals at higher risk of T2DM and CV disease or events, especially when conventionally used biomarkers of obesity are not detected at the appropriate diagnostic levels. Large investigations are required to understand the role of apoptotic EMPs in pathogenesis of different phenotypes of abdominal obesity, because they may be a target of the therapy as well as predictive biomarkers.

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Conflict of interest

The author declares no conflict of interest.

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