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# Growth-Differentiation Factor-15 at Risk Stratification in Diabetes Patients: Usefulness, Discrepancies, and Hype

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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 cardiovascular (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 Growth-Differentiation Factor-15 in T2DM subjects.

**Keywords**

Cardiovascular diseases, Cardiovascular risk, Diabetes mellitus, Biomarkers, Growth-Differentiation Factor-15, Inflammation, Prediction

**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

## 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 had 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 preexisting traditional CV risk factors with negative effect of glucose metabolism, lipotoxicity, adipose tissue dysfunction, excessive oxidative stress [4]. All these factors are able to induce an endothelial dysfunction, lead to cardiac remodeling and hypertrophy that contribute in vascular dysintegrity and cardiac dysfunction [5].

Although there is a large body of evidence that diabetes increases substantially the risk of death, CV events and heart failure, a deeper understanding of the complex pathogenic mechanisms of the CV remodeling in diabetes is required. In fact, the traditional CV risk factors do not completely predict the presence of subclinical injury of heart and vessels in diabetic population [6,7]. In this context, the early stage of target-organ damage in diabetes might be determined by biological markers that reflect different faces in pathogenesis of the disease. Because an 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 correlates well with CV complications, poorer metabolic control and severe hypoglycaemia, 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 GDF15 in prediction of CV outcomes and target-organ damages in T2DM.

## Biological Role and Function of Growth Differentiation Factor-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

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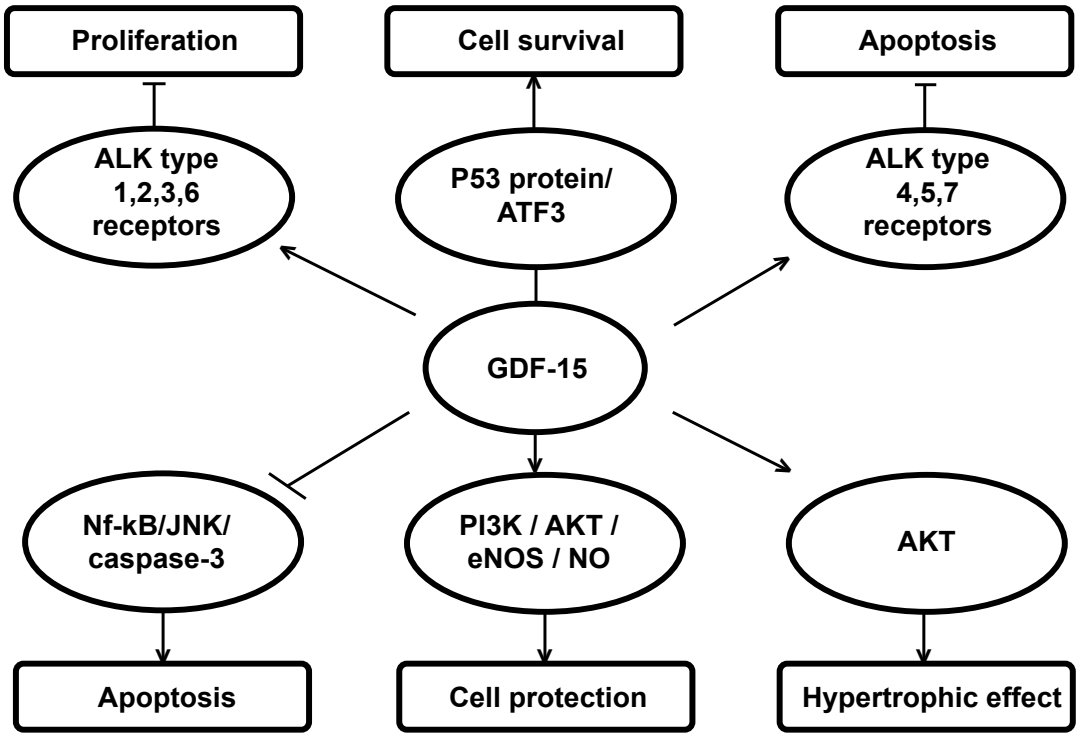


**Figure 1:** Molecular targets and controversial effects of GDF-15. Figure shows that GDF-15 is able to act the regulation of the inflammatory response, growth and cell differentiation through several ways that are linked with the progression and prognosis of the CV diseases.

peripheral nervous system) and organs (heart, brain, liver, placenta). GDF-15 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 of tissues is still not understood. Overall, GDF15 may act as protective, anti-apoptotic and sometimes pro-apoptotic factor with metabolic capacities contributed growth tissue, maturation and differentiation of various cells (Figure 1).

## Diagnostic and Predictive Value of Elevated Serum Growth Differentiation Factor-15

GDF-15 is discussed a putative stress-responsive anti-inflammatory cytokine that increased in patients with established CV diseases, stroke, T2DM, chronic kidney disease, infection, liver cirrhosis, malignancy, respiratory and kidney failure, ineffective erythropoiesis in several anemias [22-32]. Age, smoking, and environmental factors (chemical pollutants) are other risk factors that might increase serum GDF-15 level. 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]. Therefore, Dominguez-Rodriguez et al. [37] reported that elevated GFD-15 might predict diabetic cardiomyopathy.

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 [45,46]. Velders et al. [46] reported that NT-proBNP and GDF-15 measured on admission in patients with ST elevated myocardial infarction treated with primary percutaneous coronary intervention might provide incremental risk stratification. According opinion of investigators, both biomarkers are the most valuable due to the association with both CV disease and spontaneous myocardial infarction [46]. Wallentin et al. [47] have reported that GDF-15 was

able to improve prognostication of both CV and cancer mortality / morbidity beyond established risk factors and biomarkers of cardiac, renal dysfunction and inflammation. Therefore, GDF-15 was found a risk factor for major bleeding, mortality, and stroke in atrial fibrillation [48].

Accumulating evidences have shown that GDF15 could associate with the development and prognosis of T2DM. 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. Surprisingly, in individuals before T2DM manifestation the concentration of GDF-15 was not independently associated with incident T2DM in follow up period [49]. Inversely, elevated GDF-15 has demonstrated a predictive value for CV complications, all cause mortality and CV mortality in diabetic individuals with established CV diseases, nephropathy, hypertension, rheumatic diseases [37,50-52]. Overall these findings indicate that clinically significance of similar associations between circulating levels of anti-inflammatory cytokines. i.e. GDF-15, incident T2DM, and all cause mortality and CV mortality strongly requires a confirmation preferably in prospective epidemiological studies. Whether GDF-15 is an important prognostic marker in diabetics without existing CV disease is still not clear and this question might be addressed to future studies.

In conclusion, the role of elevated GDF-15 as prognostic marker in diabetics is widely discussed. GDF-15 was found a predictor of subsequent insulin resistance and impaired glucose control in obese subjects. The prediction of elevated GDF-15 in T2DM individuals without CV diseases or other co-morbidities that might increase the CV risk is under recognized. The future perspectives regarding utility of GDF-15 in routine clinical practice probably affects their ability to predict CV outcomes and mortality, while novel validated models for risk stratification of T2DM patients with pre existed CV diseases are needed.

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