Heart Health Open Access

Received: Jun 21, 2015
Accepted: Jul 14, 2015
Published: Jul 16, 2015

http://dx.doi.org/10.14437/2378-7716-2-110 Editorial Alexander E Berezin. Heart Health Open Access 2015. 2:1

Is Elevated Circulating Level of Galectin-3 A Marker with Diagnostic and Predictive Value in Diabetic Patients?

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Abstract

Within past decade substantial progress has been made in our understanding of the molecular mechanisms by which low-intense inflammation might induce metabolic disorders, such as diabetes and metabolic syndrome. Gal-3 is low molecular chimaera-type galectin, which highly expressed in a variety of cells that has been recently recognized as a biomarker of cardiovascular fibrosis and inflammation. The main biological role of Gal-3 is regulation of cell migration, adhesion, growth and differentiation, modulation of mRNA splicing, as well as Gal-3 affects extracellular matrix interactions, angiogenesis and malignancy. Recent clinical studies have shown that Gal-3 in both general and diabetic populations might contribute increased risk of CV outcomes. The possible capacity of Gal-3 to predict diabetes manifestation and development beyond other classical CV risk factors and CV diseases requires more investigations. This editorial comment is dedicated a consideration of possible role of Gal-3 as diagnostic and predictive biomarker in patients with diabetes.

Keywords: Galectin-3; Diabetes Mellitus; Cardiovascular Diseases; Clinical Outcomes

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Introduction

Within past decade galectin-3 (Gal-3) has been discussed an emerging biomarker playing a pivotal complex role in intracellular pathways of Cardiovascular (CV) remodeling [1]. By now, Gal-3 demonstrated strongly association with CV mortality [2, 3] and this biomarker was approved in the risk stratification of Heart Failure (HF) in general and several limited populations [4, 5]. Therefore, there is expectation that Gal-3 might be a promising biomarker in predicting mortality in patients with dysmetabolic states, i.e. pre-diabetes, diabetes and obesity, while evidences regarding molecular effects of Gal-3 in diabetes appeared to be controversially [6]. Indeed, Gal-3 deficiency exacerbated hyperglycemia, but up-regulated Gal-3 level in diabetes was previously reported [7, 8]. Overall, the predictive role of this marker in subjects with diabetes mellitus especially compared to other biomechanical stress biomarkers, such as NT-proBNP, ST2, was not exactly still established. Theoretically, increased biomechanical myocardial stress or cell injury due to diabetes mellitus, accelerated atherosclerosis or ongoing ischemia might contribute CV remodeling and lead to increased serum Gal-3 level [9]. Whether elevated Gal-3 level appears prior to diabetes and CV complications in subjects at high CV risk or inversely Gal-3 reflects the remodeling response of the tissue in resulting of inflammation, fibrosis, apoptosis is not still clear. The aim of the mini review is consideration of possible role of Gal-3 as diagnostic and predictive biomarker in patients with diabetes.

Biological function of Gal-3

Galectins are members of a family of soluble β-galactoside-binding proteins that belong to lectins and play an important role in fibrosis, inflammation, immunity, and malignancy [7]. Gal-3 is low molecular (29-35 kDa) chimaera-type galectin, which highly expressed in a variety of cells and occurs in the cell nucleus, the cytoplasm and on the cell surface [10, 11]. The molecule of Gal-3 contains N-terminal domain constituted short amino acid segments and C-terminal carbohydrate-recognition domain. Both domains distinguish each other their responsibility to signal molecules. Biological activity of galectin-3 fully relates to N-terminal domain, C-terminal domain is necessary for lectin activity.

The main biological role of Gal-3 is regulation of cell migration, adhesion, growth and differentiation, modulation of mRNA splicing, as well as Gal-3 affects extracellular matrix interactions, angiogenesis and malignancy [11]. Indeed, acting via appropriate membrane receptors for cell adhesion molecules Gal-3 regulates cell-cell cooperation and cell-matrix interactions through protein kinase C-related mechanism. In activated fibroblasts Gal-3 induces synthesis of pro-collagen type I and results in extracellular fibrosis and remodeling [12]. Probably, Gal-3 may regulate through gene expression of HIF-1α. However, both elevated transcriptional and translational levels of Gal-3 were found in the myocardium in early ischemic period [13]. Nevertheless, Protein Kinase C (PKC) pathway of Gal-3 expression appears to be crucial for over production of this lectin. Moreover, other factors, i.e. angiotensin II, that activate the PKC may contributes to cardiac and vascular fibrosis and modulate the development of CV disease via Gal-3-dependent mechanisms [14]. Consequently, Gal-3 regulates migration of macrophages through endogenous peptide N-acetyl-seryl-aspartyllysyl-proline that plays a pivotal role in target organ damages [15] thus leading to cardiac fibrosis, cardiac remodeling, cardiac dysfunction and atrial fibrillation [16]. There are evidences of important role of Gal-3 in regulation of immunity through induce of pathogen phagocytosis and Fcγ receptor-mediated phagocytosis of opsonized cells and particles [17]. All these finding help us to understand innate mechanisms affected immune response and malignancy through Gal-3 presentation on several cells.

To date, Gal-3 might have up-regulatory effect on advanced glycated human serum albumin-induced expression of endothelial cell specific molecule-1 or endocan [18]. In fact, expression of endothelial cell specific molecule-1 gene is under regulation of inflammatory cytokines, which contribute diabetes-induced endothelial dysfunction [19]. There are evidences that Gal-3 may directly activate PPARγ on adipocytes and leads to adipocyte differentiation in vitro and in vivo [20]. Thus, Gal-3 may consider a biomarker of vascular injury at early stage development of diabetes mellitus.

Diagnostic role of Gal-3 in cardiovascular disease patients

Gal-3 is well-known risk factor for the development of atherosclerosis in general population. Indeed, the positive correlations between serum Gal-3 level and body mass index, high-sensitivity C-reactive protein, the total number of coronary artery vessels with documented plaques, and the number of plaques were determined [21]. Obviously, elevated serum Gal-3 level might reflect innate underlying pathogenetic mechanisms involved in atherosclerosis etiology, development, and plaque rupture, i.e. inflammation, infiltration of plaque by antigen-presenting cells and oxidative stress. Regarding this Gal-3 may help to detect atherosclerosis at early stage prior to clinical presentation.

Increased expression of Gal-3 was found in coronary plaque and cardiac tissues with closely relation to severity of ischemic injury and necrosis [21]. Moreover, circulating Gal-3 levels were significantly higher in ST-Elevation Myocardial Infarction (STEMI) than control patients over a short time period in relation to timing of reperfusion [22, 23]. In this context, Gal-3 is discussed a marker that might identify vulnerable STEMI patient. Therefore, elevated level of Gal-3 was fond in heart failure patients and probably might help to recognize subjects with early heart failure with preserved left ventricular ejection fraction that frequently appears in patients with arterial

hypertension, diabetes, obesity [24]. Probably, Gal-3 measurement might add powerful incremental predictive information regarding cardiac remodeling. Moreover, Gal-3 is discussed an important biomarker for risk stratification in patients with chronic heart failure and it is enables informed decision-making about treatment and end-of-life care [25]. Regarding this Gal-3 has also been an emergence of biomarker for evaluation of acutely decompensated heart failure that assists in the differential diagnosis of dyspnea beyond the natriuretic peptides [26]. Probably continued monitoring of circulating Gal-3 level might become a useful tool for biomarker-based management of heart failure [27, 28], while this assumption needs to be confirmed in the large studies.

Predictive value of Gal-3 in heart failure

Resent clinical studies confirm compared the predictive power of Gal-3 in patients with CV diseases including heart failure without classical CV risk factors [29-31]. Elevated Gal-3 was associated well with increased risk of short-term death and the necessity for 30-day re-admission [27]. However, the predictive power of Gal-3 was weaker then NT-proBNP but both biomarkers remained significant, independently of each other in heart failure patients [9]. Overall, according results of the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure) sub-study Gal-3 was not associated with biomarkers of neurohumoral activation, fibrosis, inflammation or myocardial necrosis, congestion or quality-of-life impairment, cardiac remodeling or dysfunction, or exercise intolerance [32]. Although recent analysis of several studies revealed that a rise in Gal-3 level over 15% from baseline within six months in STEMI subjects with heart failure reflects an increased risk of adverse CV outcomes [33], possible smaller fluctuations in Gal-3 concentrations are expected when serial measurements of the biomarker levels are performed. Interestingly, that there was not closely correlation between circulating and tissue levels of Gal-3, however, exaggerated serum Gal-3 level was an independent predictor of survival in CV subjects with CV diseases including heart failure independently left ventricular ejection fraction [34, 35]. Whether tissue expression of Gal-3 would have similar predictive value is still not clear.

The role of Gal-3 in diabetic patients

In diabetics increased level of Gal-3 was found in closely interrelation with glycosylated hemoglobin (HbA1c) and N-terminal fragment B-type natriuretic peptide [36]. The results of investigation presented by Yilmaz et al. [8] have shown that Gal-3 might be an independent predictor of diabetes in general population. These data pick up discussion around the role of Gal-3 in prediction of diabetes beyond other CV risk factors and CV diseases. The conflicting results regarding level of Gal-3 in diabetic population probably relate to presentation of both co-morbidities, i.e. asymptomatic atherosclerosis and Coronary Artery Disease (CAD). In fact, Gal-3 predicts well atherosclerotic lesion of coronary arteries, as well as coronary plaque burden, inflammatory-induced infiltrative changes, and even plaque cap structures [21]. Inversely, low Gal-3 intra-plaque concentration correlates with clinically and ultrasonically defined unstable human carotid plaques [37]. Because lack of relations between tissue and serum levels of Gal-3 was previously defined, it has been suggested that elevated Gal-3 level in diabetics might reflect CAD presentation rather than inflammatory state. Opposite, Libhaber et al [38] thought that Gal-3 probably contributes toward adverse CV outcomes through an effect on aortic stiffness and that this effect is not attribute of general inflammatory changes, which are suitable for CV disease development.

Diabetes and extracellular matrix remodeling associated with fibrosis is considered as interrelating settings, moreover, type two diabetes mellitus is age-related disease. Recent clinical studies have shown that Gal-3 level associated with age, homeostasis model assessment for insulin resistance, the insulin sensitivity index with a strong gender interaction for these correlations [39, 40]. Whether serum Gal-3 might be a useful tool for vascular aging and strongly biomarker for risk stratification of patients with pre-diabetes and diabetes is not understood, while it appears to be attractive. Future studies are expected to evaluate

the possible predictive role of Gal-3 in diabetes and clarify the role of Gal-3 in the pathophysiology of diabetes-induced CV complications.

In conclusion, Gal-3 in both general and diabetic populations might contribute increased risk of CV outcomes. The possible capacity of Gal-3 to predict diabetes manifestation and development beyond other classical CV risk factors and CV diseases requires more investigations.

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