

Promising Utilities of Growth Differentiation Factor 15 in Cardiovascular Diseases

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Abstract

Recent clinical trials have shown that biological markers presumably natriuretic peptides, galectin-3, soluble ST2 could be the best tool for cardiovascular (CV) risk stratification in general population as well as in individuals with CV diseases. However, abilities of these biomarkers to predict CV mortality rate are variable and depends on age, sex, kidney function and metabolic comorbidities. Growth-differentiation factor-15 (GDF-15) belongs to the transforming growth factor- β superfamily that regulates mitochondrial function of wide range of cells that involve in inflammation, oxidative stress, apoptosis, immune reaction, fibrosis, reparation and malignancy. This short commentary is depicted the possibilities to extrapolate the predictive capabilities of GDF-15 from metabolic and tumor diseases to CV diseases.

Keywords: heart failure; cardiovascular disease; biomarkers; growth-differentiation factor-15; prognosis; clinical outcomes; predictive value

Introduction

Cardiovascular (CV) diseases are the leading causes of mortality and disability in general population worldwide [1]. Contemporary decision-making of both prevention and treatment of CV diseases bases on risk stratification and enroll the appropriate patients for further procedures and medical care [2, 3]. Because there is considerable heterogeneity in CV risk assessment with clinical tools and even when one more CV risk score systems are used, the exact CV risk determination

might be facilitated by an implementation of individual CV risk stratification with biomarkers reflected numerous various faces of pathogenesis of the disease [4]. Recent clinical trials have shown that N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponins, galectin-3, and soluble ST2 could seemingly be biomarkers of predictive abilities in patients with CV diseases [5-8]. Although growth-differentiation factor-15 (GDF-15) is an established biomarker of inflammation, fibrosis and apoptosis, it took close discussion within recent several years as promising candidate to identify individuals at high risk of poor CV clinical outcomes [9]. This short commentary is depicted the predictive role of GDF-15 in CV diseases.

Biological role and function of growth-differentiation factor-15

GDF-15 belongs to the transforming growth factor- β superfamily and was found an important regulator of mitochondrial function of wide range of cells that involve in the pathogenesis of immune reaction, inflammation, oxidative stress, fibrosis, reparation and malignancy [10]. In physiological and pathological conditions GDF-15 exhibited anti-inflammatory properties, which are produced by binding of this molecule with a currently unknown receptor. There is evidence that GDF-15 may specifically bind to an orphan member of the GDNF family receptor α -like (GFRAL) and that intracellular signaling promoted by GDF15-GFRAL cooperation involve in the regulation of food intake by a central mechanism [11]. Over-expression of GDF-15 is up-regulated by several Th2-dependent cytokines (interleukin [IL]-13, IL-4) via the Janus kinase-activated STAT6 pathway and metabolites (impaired fasting glucose, free radicals) through p53 and FoxM1-related intracellular signal system [12]. Thus, Th2-dependent cytokines, which produced in white adipose tissue and perivascular adipose tissue, may regulate intra-adipose and systemic lipid and glucose metabolism via GDF-15 expression [13]. It has found that over-expression of GDF-15 led to lowered production of pro-inflammatory cytokines (IL-1 β , IL-6, IL-10, tumor necrosis factor [TNF]- α), various growth factors (fibroblast growth factor, insulin-like growth factor), active molecules (ICAM-1), as well as fibrotic mediators through a prevention of activation of Th1 cells. This effect is mediated by the Foxo3 and NF κ B signaling pathways. Additionally, over-expression of GDF-15 reduced expression of phosphorylated RelA p65, pre-inflammatory and pro-apoptotic genes and thereby inhibited cell apoptosis and necrosis, as well as reduced mononuclear infiltration of tissues due to injury. Taking into consideration the fact regarding elevation of serum level of GDF-15 in various inflammatory and metabolic diseases they are considered GDF-15 could synthesize and secrete as a result in an adaptation to stress and inflammation via signaling pathways activated by mitochondrial stress [14].

Interestingly, there is evidence that the circulating GDF-15 produced by cardiac myocytes in turn acts on the liver cells to inhibit growth hormone signaling and thereby coordinates a cardiac function and growth / development of body that may have an important value in pediatric population with concomitant heart disease

and failure to thrive [15]. Probably, GDF-15 could be a central autocrine/paracrine factor that plays a pivotal role in intercellular communication within the myocardium aimed preventing stress-induced, ischemia-induced and inflammatory-related cardiac diseases.

The essential role of GDF-15 in neovascularization and angiogenesis was confirmed in animal investigations and regarded an ability of the cytokine to promote the proliferation of human umbilical vein endothelial cells and remarkably improved vascular reparation [10]. In fact, GDF-15 acting as an angiogenic cytokine promoted tissue reparation in the healing and injury. In contrast, in cancer GDF-15 acted as a promotor of antitumour immunity and revealed anti-inflammatory and immunosuppressive properties [13]. The role of angiogenic ability of GDF-15 in metastatic malignancy is under investigation and requires to be scrutinized in details. Overall, GDF-15 appears to be a pleotropic cytokine, the role of which in pathogenesis of CV, metabolic and inflammatory disease requires to be investigated in details.

Growth-differentiation factor-15 in inflammatory and metabolic diseases

Initially, GDF-15 is considered as an anti-inflammatory factor with reparative ability. Indeed, in diabetes mellitus, obesity and metabolic syndrome fasting serum levels of GDF-15 associated positively with some metabolic parameters (fasting glucose, glycated hemoglobin, HOMA index) and body mass index, age and men sex. In nondiabetic patients GDF-15 correlated well with impaired fasting glucose and predicted an insulin resistance in general population [12]. Noted, GDF-15 is able to delay gastric emptying, modify a food preference, and regulate body energy intake and improve metabolic status through direct activation of central neurons in area postrema [15]. The XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) trial was shown the interrelationship between the high levels of GDF15 in obese individuals and the risk of type 2 diabetes mellitus manifestation for 4 year follow-up period [16]. All these data clarify that GDF-15 could be a promising therapeutic target for the treatment of various diseases including obesity, diabetes mellitus and probably malignancy.

Association between growth-differentiation factor-15 and CV diseases

GDF-15 in elevated concentrations was found in numerous CV diseases, such as LV hypertrophy, stable CAD, myocardial infarction / acute coronary syndrome, acute and chronic HF, asymptomatic atherosclerosis [17-20]. Moreover, GDF-15 has positively associated with LV mass, levels of IL-6 and matrix metalloproteinase (MMP)-9 levels [17]. In patients with pulmonary arterial hypertension secondary to congenital heart disease (CHD) serum levels of GDF-15 were significantly increased compared with CHD individuals without pulmonary arterial hypertension [18]. Authors reported that elevated plasma levels of GDF-15 positively associated with NYHA functional class, serum uric acid, NT-proBNP, pulmonary artery systolic pressure, mean pulmonary artery pressure,

pulmonary blood flow, systemic blood flow and pulmonary vascular resistance, and as well as a lower mixed venous oxygen saturation [19]. It has been determined that the diagnostic value of NT-pro BNP and GDF-15 in turn of pulmonary arterial hypertension was similar. In atherosclerosis GDF-15 appears an ability to prevent ischemia and necrosis of cardiac cells, while a concentration of it in peripheral blood correlates well with cardiac fibrosis.

Growth-differentiation factor-15 in CV prediction

GDF-15 was defined as good prognosticator of CV complications in patients with diabetes mellitus [20]. There is evidence received in the KAROLA study that elevated levels of GDF-15 predicted both 10-year CV mortality rate and all-cause mortality rate [9]. In the JUVENTAS (Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-Arterial Supplementation) trial in patients with established peripheral artery disease elevated levels of GDF-15 were found a predictor of critical limb ischemia, increased risk of major amputation and all-cause mortality [21]. Elevated GDF-15 associated with a lack of reverse remodeling and increased mortality after transcatheter aortic valve replacement procedure and improves risk prediction of CV mortality rate adding to traditional score model [22]. It has found that are associated with an increased yearly rate of all-cause chronic obstructive pulmonary disease exacerbations in out-patients [23]. Because GDF-15 was found as an independent biomarker of all-cause mortality, CV death and non-fatal CV events in patients with coronary artery disease and atherosclerosis, it could support prescreening and selection high risk patients with non-ST-elevation acute coronary syndrome for early revascularization and aggressive medical therapy. Additionally, GDF-15 is considered as promising prognostic biomarker that predicts poor survival in not just individuals with chronic diseases, but in patients with critically illness including acute heart failure, sepsis, multiple organ failure [24, 25].

The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study was yielded that GDF-15 in plasma positively associated with severity of chronic heart failure (HF), peak concentration of NT-proBNP, all-cause death rate and inversely related to peak oxygen uptake on cardiopulmonary exercise testing [26]. Interestingly, in the study the serum levels of GDF-15 in chronic HF patients with preserved left ventricular (LV) ejection fraction (EF) were similar to those in reduced LVEF (HFrEF), while it associated with the severity of HF symptoms, echocardiographic parameters of LV dysfunction, 6 minute walk test distance and SF-36 physical score [26]. However, in chronic HF with preserved LVEF (HFpEF) GDF-15 did not improve diagnostic discrimination when it is added to clinical status, cardiopulmonary exercise test findings and traditional biomarkers including high sensitive troponin T, galectin-3, soluble ST2 and NT-proBNP [27]. In contrast, in HFrEF diagnostic accuracy of GDF-15 was not inferior as that of NT-proBNP and combining both biomarkers may improve diagnostic discrimination [28]. Probably, multiple biomarkers including

GDF-15 (i.e., high sensitive C-reactive protein + soluble ST2 ± galectin-3 / NT-proBNP) added to novel score could predict HFpEF [29].

In conclusion, GDF-15 appears to be a promising biomarker for individual CV risk stratification, while this biomarker should be probably considered as a component of multiple biomarkers' CV score for future implementation in the clinical practice. However, the role of GDF-15 requires to be investigated in large clinical trials with higher statistical power.

Funding and grants: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interests: not declared

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Received: January 5, 2018; Published: January 25, 2018