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GALECTIN-3: A NOVEL BIOMARKER FOR THE PROGNOSIS OF HEART FAILURE

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Abstract

Heart failure (HF) is still a global burden which carries substantial risk of morbidity and mortality. Thus, appropriate approach of diagnosis and layering the prognosis of HF are of great importance. In this paper we discuss and review a novel biomarker, which is called galectin-3 and already approved by Food and Drugs Administration (FDA) as a prediction tool for HF.

Galectin-3, which is secreted by macrophages under the influence of mediators like osteopontin, has been known for its significant role in mediating cardiac fibrosis and inflammation. Numerous studies have shown galectin-3 as a novel prognostic biomarker with high predictive value for cardiovascular mortality and re-hospitalization in HF patients. However, there are also other contradictive studies displayed galectin-3 inferiority against other existed HF prognostic biomarkers like NT-proBNP and ST2. Nevertheless, galectin-3 has some advantages such as more stability and resistance against hemodynamic loading and unloading state, and also it could act as an early indicator of cardiac fibrosis, ventricular remodeling, and renal impairment in HF patients.

Keywords: galectin-3, prognosis, heart failure

Introduction

Heart failure (HF) is a terminal cardiac disease, which remains as a carrier of substantial risk of morbidity and mortality [1]. Many diseases are ended up with heart failure, for example coronary artery disease and cardiac amyloidosis [2]. Therefore, appropriate approach of diagnosis and prognosis of heart failure is of great importance. Up until now, there are already several biomarkers widely used for diagnosis and prognosis stratification of HF. Two prospective cohorts by Huges et al. showed that the biomarkers model combination of C-reactive protein (CRP), N-terminal pro-B-type natriuretic peptide (NTproBNP), and troponin-I improved one decade cardiovascular disease prediction for intermediate and high risk patients [3]. A new biomarker, galectin-3, has already been established for the prediction of poor outcome and has been assented by the Food and Drug Administration (FDA) for use in combination with clinical assessment [4].

Galectin-3 is a family member of an old-aged lectin family, which is distinguished by particular binding of β-galactosides through preserved chain constituents of the carbohydrate-concession domain [5]. Furthermore, it could conform oligomers through a proline- and glycine-rich N-terminal domain. This N-terminal domain is responsible for complete biological action of galectin-3 [6]. During the secretion of galectin-3 into the extracellular space, its interaction with cell surface receptors could commence transmembrane signaling pathways for several cellular actions [7]. Galectin-3 has already known to play part in cell growth and differentiation, cell-cell and cell-extracellular matrix adhesion, the cell cycle, signaling, apoptosis, and angiogenesis [5,8].

Recently, galectin-3 has been associated with HF [9]. Thus several processes in HF are linked with galectin-3, for example fibrogenesis, tissue repair, myofibroblast proliferation, inflammation, and ventricular remodeling [10,11]. We review the possible role of galectin-3 as a new biomarker for HF prognosis.

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Galectin-3 and HF

HF is characterized by complex neuro-hormonal syndrome appearing with various hemodynamic congestion symptoms due to cardiac dysfunction [12]. Thus, its nature is associated with myocardial injury and remodeling event. During myocardial injury and remodeling sequence events, a series of immune-inflammatory responses occur. Immune cells and macrophages are mobilized to relieve the process [13]. Hence the activation of the latter has been implied with fibrosis in HF pathogenesis [14].

Macrophages secrete galectin-3 extra-cellularly under the influence of mediators like osteopontin [15]. Hence it could activate fibroblasts to secrete matrix protein. Thereafter, cardiac fibroblasts will proliferate, which will result in the accummulation of collagen type I massively in extracellular spaces, thus causing cardiac function disorder [9]. Moreover, several markers of fibrosis like alpha-smooth muscle actin (α-SMA-intracellular marker of fibrosis), α-1 chain type 1 collagen (COL α-1 extracellular marker of fibrosis, and TGF-b1 are associated with the increased of activity and expression of galectin-3 [9,15]. Consequently, galectin-3 also has a significant role in preventing extracellular matrix degeneration. Homologous phosphatase tensin activity, which is moderated by galectin-3, could decrease the production of matrix metalloproteinase (MMP)-14 [15].

Despite its significant role in mediating cardiac fibrosis, galectin-3 also contributes to the inflammation process, which are correlated [16]. There is an increased level of pro-inflammatory cytokines with the increase of galectin-3 [17]. Hence galectin-3 could enhance the fibrosis process through a modulation of immune responses. Other evidence of the association between galectin-3 and the modulation of immune responses was also demonstrated on some animal studies. Infusion of galectin-3 into the pericardium of normal rats resulted in progression of cardiac remodeling [9]. In addition, the animal group with highest stage of cardiac fibrosis and already developed HF had the highest level of galectin-3. Furthermore, a study by Boer et al., showed that failure-susceptible hypertrophied hearts could be detected by prior increase of galectin-3 expression [15].

Galectin-3 as a prognostic marker in HF

The galectin-3 value is ranging from 1.4-94.8 ng/mL for clinical samples [18]. Thus, this biomarker has already been investigated for its prognostic value in HF. Investigation by Lok et al., 240 HF patients with New York Heart Association (NYHA) functional class III and IV were followed up for + 8.7 years and measured for echocardiography profile, N-terminal pro brain natriuretic peptide (NT-proBNP), and galectin-3 [19]. The results demonstrated that patients with decreased left ventricular end-diastolic volume (LVEDF) over time, had significant lower galectin-3 values in comparison with stable and increased LVEDF patients respectively (14.7 vs 17.9 vs 19.0 ng/mL; p=0.004). However, no significant differences of NT-proBNP values in all of these groups were evidenced. In addition, based on Kaplan-Meier survival curve, galectin-3 values were correlated with long-term mortality follow-up (log rank, p = 0.001) [19].

Other pooled analysis from 3 cohorts study of galectin-3 (the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH), the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE), and University of Maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea (UMD H-23258)) also showed its significant independent predictor of HF prognosis as represented by HF rehospitalization [20]. Patients with galectin-3 concentrations over 17.8 ng/mL significantly tended to be rehospitalized for HF at 1-4 months after discharge with odds ratios (ORs) of 2.80 (95% CI 1.41-5.57), 2.61 (95% CI 1.46-4.65), 3.01 (95% CI 1.79-5.05), and 2.79 (95% CI 1.75-4.45) for each month respectively. Even after adjustment for patient characteristics, renal and cardiac function, and BNP levels, galectin-3 persisted as an independent predictor for HF rehospitalization [20].

Certainly, the biomarker displays progress of the disease, thus several repeated measurements are required as prognosis and therapeutic evaluation marker. In addition, data from Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial, 1329 chronic HF patients whose galectin-3 level was measured at baseline and 3-month follow-up, for galectin-3 level were included to the study with in which the primary end-point was the composite of all-cause mortality and re-hospitalization during follow-up [21]. In this analysis, the cut-off value for galectin-3 was 17.8 ng/mL. The galectin-3 level was categorized into 2 groups: low (<17.8 ng/mL) and high (>17.8 ng/mL). Subsequently, patients were classified into 4 groups of galectin-3 level change as follows: (1) low-to-low; (2) high-to-low; (3) low-to-high; and (4) high-to-high. Other categorizations for the patients are the continuous percentage alteration over time. First category is > 15% increased of galectin-3 level over time; second is < 15% decreased; and the last is within the baseline of + 15% [21]. Patients classified in low-to-high galectin-3 level had significantly worse prognosis in all-cause-mortality and HF hospitalization compared to low-to-low galectin-3 level (HR, 1.53; 95% CI, 1.10-2.13; p=0.011). Inversely, patients in high-to-low galectin-3 levels had significantly improved of all-cause-mortality and HF hospitalization events than the patients in high-to-high galectin-3 level (HR, 0.66; 95% CI, 0.46-0.95; p=0.026). Furthermore, 15% increase of galectin-3 level from the baseline significantly increased the risk of mortality and HF hospitalization by 50% compared to the patients in stable galectin-3 levels. This result was independent of age, sex, diabetes mellitus, eGFR, LVEF, and NTpro-BNP (HR, 1.500; 95% CI, 1.173-

1.917; p=0.001). Patients with 15% decreased of galectin-3 level over time displayed lower tendency of event rate, even though it did not reach statistical significance compared to the patients who stayed within 15% of the baseline level [21].

Additionally, meta-analysis by Chen et al demonstrated that from pooled analysis of 9 studies, every 1% increase of galectin-3 level was also followed by 28% increased risk of all-cause mortality (HR 1.28 95% CI 1.10-1.48) with significant heterogeneity (I2 = 82.1%) [22]. Despite promising values of galectin-3 as HF biomarker prognosis, there are some limitations of all these studies up to now including publication bias and short follow-up time [22]. Moreover, some studies reported that renal function and/or BNP levels reduced the prognostic value of galectin-3 [23,24].

Galectin-3 challenge as a novel biomarker in HF

Indeed, some studies already demonstrated that galectin-3 could be a prognostic marker in HF independently of patient characteristics, renal and cardiac function, and NT-proBNP [20,21]. However, other contradictory studies also emerged. In one prospective study of HF patients with reduced LVEF, the increased galectin-3 levels were associated with increased NT-proBNP and reduced eGFR in a multivariate analysis [25]. In addition, some studies also displayed that the independent long-term prognostic value of galectin-3 had vanished after adjustment for NT-proBNP [23,26]. Furthermore, the study by Zamora et al., showed galectin-3 prognostic value perished after adjustment of renal function [27]. Thus, the possible mechanism of the association of galectin-3 and NT-proBNP in regard to increased wall stress or neurohormonal activation still remains to be elucidated [25]. Additionally, also the correlation between galectin-3 and eGFR possibly due to impaired renal clearance in HF patients [28].

Another study also compared the performance of galectin-3 prognostic value in HF with other biomarkers [29]. In a cohort study of 876 ambulatory HF patients with + 4.2 years follow-up, galectin-3 and ST2 were compared for long-term risk stratification. The end-points were 5-year all-cause and cardiovascular mortality, and the-combined all-cause death/HF hospitalization. For all end-points, galectin-3 and ST2 remained independent by bivariate analysis. However, after multivariate analysis, only ST2 was still associated with cardiovascular mortality (HR 1.27, 95% CI: 1.05-1.53, p=0.014) [29].

Despite the limitation of galectin-3 compared to other prognostic biomarker in HF [29], it could provide a novel approach in HF prognosis stratification. Galectin-3 levels are correlated with elevated risk for new HF in healthy people and acute myocardial infarction with reduced ejection fraction patients [30,31]. Thus, it is probable that galectin-3 has a more important role in the beginning stage of HF including early fibrosis and ventricular remodeling [29]. In comparison with NT-proBNP level that is affected by hemodynamic loading/unloading, galectin-3 has the advantage to be more stable and resistance against these [19,32]. In addition, due to the close-related pathophysiology of cardiac and renal impairment, galectin-3 may also indicate renal failure in HF patients or cardio-renal syndrome [33]. Finally, galectin-3 may also complement other biomarkers for risk stratification in HF [33].

Conclusions

Galectin-3, which is secreted by macrophages under influence of mediators like osteopontin, has been known for its significant role in mediating cardiac fibrosis and inflammation. Thus, several studies already proved galectin-3 could be a well prognostic marker in HF for predicting cardiovascular mortality and re-hospitalization after multivariate analysis, despite the fact that other studies showed its inferiority as a prognostic marker against other existed biomarkers like NT-proBNP and ST2. Galectin-3 has some advantages such as more stability and resistance against hemodynamic loading and unloading state, and it also could act as an early indicator of cardiac fibrosis, ventricular remodeling, and renal impairment in HF patients. For future direction, additional prospective studies using prognostic biomarker combination model of NT-proBNP and galectin-3 would be of great importance especially for high-risk HF patient stratification. Finally, galectin-3 could be also developed as target therapy in HF.

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