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Review

Diabetes mellitus related biomarker: The predictive role of growth-differentiation factor-15

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ABSTRACT

Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine, which belongs to super family of the transforming growth factor beta. GDF-15 is widely presented in the various cells (macrophages, vascular smooth muscle cells, adipocytes, cardiomyocytes, endothelial cells, fibroblasts), tissues (adipose tissue, vessels, tissues of central and peripheral nervous system) and organs (heart, brain, liver, placenta) and it plays an important role in the regulation of the inflammatory response, growth and cell differentiation. Elevated GDF-15 was found in patients with established CV diseases including hypertension, stable coronary artery disease, acute coronary syndrome, myocardial infarction, ischemic and none ischemic-induced cardiomyopathies, heart failure, atrial fibrillation, as well as stroke, type two diabetes mellitus (T2DM), chronic kidney disease, infection, liver cirrhosis, malignancy. Therefore, aging, smoking, and various environmental factors, i.e. chemical pollutants are other risk factors that might increase serum GDF-15 level. Although GDF-15 has been reported to be involved in energy homoeostasis and weight loss, to have anti-inflammatory properties, and to predict CV diseases and CV events in general or established CV disease population, there is no large of body of evidence regarding predictive role of elevated GDF-15 in T2DM subjects. The mini review is clarified the role of GDF-15 in T2DM subjects.

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Contents

1. Introduction

Cardiovascular (CV) diseases remain to be leading cause of mortality and morbidity worldwide [1]. Recent clinical studies have shown that the majority of CV deaths occurred in patients who not experience a non-fatal CV or renal event whiled who had diabetes or diabetes-associated settings, i.e. obesity, insulin resistance, peripheral artery disease [2,3]. The significant impact of diabetes on CV events and outcomes relate to interplay of preexisted traditional CV risk factors with negative effect of glucose metabolism impairment, lipotoxicity, adipose tissue dysfunction, excessive oxidative stress [4]. All these factors are able to induce endothelial dysfunction, lead to cardiac remodeling and hypertrophy, worse vascular integrity and cardiac function [5].

Although there is a large body of evidence that diabetes increases substantially the risk of death, CV events and heart

Abbreviations: AKT, serine/threonine kinase; ATF3, pro-survival protein activating transcription factor 3; eNO, endothelial nitric oxide; eNOS, endothelial nitric oxide synthase; PI3K, phosphoinositide 3-kinase; NF-kB, nuclear factor kappa-B.

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failure, a deeper understanding of the complex pathogenic mechanisms of the metabolic CV remodeling in diabetes leaded to appearance regarding the fact that traditional CV risk factors do not predict the presence of subclinical injury of heart and vessels in diabetic population [6,7]. In this context, the early stages of target-organ damage associated with diabetes might be determined using biological markers that reflect different faces of pathogenesis of disease. Because inflammation plays an important role in manifestation and nature evolution of diabetes and diabetes-related CV complications, inflammatory biomarkers became to use in the diagnostic assessment of diabetics suspected of CV diseases [8]. Therefore, predictive role of peak concentration of various inflammatory biomarkers in diabetics is suggested [9,10].

The most commonly used inflammatory biomarker in established diabetes is highly selective C-reactive protein (hs-CRP), which well correlates with CV complications, poorer metabolic control and severe hypoglycaemia in diabetes, although low sensitivity and specificity of this biomarker was found [11–14]. Apart from serial testing of hs-CRP, which is time-consuming, other novel pro-inflammatory biomarkers like Growth-Differentiation Factor-15 (GDF-15) have been proposed risk stratify patients with diabetes including type two diabetes mellitus (T2DM) [15]. The aim of the mini review is clarified the role of GDF-15 in prediction of CV outcomes and target-organ damages in T2DM.

2. Biological role and function of GDF-15

GDF-15 (recently known as macrophage inhibitory cytokine-1) is a member of the transforming growth factor beta (TGF-β) super family [16]. It is widely presented in the various cells (macrophages, vascular smooth muscle cells, adipocytes, cardiomyocytes, endothelial cells, fibroblasts), tissues (adipose tissue, vessels, tissues of central and peripheral nervous system) and organs (heart, brain, liver, placenta), where it has been shown to play an important role in the regulation of the inflammatory response, growth and cell differentiation [17]. The main sources of GDF-15 releasing in diabetes are macrophages, white adipose tissue and liver cells. However, the over expression of GDF-15 on surfaces of cardiomyocites in diabetics unless CV diseases including heart failure was not found. Probably, patients with established ischemic-induced CV disease might have extended source for GDF-15 releasing.

The triggers of production of GDF-15 are biomechanical stress, ischemia, anoxia and inflammatory cytokines (tumor necrosis factor alpha, interleukins (IL)-2, IL-4, IL-6), angiotensin II, macrophage colony stimulating factor, and TGF-β. The direct molecular biological target of GDF-15 is p53 protein, which is induced by oxidative stress and has anti-apoptotic effects on target cells. This effect closely associates with the pro-survival protein activating transcription factor 3 (ATF3), which is negatively regulated by p53 protein expression. Therefore, GDF15 inhibits c-Jun N-terminal kinase, Bcl-2-associated death promoter, and epidermal growth factor receptor, as well as activates various intracellular signaling pathways, i.e. Smad, endothelial nitric oxide (eNO) synthase, phosphoinositide 3-kinase, and serine/threonine kinase. The final result of this interrelation is suppression of both tumor necrosis factor alpha and IL-6 synthesis, protect of pressure-induced cardiac hypertrophy, improvement of vascular integrity, and increasing cardiomyocyte and endothelial cell viability [18].

Several animal studies were determined the positive effect of over-expressed GDF-15 on cell viability independently related to encoding a novel microRNA 3189 that functions as a potent ATF3 mediated regulator of cell death [19]. Inversely, GDF15 probably is able to bind with matrix metalloproteinase 26 that facilitate the pro-apoptotic effect of this cytokine [20]. Moreover, hyperglycemia in diabetic patients increases reactive oxygen species that may activate nuclear factor kB/Janus kinases/caspase-3 pathway, suppresses eNO synthase and induces cellular injury and cell death [21]. Adipocytokines in obese individuals may promote p53 activation in adipose tissue and leads to insulin resistance and T2DM. Whether pro-apoptotic ability of GDF-15 depends on type tissues is still not understood. Overall, GDF-15 may act as protective, anti-apoptotic and sometimes pro-apoptotic factor with metabolic capacities contributed growth tissue, maturation and differentiation of various cells (Fig. 1).

3. Diagnostic and predictive value of elevated serum GDF-15

GDF-15 is discussed a putative stress-responsive anti-inflammatory cytokine that increased in patients with established CV diseases including hypertension, stable coronary artery disease, acute coronary syndrome, myocardial infarction, ischemic and none ischemic-induced cardiomyopathies, heart failure, atrial fibrillation, as well as in individuals with stroke, T2DM, chronic kidney disease, infection, liver cirrhosis, malignancy [22–27]. Age, smoking, and environmental factors (chemical pollutants) are other risk factors that might increase serum GDF-15 level.

Recent clinical studies have shown that elevated level of GDF-15 was found as a marker of asymptomatic atherosclerosis, coronary artery disease, heart failure, hypertrophic cardiomyopathy, pulmonary hypertension, respiratory and kidney failure, ineffective erythropoiesis in several anemias [28–32]. Interestingly, that GDF-15 was able to be an independent marker of CV dysfunction and CV disease in the elderly [33].

Among T2DM population serum level of GDF-15 was positively associated with body mass index, body fat, fasting glucose level, glycated hemoglobin, insulin resistance index, waist to height ratio, age, arterial blood pressure, triglycerides, creatinine, glucose, hs-CRP [34], diabetic nephropathy [35,36] and inversely with insulin, anemia [34,35]. Dominguez-Rodriguez et al. [37] reported that elevated GFD-15 might predict diabetic cardiomyopathy in T2DM patients.

In fact, GDF-15 was found a predictive biomarker in CV mortality in general population and among subjects with asymptomatic atherosclerosis [38]. Elevated GDF-15 predicted survival in patients with idiopathic pulmonary arterial hypertension [39], heart failure [40], myocardial infarction [41], stable CAD [42], after cardiac resynchronization therapy [43], and patients with aortic stenosis [44]. Moreover, GDF-15 associated well with CV recurrent events after acute coronary syndrome independently of clinical predictors, B-type natriuretic peptide, and high-sensitivity C-reactive protein [45,26]. Velders et al. [26] reported

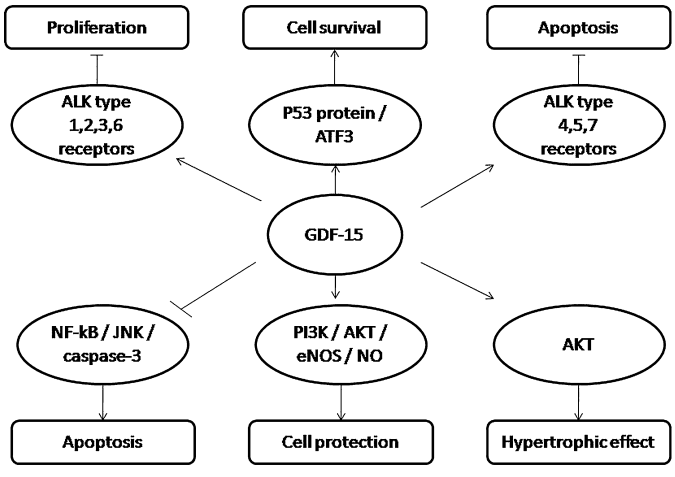

Fig. 1. Molecular targets and controversial effects of GDF-15.

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