REVIEW ARTICLE

Can Biomarkers be Useful for Cardiovascular Risk Assessment in Patients with Different Phenotypes of Obesity?

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ABSTRACT

Obesity remains a leading cause of cardiovascular (CV) events and diabetes worldwide. Although there are at least two main body-size phenotypes (metabolically healthy and metabolically non-healthy) of individuals with established obesity, the cardio metabolic risk amongst these patients' populations extremely distinguishes. The editorial is discussed the controversies regarding obese paradox and the probabilities to stratify the patients with established obesity in cardio metabolic risk. It is suggested that the biomarkers could predict CV events in patients depending on obese phenotypes. The role of metabolic biomarkers, progenitor cells, natriuretic peptides, inflammatory cytokines and galectin-3 are discussed.

Key words: Obese, metabolically healthy obese, cardiovascular risk, stratification, endothelial progenitor cells

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INTRODUCTION

Obesity is common endocrine disorders, a prevalence of which progressively arises worldwide for last decades.[1] Recent observation and clinical studies have confirmed that leading role of obese in metabolic (metabolic syndrome, diabetes) and cardiovascular (CV) complications (asymptomatic atherosclerosis, vascular calcification, coronary artery disease, peripheral artery disease, hypertension, and stroke).[2-5] Although there are at least two main body-size phenotypes (metabolically healthy and metabolically non-healthy) of individuals with established obesity,[3] the cardio metabolic risk amongst these patients' populations extremely distinguishes.[6] The majority of obese patients, who were involved in the large longitudinal studies, have been qualified neither metabolically non-healthy individuals nor patients with abdominal obesity and metabolic syndrome/type two diabetes mellitus (T2DM). Dramatically raise of the risk of cardiovascular (CV) incidences in metabolically non-healthy obese is now well known.[7] In contrast, other metabolically healthy obese individuals, for whose mild-to-moderate increase of CV risk is uncertainly established, were discovered not a bit carefully. Whether the same prognostication models would be effective to much more accurate stratify individuals with both obese phenotypes at higher CV risk is not fully understood. Consequently, a risk prediction of CV events and CV diseases for both obese phenotypes patients might base on different biomarkers and distinguished frequently pragmatic approaches. The aim of the editorial is to summarize our knowledge regarding the role of biomarkers in prognostication of CV events amongst patients with established obese depending on their phenotypes.

Definition of metabolically healthy and metabolically non-healthy obese

Based on the Adult Treatment Panel-III (ATP-III) criteria, there is a concept accordingly of which the levels of body mass index (BMI) and other very simple anthropometric parameters, i.e., height, and waist and hip circumferences, might identify plenty accurate overweight and obesity.[6] Consequently, subjects with established obesity and co-existing other 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.[7,8] 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.[9] However, accordingly the contemporary "fit but fat" concept an absence of follow sings i.e., abdominal type of obesity, insulin resistance, impaired fasting glucose/glucose tolerance, and low level of cardiorespiratory fitness, is considered plenty acceptable criteria of metabolically healthy obese.[10]

Cardiovascular risk in obese

Recent clinical studies have shown that the normal weight individuals exhibit a 60% lower CV risk with compared to obese patients regardless phenotypes of the disease.[11] Interestingly, metabolically non-healthy obese patients exhibit higher risk of CV events and T2DM that is accompanied with exaggerated frequency of atherosclerosis- and thrombotic-related outcomes including stroke when compared with those who were referred as metabolically healthy obese individuals.[12] Moreover, there are serious noticeable variations in CV disease risk, T2DM risk and risk of cancer between different ages, sexes and ethnic populations of individuals with obese, which did not independently affect phenotypes of the disease. However, there is evidence regarding being of more sophisticated relationships between obesity and several CV diseases. Indeed, while the risk of new heart failure incidences, CV complications after vascular surgery, cardiac resynchronization therapy and venous thrombosis has been shown to be significantly higher in obese patients, there is a survival advantage for overweight / obese patients compared with normal weight (BMI=18.6 to 24.9 kg/m^2) or underweight (BMI ≤ 18.5 kg/m^2) patients. Similar typically U shaped relation between with an increased CV risk in underweight subjects and a beneficial effect of overweight and obese individuals was recently described as specific phenomenon called "obesity paradox".[13-15] Interestingly, this obesity paradox has been established in several populations of the obese patients corresponding to CV risk

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factors in abundant. In contrast, weight gain strategy in hypertensive patients leads to reduction of blood pressure and ameliorates the CV risk profile regardless obese.[16] In this context, ccontroversial findings are reported on the CM risk of obese require the plenty accurate biomarker or combination of them, which could improve a prediction of CV events and disease in obese individuals without known CV disease and attenuates stratification at risk of the patients with established CV disease. Taken together, all these sufficiently obscure understanding the role several biomarkers in prediction of CV events in both types of obese.

Metabolomisc and CV risk in obese individuals

Surprisingly, there is limited evidence regarding that the CV disease i.e., ischemic stroke is accompanied to poor metabolic health rather than with obesity.[5] Whether metabolomics abnormalities would be powerful tool to stratify the patients with different obese phenotypes at CV risk is not clear.[16] However, there are huge spectrum of several plasma metabolites i.e., fasting glucose, including 1,5-anhydroglucitol, mannose, valine, 3-methoxytyrosine, docosapentaenoate (22:5n3), bradykinin-hydroxy-pro(3), alanine, phenylalanine, tyrosine, palmitoylcarnitine, diacyl-phosphatidylcholines C32:1, C36:1, C38:3, and C40:5, glycine; sphingomyelin C16:1; acyl-alkyl-phosphatidylcholines C34:3, C40:6, C42:5, C44:4, and C44:5; and lysophosphatidylcholine C18:2, which associate with metabolically non-healthy obese/T2DM and may improve CV risk prediction in several populations.[17,18] In fact, novel plasma metabolites may increase sensitivity and specificity of the prediction model when they are added to combination of the traditional factors: impaired fasting glucose, insulin resistance, BMI and abdominal type of obese.[19] In contrast, the metabolites may significantly improve a discrimination of T2DM development and progression compared with established risk factors.[20-22] Probably, these findings might be much more useful for patients with metabolically healthy obese. Whether the novel broadest panels of non-targeted and probably targeted metabolites would be the strongest predictive biomarkers for CV events and CV disease than BMI and insulin resistance in obese beyond hyperglycemia/diabetes is not completely understood.

Endothelial progenitor cell dysfunction

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.[23,24] In this context, endothelial progenitor cell (EPC) dysfunction may play a pivotal role in target organ damage at the different stages of obese and its transformation in various phenotypes.[25] Probably, clinically use of biomarkers of altered endothelial function for prediction of and risk stratification of obese patients appears to be promised.[26]

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.[27] 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.[28] These processes are under closely paracrine and epigenetic regulation affected in particularly migration, proliferation, and mobilization of EPCs from bone marrow and peripheral tissues.[29,30]

Increased adipocyte size is hypothesized to signal the recruitment of various types of progenitor cells including endothelial progenitor cells. In metabolically healthy obese individuals the number of EPCs in the circulation is frequently increased or near normal. In contrast, development of metabolically non-healthy obese associates with the reduced ability of EPCs to realize their potency in proliferation, differentiation, adhesion, migration, incorporation into tubular structures, and survival is now defined as EPC dysfunction.[31] The wear EPCs functionality may associate with lowering EPCs' count in the peripheral blood that is considered an initiation of endothelial dysfunction.[32,33] Nevertheless, EPCs dysfunction well predicts CV risk in general population and in subjects with established CV and metabolically non-healthy obese.[34-36]

The primary reason of deficiency of circulating EPCs' number in metabolically non-healthy obese 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.[37] However, alteration of structure/function and reduced number of circulating EPCs has now identified in prediabetes.[33,38] In contrast, controversial results regarding being of progenitor dysfunction in obese individuals beyond diabetes were found within last decade.[39,40] The first controversial affects the metabolically non-healthy obese in children and adolescents, in which circulating EPC count is elevated accompanying to BMI that the metabolically non-healthy obese adults may present a exaggerated number of endothelial cell-originated micro particles, a low number of EPCs, and high levels of adipokines in peripheral blood beyond inflammatory condition.[41] Moreover, in adult metabolically non-healthy obese individuals circulating EPC number may decrease along with elevated serum level of visfatin, insulin resistance and accumulation of oxidative stress product.[42]

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,[43,44] 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.[25] Whether EPC dysfunction would be early biomarker 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.

Galectin-3

It is well known that there is close relation between obesity-induced insulin resistance, immune cells accumulation in white adipose tissue (WAT) and inflammation.[45,46] Indeed, in obesity WAT is characterized by an increased production and secretion of a wide range of inflammatory cytokines including TNF-alpha and interleukin (IL)-6, which may have local effects on endothelium, vasculature and target adipose tissues.[47] Therefore, activated macrophages and other antigen presenting cells that are accumulated in elevated number in fat tissue in both types of obese actively secrete a broad spectrum of locally-produced pro-inflammatory cytokines including galectin-3 (Gal-3). Gal-3 is a beta-galactoside-binding lectin belonging to multifunctional protein family, which enhances chemotaxis of immune and antigen presenting cells, reduces insulin-stimulated glucose uptake in myocytes and adipocytes and impairs insulin-mediated suppression of glucose output in hepatocytes.[46] Gal-3 may bind directly to the insulin receptor (IR) and thereby inhibit down-stream insulin resistance signaling

via diminishing interleukin-1 beta production.[47-49] Therefore, Gal-3 is a modulator of apoptosis, necrosis and fibrosis associated with extracellular remodeling.[50]

Gal-3 is increased in obesity and mediates inflammation and fibrosis in the heart and vessels, as well as in the WAT.[51] The most preclinical and clinical studies suggest that this protein protects from inflammation in obese, while there is large body of evidence regarding ability of Gal-3 to deteriorate glucose homeostasis, modulate cell adhesion and induce pro-oxidant pathways.[52,53] Interestingly, the low serum Gal-3 concentrations are closely associated with insulin resistance in patients with type 2 diabetes mellitus.[54] In contrast, an inversely correlation of serum Gal-3 and glycosylated hemoglobin in type 2 diabetes mellitus was found.[55] In clinical settings Gal-3 strongly independently predicts all-cause mortality and CV mortality in the general population and in patients with known CV disease.[56,57] In fact, in cross-sectional analyses of 2946 Framingham Heart Study participants circulating Gal-3 was associated well with abdominal adiposity, dyslipidemia, and hypertension, but Gal-3 did not predict incident CV and metabolic diseases after adjusting for cardio metabolic risk factors.[58] Whether Gal-3 could be a predictive marker of the metabolically non-healthy obese is not clear, although Gal-3 deserves further large clinical trials to understand its role in different obese phenotypes' development.

Pro-inflammatory cytokines

Recent preclinical and clinical studies have shown that the plasma concentration of inflammatory cytokines, i.e., C-reactive protein, tumor necrosis factor-alpha (TNF-alpha), IL-1 beta and IL-6, is increased in metabolically non-healthy obese in contrast to metabolically healthy obese.[59] These cytokines might interfere with insulin action by suppressing insulin signal transduction counteracting with the anti-inflammatory effect of insulin, and thereby promote inflammation and stimulates preadipocyte proliferation of WAT.[60] In this context, the measurement of circulating level of them could distinguish metabolically healthy obese from metabolically non-healthy obese.[61,62] However, there are some controversies between preclinical data and clinical findings. Ryder *et al.* have shown that similar TNF-alpha tissue expressions were found in obese individuals with and without insulin resistance.[63] Additionally, increased serum TNF-alpha has determined in metabolically healthy obese accompanied to an elevation of both IL-1β level and circulating mononuclear cells bearing on their surface the advanced glycation end product receptor (RAGE), angiotensin II receptor and s100A12 protein (RAGE ligand). Finally, recent clinical studies have exhibited an important role for IL-1 family members and probably IL-6 but not for TNF-alpha and higher sensitive C-reactive protein in metabolically non-healthy obese.[64,65] Thus, apart from theoretic explanation, inflammatory cytokines would be rather indicator of disease activity than diagnostic biomarker of both obese phenotypes with different CV risk profiles.

Natriuretic peptides

Natriuretic peptides (NPs) are "cardio metabolic" hormones with well-established cardiovascular, renal, and endocrine abilities affecting sodium reabsorption and blood pressure regulation.[66] Although MPs are markers of biomechanical cardiac stress, their role in the nature evolution of obese is not fully understood. These controversies affect the clearance of NPs in obese and pathophysiological mechanisms controlling the synthesis of them. On the one hand, secretion of NPs is resulting in stretch of the cardiac wall and volume overload of cardiac cavities.[67] On the other hand, recent epidemiological and preclinical/clinical studies have shown that the NP system acts in deficiency in obesity patients is due to worse clearance of NP receptors and neutral endopeptidases.[68] Consequently, NP system in obese do is not able to mediate a wide spectrum of cardiovascular and metabolic protective effects (i.e., vasodilation, natriuresis, diuresis, lipolysis, weight loss, lusitropy, lipid peroxidation, and also improve of mitochondrial respiration and insulin sensitivity).[67]

The elevated circulating level of NPs in a large community-based cohort free of cardiac dysfunction has strongly predicted the risk of newly diagnosed CV diseases regardless obese.[69] However, the concentration of NPs in peripheral blood of HF patients with obesity and T2DM is extremely lower than in HF subjects without these metabolic comorbidities, despite overall the circulating levels of NPs in both cohorts of HF individuals are higher compared to healthy volunteers.[70,71]

Brutsaert *et al.*[72] have reported that higher levels of brain NP have associated with decreased risk of diabetes in middle-aged adults and that the interrelation has remained after adjustment for waist circumference, low physical activity, estimated glomerular filtration rate and high sensitive C-reactive protein level. In contrast, it is suggested that the low brain NP levels observed in obesity could causally associate with the incidence of diabetes in obesity individuals. The effect of brain NPs might relate to an ability of natriuretic peptides to activate a thermo genic program in brown and white fat tissues, increase energy expenditure and inhibit food intake.[70] Thus, NPs might play several metabolic roles in development of different phenotypes of obesity, but their predictive role in CV disease development in obese patients is uncertain.

In conclusion, the biomarker strategy on risk stratification of the patients with obese appears to be promising, but lack of strong clinical evidence about possibilities to use biomarker-based care as predictors of CV event and CV disease in both obese phenotypes requires more large clinical trial in the future. It is extremely difficult to plenty accurate explain the prognostic value of novel biomarkers in obese depending phenotypes, while observational studies have shown the serious difference between them in CV risk. Based on current knowledge Gal-3 and EPCs exhibit much more diagnostic ability compared to other biomarkers in this settings. Future investigation might clear the role of both biomarkers carefully.

Conflict of interests

No financial conflicts of interest relevant to the article topic is declared.

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