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Commentary Open Access

The Rationality to Use of Galectin-3 as Target in Biomarker-Guided Therapy of Type 2 Diabetes Mellitus

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Abstract

Galectin-3 is a multifunctional chimaera-type β-galactoside binding protein that has been linked to incident Cardiovascular (CV) and renal disease, fibrosis and tissue injury. Elevated level of serum galectin-3 was found in patients with Type 2 Diabetes Mellitus (T2DM) and associate well with CV complications. The short commentary depicts the role of galectin-3 in risk stratification in T2DM individuals. Although perspectives of clinical implementation of galectin-3-guided therapy in T2DM patients are widely discussed, there is evidence regarding cyto-protective role of galectin-3 in diabetes. Whether is rationale to achieve full control under serum galectin-3 as a predictor of successful T2DM treatment is not clear. Further investigations are needed to explain the role of galectin-3 in T2DM development and progression

Keywords: Diabetes mellitus; Biomarkers; Galectin-3; Risk stratification; Targeting for therapy

Commentary

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder appears to be increased prevalence rate that is reaching epidemic proportions worldwide [1]. Due to its chronic complications, including Cardiovascular (CV) events, T2DM causes high human, social, and financial costs irrespective in race, sex, and aging in various patient populations [2,3]. It is postulated that the real prolongation of life in T2DM individuals associated with decreased CV and all-cause mortality rates, improved well-being and quality of life, might be related with achieving of full control of glucose, dyslipidemia, lipo-toxicity, traditional CV risk factors, as well as increased complains of the diabetics to style-life modification and medical care [4,5]. In this context an accurate risk assessment of CV complications among T2DM is essential to effectively balance the risks and benefits of therapy for primary prevention [6]. It has been suggested that cardiac biomarkers reflected different faces in pathophysiology and development of CV disease related to T2DM might be useful to risk stratification in this patient population [7]. Moreover, several pro-inflammatory biomarkers, i.e. galectin-3, might benefit the feasibility of an accurate newly CV disease diagnosis, target organ damage, and probably they could be reasonable as targeting in diabetes treatment to prevent T2DM-related complications and CV events [8].

Galectin-3 is a multifunctional 29-35 kDa chimaera-type lectin that belongs to a family of β-galactoside binding proteins and widely distributes in the heart, brain, lung, visceral adipose tissue, and blood vessels [9]. In tissues that are targets of diabetic vascular complications, such as the mesangium and the endothelium, galectin-3 is not constitutively expressed or only weakly expressed under basal conditions [10]. However, up-regulated expression of galectin-3 might be defined in several tissues in metabolic diseases, such as T2DM and obesity, contributes in tissue remodelling.

The main biological function of galectin-3 is regulation of cell-cell cooperation, extracellular interactions during self/non-self-antigen recognition and cellular activation, as well as mediating proliferation, differentiation, migration and apoptosis [11]. It has reported that galectin-3 is produced by activated mononuclears and contributes to macrophage phagocytosis through an intracellular mechanism playing a pivotal role in both innate and adaptive immunity by contributing to phagocytic clearance of microorganisms and apoptotic cells [12]. Galectin-3 is also necessary for normal macrophage function and migration. Therefore, galectin-3 is a shared factor in fibrosis of different organs (myocardium, kidney, liver, and lung), apposition of matricellular proteins and extracellular collagen turn-over [13]. In fact, galectin-3 interacts with cell adhesion molecules and has a high binding affinity for advanced glycation end products mediating free reactive radical production, development of endothelial dysfunction and target organ damages including retinopathy, nephropathy and vasculopathy in diabetes [10,14,15]. It has been found that adipocytes are able to synthesize galectin-3 and that deficiency of galectin-3 supports survival and function of islet beta cells protecting from inflammation associated with metabolic diseases [16].

Recent clinical studies have shown that circulating galectin-3 was similarly elevated in T2DM and obesity compared with normal-weight individuals and revealed a body mass index-dependent positive correlation with leptin, resistin, IL-6, and age [17]. Therefore, elevated level of galectin-3 was found in diabetic patients, especially when newly CV disease and CV complications were exhibited in them [18]. Moreover, increased levels of galectin-3 were associated with prediabetes and T2DM [19], as well as with vascular complications in T2DM [20].

Because fibrosis and inflammation are a part of maladaptive mechanism to the tissue injury, galectin-3 is proposed as an immune-phenotypical marker for risk stratification in general population, in patients at higher risk of CV disease presentation, and in individuals with known CV disease including atherosclerosis, heart failure, myocardial infarction, atrial fibrillation [21-24]. Current clinical

guidelines recommend to measure a serum galectin-3 level as a biomarker of heart failure development and progression, as well as a predictor of CV mortality and readmission [25,26].

Whether elevated circulating level of galectin-3 would be a marker with diagnostic and predictive value in diabetic patients beyond known CV disease has not been yet fully elucidated [2,11]. In fact, galectin-3 is considered not only as a marker of tissue injury, but also as a mediator of the cell damage due to its pro-fibrotic and pro-inflammatory actions [21]. In this context, galectin-3 could be useful for therapeutic targeting of individuals with T2DM. Although preclinical studies have demonstrated controversial results [27,28], the perspectives of galecin-3-guided therapy in T2DM are widely discussed. The controversial opinions of investigators usually relate to being of data with respect to galectin-3 deficiency that leads to exacerbated metabolic derangement and endothelial dysfunction contributed both to the T2DM pathogenesis and the associated vasculopathy. Furthermore, galectin-3 is involved in the glycation and oxidative stress under diabetic conditions and may play cytoprotective role [29]. Ohkura et al. [30] reported that low levels of serum galectin-3 are associated with insulin resistance in patients with T2DM. Authors suggested that low levels of plasma galectin-3 might reflect insulin sensitivity in skeletal muscle, because the glucose clamp technique mainly reflects insulin sensitivity in skeletal muscle and that galectin-3 is associated with adiponectin rather than inflammation in patients with T2DM. Thus, galectin-3 is probably factor, which could prevent of tissue injury.

Is there a real perspective to achieve control under serum galectin-3 as a predictor of successful T2DM medical care? Unfortunately, there is not a large body of evidence regarding success use of galectin-3 in biomarker-guided therapy in patients with dysmetabolic disease including T2DM. Eliaz et al. [31] reported that lipoprotein apheresis leaded to statistically significant decrease of galectin-3 in T2DM individuals. Authors concluded that this effect combined with reducing atherogenic LDL and other inflammation mediators (e.g., CRP, fibrinogen) may enhance apheresis clinical benefits. Weigert et al. [32] have found that metformin treatment was associated with lower systemic galectin-3 and that its reduced serum level may be a direct effect of this drug. Contrary, rosiglitazone enhanced the up-regulation of galectin-3 in cultured human renal mesangial cells induced by advanced glycosylation end products. Authors concluded that rosiglitazone may play a role of reno-protection via up-regulation of galectin-3. However, the results of the studies depicted the role of galectin-3 in treatment of T2DM are controversial and required more explanations.

Finally, perspective of clinical implementation of galectin-3-guided therapy in T2DM patients is not still clear. Further investigations are needed to explain the role of galectin-3 in T2DM development and progression.

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