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GALECTIN-3, MMP-9 AND ST-2: BIOCHEMICAL MARKERS IN CARDIOVASCULAR DISEASES

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ABSTRACT

Galectin-3 is a reasonably stable biomarker. It can be detected even before the onset of heart failure occurs. Heart Failure (HF) is one of the complications of AMI as well as one of the major cardiovascular parameters. One study showed that elevated levels of Galectin-3 that persisted up to 3-6 months of the follow-up period in patients with heart failure were associated with a poorer prognosis. Many studies explain that the role of Galectin-3 is strong in cardiac remodeling/fibrosis and the occurrence of heart failure. Inhibition of Galectin-3 by pharmacological agents has been shown to be able to the prevent that cardiac fibrosis process, particularly in patients with advanced heart failure. Since its discovery as a gene product induced by cardiomyocyte stretch in vitro, ST2 has emerged as a powerful player with IL-33 in modulating ventricular function and remodeling via effects on apoptosis, inflammation and myocardial fibrosis. Clinically, measurement of sST2 appears promising as a biomarker for remodeling and outcome across the AHA HF Stages. Circulating levels of safe strongly related to short and long-term post-discharge mortality in acute coronary syndromes and HF, as well as markers of cardiac structure and function. Current pre-clinical and clinical documentation strongly support MMP-9 as a panel member in the biomarker list to diagnose or treat the pathophysiology of post -MI ventricular remodeling and congestive heart failure. Based on the evidence provided, further prospective studies are required to assess the prognostic value of MMP-9 for post-MI remodeling, particularly in comparison with traditional markers.

Key word: Galectin-3, ST-2, MMP-9, cardiovascular diseases

INTRODUCTION

Despite significant advancements in risk prediction, cardiovascular disease remains a leading cause of death. Myocardial Infarction (MI) is one of the most highly prevalent cardiovascular diseases, with over 1.2 million Americans being diagnosed with MI annually. While short-term onemonth survival rates have dramatically improved over the last 30 years, post-MI remodeling progressing to heart failure remains a significant clinical issue. This issue is further fueled by increased incidences of obesity, metabolic syndrome and diabetes, all of which exacerbate the cardiac remodeling response. Because heart failure is associated with substantial morbidity and mortality, as well as an impaired quality of life, improved methods to identify at risk patients before they develop heart failure is a primary goal. Myocardial infarction modulates several biological pathways that converge in the remodeling response, which is characterized by changes in left ventricle (LV) size, shape and function. Before 2006, Galectin-3 role in tumor or malignant cases has been extensively studied. Since 2010, Galectin-3 is one of the most widely studied biomarkers in other systems, one of them is the cardiovascular system. The high levels of Galectin-3 have been reported especially in patients with heart failure because closely related to the inflammatory process and ventricle remodeling. Galectin-3 is a relatively new biomarker and approved by the US Food and Drug

Administration (FDA) in 2010 as a marker for risk stratification in patients with heart failure. Matrix Metalloproteinase (MMP) and ST2 are also relatively new biomarkers and their correlation with early left ventricular remodeling events are widely investigated.

GALECTIN-3

Biochemical structures and physiologic functions

The Galectin-3 molecule is one type of protein that binds to beta-galactoside. The Galectin-3 is coded by a single gene, LGALS3, located on chromosome number 14, consists of six exons and five introns. Galectin-3 which is a betagalactoside-binding lectin consists of two domains, an atypical N-terminal domain, and a C-terminal carbohydrate recognition domain (Figure 1).¹

Galectin-3 is released when monocytes differentiate into macrophages, it is mainly expressed in the intracellular (at the nucleus, cytoplasm and mitochondrial levels) by inflammatory cell markers such as neutrophils, mast cells, macrophages and fibroblasts.² In addition, Galectin-3 is also expressed extracellularly with binding to several protein matrix such as tenascin, laminin and fibronectin.

Galectin-3 primarily plays a role in acute inflammatory processes, such as activation and adhesion of neutrophils, opsonization of apoptotic neutrophils and mast cells activation. A chronic inflammatory process may result in



Figure 1. The molecular structure of Galectin-3 as monomer and pentamer¹

damage and loss of tissue structure and results in fibrogenesis. Galectin-3 bridges the process of acute inflammation and fibrosis. It also plays a role in cell proliferation and cell cycle progression. Galectin-3 also functions in cell differentiation, monocyte chemoattractant and as a pro-inflammatory factor through the interaction of its molecular domain C with ligands located on the surface of inflammatory cells. Galectin-3 plays an important role in fibrotic processes, such as hepatic cirrhosis, renal failure, idiopathic pulmonary fibrosis, and other conditions that have fibrosis as the mechanism. Inflammation and fibrosis are an important mechanisms in ventricular remodeling and the occurrence of acute heart failure. Galectin-3 overexpression in macrophages is reported in patients with heart failure. Increased Galectin-3 will cause augmentation of tumor growth factor (TGF)-beta/smad signaling pathway which will further activate cardiac fibroblasts and collagen type I secretion that will result in ventricular dysfunction. High plasma concentrations of Galectin-3 in chronic heart failure patients are associated with the mortality predictor. Galectin-3 is a tissue damage biomarker, regardless of the condition or the burden of the heart. Galectin-3 is also expressed in other organs such as kidney, liver, lung, pancreas and intestine.¹

Galectin-3 as biochemical markers in cardiovascular diseases

The role of Galectin-3 is associated with pro-fibrotic hormones, such as aldosterone. Aldosterone is part of the renin-angiotensin-aldosterone system and has effects in several organs, such as the kidney. In the kidney, as well as its impact on heart and vascular, Galectin-3 also triggers the occurrence of renal sclerosis, and fibrosis. One study showed that administration of aldosterone or spironolactone inhibitor in the sample would prevent the formation of extracellular matrix, as well as when the sample was administered with the Galectin-3 inhibitor (Figure 2).¹

Galectin-3 is also associated with the occurrence of new-onset atrial fibrillation (AF) in long-term follow-up periods.1 A large cohort study showed that Galectin-3 was a predictor of long-term cardiovascular disease mortality, as well as after adjustment to NT pro-BNP levels, the mortality predictor was found to be significant.



Figure 2. The role of aldosterone and Galectin-3 in the formation of fibrosis in several organs.1

Galectin-3 is a fairly stable biomarker. One study showed that elevated levels of Galectin-3 that persisted up to 3-6 months of the follow-up period in patients with heart failure were associated with a poorer prognosis. Many studies explain that the role of Galectin-3 is strong in cardiac remodeling/fibrosis and the occurrence of heart failure. Inhibition of Galectin-3 with pharmacological agents has been shown to be able to prevent cardiac fibrosis process, particularly in patients with advanced heart failure (Figure 3).¹

In CHD, Galectin-3 is a mediator of the inflammation process and atherosclerosis. Patients with the three-vessel disease have higher serum Galectin-3 levels than either one or two-vessel disease.³

In AMI patients, especially STEMI, elevated Galectin-3 levels as a result of ischemic injury, leading to myocyte necrosis and activation of inflammatory mediators. In the early phase of myocardial damage, Galectin-3 plays a role in the inflammatory response. After reperfusion procedure, Galectin-3 levels in plasma begin to decrease, which in a study showed that there was a significant decrease of concentration being measured 24 hours post-onset (after reperfusion procedure). This study showed the correlation between decreased levels of Galectin-3 in plasma and infarct resolution.^{1,4} Serum levels of Galectin-3 will remain elevated until reperfusion procedure or cessation of ischemic insult is performed. The relationship between the variation of Galectin-3 levels in the plasma over a 24 hours period with reperfusion time would be a consideration in its clinical application when it is best to examine it in plasma so that Galectin-3 can be used as a reference and at the same time to determine the prognosis of the patient.⁴

The Galectin-3 level in plasma of Acute Myocardial Infarction (AMI) patients in a study conducted by Tsai *et al.*, defined \geq 7.67 ng/mL was the strongest predictor for major 30-day cardiovascular events (74.5% sensitivity and 72.4% specificity), where heart failure condition was included. In relation to the inflammatory process, there was a significant correlation between high Galectin-3

levels and elevated white blood cells of AMI patients.⁵

Galectin-3 and early left ventricle remodeling process

It is estimated that as many as a third of heart failure patients that come to the emergency department are a new onset of heart failure. Galectin-3 is a stable biomarker, can be detected even before the onset of heart failure occurs. Heart failure is one of the complications of AMI as well as one of the major cardiovascular parameter.^{4,5}

A case-control study has been conducted in patients with an acute coronary syndrome involving 100 patients with new onset acute heart failure post-AMI adjusted by age, sex and acute coronary syndrome type. This study showed that patients with elevated Galectin-3 baseline serum levels had a risk twofold higher to develop heart failure later in life.⁶ There was an increase in Galectin-3 levels when examined seven days post-infarction. Galectin-3 could predict the risk of early reinfarction after the first infarction and there was a positive relationship between the high levels of Galectin-3 with remodeling process in patients with an ejection fraction> 49%.¹ Analysis of Receiver Operating Characteristics (ROC) curve by Tsai et al., showed that a high plasma level of Galectin-3 is a predictor of heart failure occurrence after AMI, related with reduction of ejection fraction <40% (sensitivity 62.8% and specificity 81.7%).5

Research that has been conducted by Tsai *et al.*, about Galectin-3 serum level in patients with AMI who underwent PCI procedure showed a significant correlation (p < 0.001) with lower ejection fraction, advanced acute heart failure incidence, unstable hemodynamic condition and multivessel disease in AMI patients.⁵



Figure 3. Some cohort studies that showed Galectin-3 serum level during the follow-up period.1

Galectin-3 and early left ventricle remodeling process

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ST2

Molecular biology of ST2

A member of the interleukin (IL)-1 receptor family, ST2 is a biomarker of mechanical stress, upregulated in isolated cardiomyocytes exposed to mechanical strain and rearangement of ST2 signaling leads to a phenotype quite consistent with myocardial remodeling. As would be expected, therefore, in patients with acute myocardial infarction, elevated soluble ST2 (sST2) levels are associated with an increased risk of mortality or HF, independent of natriuretic peptides, whereas serial alterations in sST2 level over time predict outcomes independent of natriuretic peptides. Furthermore, in patients with HF, sST2 levels are strongly associated with the severity of heart failure and forecast one year mortality additive to NT-proBNP.⁷

Recently, IL-33 has been identified as the ligand for ST2, providing a potential mechanism for ST2 in the pathogenesis of HF. In an in vitro model of rat cardiomyocyte stretch, demonstrated a direct relationship between the duration of biomechanical strain and IL-33 and ST2 expression. Furthermore, administration of sST2 to rat myocytes cultured with IL-33 blocked the prohypertrophic influence of IL-33 in a dose-dependent fashion, suggesting that soluble ST2 may serve as a "decoy receptor" for circulating IL-33.

In an in-vivo model of pressure overload, endomyocardial biopsies from mice deficient in ST2 demonstrated a higher degree of myocyte hypertrophy and fibrosis and poorer fractional shortening than wild-

of transaortic constriction. Although IL-33 rescued the hypertrophic phenotype in wild-type mice, it was unable to attenuate cardiac hypertrophy, and fibrosis in ST2-deficient mice, suggesting that IL-33/ST2 signaling may protect against adverse cardiac remodeling in vivo. Moreover, cardiomyocytes from ST2-deficient mice had a higher expression of transcripts encoding natriuretic peptides and nuclear factor (NF)-KB compared with wild-type mice. Again, IL-33 decreased expression of these genes in wild type, but not in ST2-deficient, mice. Given the role of the NF-kB system in the molecular pathogenesis of cardiac hypertrophy, these results suggest a potential mechanism for IL-33/ST2 signaling in mediating adverse remodeling and subsequent HF. IL-33 decreased caspase-3 activation (a critical step in the apoptotic cascade) and increased expression of the antiapoptotic gene Bcl-2. sST2 attenuated these antiapoptotic effects. Therefore, the current understanding is that intact ST2 signaling plays a pivotal role in the ability of IL-33 to mediate cardiac pressure overload states.⁷

ST2 and prognosis in acute HF syndromes

Clinically, measurement of sST2 has yielded significant insights into the biological processes that lead to adverse outcomes across a broad spectrum of cardiac disease states. Indeed, a growing and significant body of literature has emerged in the past several years linking ST2 to deleterious correlates of cardiac structure and function in patients with acute HF syndromes with similar prognostic meaning. Although sST2 concentrations did not predict a diagnosis of HF as well as NT-proBNP, levels of sST2 were nonetheless significantly higher in patients with acute HF compared to patients with non-HF dyspnea (0.50 vs. 0.15 ng/mL; P< 0.001) and the risk of a HF diagnosis was higher in patients in the highest deciles of sST2. Importantly, the prognostic meaning of sST2 was considerable: concentrations of the marker were higher in patients who were dead at one year compared with survivors (1.08 vs. 0.18 ng/mL; P< 0.001). There was a dose-dependent relationship between sST2 concentrations and risk of death at one year and in multivariate regression analysis for predictors of death at one year, a sST2 concentration greater than 0.20 ng/mL strongly predicted a one year mortality in patients with and without HF.

Notably, the prognostic value of sST2 was additive to that of NT-proBNP, such that patients with elevations in both NTproBNP, and sST2 experienced the highest rate of mortality at one year. Those with a low sST2 and high NT- proBNP or those with a high sST2 and low NT-proBNP had intermediate levels. Subjects with low values for both markers had the best shortterm prognosis. Examining patients as a function of sST2 and NT-proBNP values, the risk of death (regardless of HF or non-HF cause of dyspnea) emerged almost immediately after enrollment and continued to increase with time. This association between sST2 and NT-proBNP with prognosis remains intact out to four years from the presentation.

In a study of 346 patients with acute HF from the PRIDE (Pro-BNP Investigation of Dyspnea in the Emergency Department) study examined the association between sST2 concentrations clinical characteristics and prognosis. sST2 concentrations at presentation correlated with the New York Heart Association functional class, left ventricular ejection fraction (r = 0.13), creatinine clearance (r = 0.22), BNP (r = 0.29), NT-proBNP (r = 0.41) and C-reactive protein (r = 0.43; all P < 0.05). Unlike natriuretic peptides, sST2 levels were not related to age, prior diagnosis of HF, body mass index (BMI), atrial fibrillation, or etiology of cardiomyopathy (ischemic vs nonischemic).⁷

As evidenced in the PRIDE study, sST2 levels were higher in patients with acute HF who died at one year. In multivariate Cox regression analysis of independent predictors of death, sST2 was associated with a two-fold risk of mortality independent of other clinical and biochemical parameters of risk (including natriuretic peptide levels) and the impact of sST2 concentration on admission on one-year mortality was similar in patients with preserved and depressed left ventricular function. Patients with both an elevated sST2 and NT-proBNP level experienced the highest risk of death at one year (> 40%), whereas patients with both biomarkers below the median levels experienced a remarkably low mortality (< 10%). Interestingly, a high sST2 level reclassified risk of death in patients with a low natriuretic peptide level, suggesting that sST2 significantly augments traditional markers of risk stratification in acute HF. Moreover, in patients with a sST2 level lower than 0.49 ng/mL (the median level in the combined PRIDE and Linz cohort), a high natriuretic peptide level did not forecast one year mortality.⁷

Regarding the composite operating characteristics for sST2 in the prediction of 1 year mortality, a sST2 level higher than 0.49 ng/ mL had a 72% sensitivity, 56% specificity, a 39% positive predictive value and 84% negative predictive value. Using the PRIDE cut-off median level greater than 0.20 ng/mL, a negative predictive value 96% for one year mortality emerged.⁷

ST2 and monitoring in acute and chronic HF syndromes

In the wake of evidence suggesting a potential role for serial natriuretic peptide concentrations in monitoring acute and chronic HF, an emerging research has investigated a similar role for sST2. In 150 patients in a Veterans Administration Medical Center admitted for acute HF, levels of sST2 drawn serially during hospital stay were related to a 90-day mortality. Interestingly, similar to results with NT-proBNP, patients who experienced a decrease in sST2 concentration greater than 15.5% during the index hospitalization experienced a low (7%) risk of death, whereas patients who did not have a decrease in sST2 concentration had a dramatically higher (33%) risk of death. The impact of sST2 changes during hospitalization on a 90-day mortality was independent of natriuretic peptide levels. Data from the PROTECT study (NCT00351390) investigating the effect of sST2 on outcomes in outpatient chronic HF management will clarify whether serial sST2 measurement in chronic HF will be clinically useful beyond standard, intensive HF management.⁷

ST2 and Acute Coronary Syndromes

In the current AHA HF Stages, patients with acute coronary syndromes are considered as stage A (at risk), stage B (asymptomatic HF), or stage C/D (symptomatic HF). Furthermore, as acute coronary syndromes are perhaps one of the highest risk situations to rapidly traverse from stage A through C/D, identification of biological markers that identify those at highest risk for progressive HF is of the utmost importance.⁷

sST2 levels in 810 patients in the Thrombolysis in Myocardial Infarction (TIMI) 14 and Enoxaparin and TNK-tPA with or without GPIIb/IIIa inhibitor as reperfusion strategy in STEMI (ENTIRE)- TIMI 23 clinical trials, finding that sST2 concentrations were higher in patients who died or experienced new HF at one month. sST2 levels were associated with a more decompensated hemodynamic and inflammatory/ischemic profile on admission, with a positive association with heart rate, cardiac troponin I level, C-reactive protein, BNP and serum creatinine. Higher levels of sST2 predicted death or a composite of death and new HF at one month independent of traditional clinical risk factors.

In a study of 1239 patients with ST-segment elevation myocardial infarction in the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial, sST2 was again found to be independent of traditional clinical risk factors, including age, the presence of hypertension, prior myocardial infarction, or HF. Patients with poorer TIMI flow or myocardial perfusion grade, and patients who experienced cardiovascular mortality, new HF, or a composite of death or HF had higher levels of sST2. Values for sST2 were related to cardiovascular death or HF in a dose-dependent fashion, independent of NT-proBNP concentrations. Patients in the highest quartile of sST2 level had a nearly 3.5-fold risk of cardiovascular death or HF at 30 days compared with patients in the lowest quartile. Similar to studies in HF, the impact of elevated sST2 was additive to NT-proBNP levels, with patients in the highest quartiles of both sST2 and NT-proBNP levels experiencing the poorest 30-day outcome (a 6.5-fold risk of death or HF). In a receiver operator characteristic model involving both NT-proBNP and sST2 levels, discrimination for composite cardiovascular mortality or HF was significantly improved, compared with clinical characteristics alone.⁷

MATRIX METALLOPROTEINASE (MMP-9)

MMPs are zinc-dependent endopeptidases that cleave several ECM proteins and as such modulate the outcome of various physiological and pathological processes including MI, atherosclerosis and congestive heart failure. In addition to structural ECM components, MMP substrates also include a multitude of ligand and receptor substrates such as cytokines, chemokines, growth factors and adhesion molecules that alter cellular migration, adhesion and activation. MMPs, therefore, exert a strong influence on cardiac remodeling through multiple mechanisms. MMPs are endogenously inhibited by the tissue inhibitors of metalloproteinases (TIMPs), a family comprised of four members, TIMP-1, -2, -3, and -4. Pre-clinical and clinical studies in the post MI setting indicate that MMP-1, -2, -3, -7, -8, -9, -12, -13, and -14 and TIMP-1, -2 - 3, and -4 are relevant to MI and LV remodeling.⁸

For the most part, MMPs are secreted from the cell as proMMPs and are activated extracellularly by tissue or plasma proteinases. The first step in activation involves cleavage of a part of the propeptide and complete activation occurs with the removal of the entire propeptide by the MMP intermediate or by other active MMPs. MMPs can also be activated in vitro by treatment with organomercurial compounds, urea, SH reagents and chaotropic agents, which chemically perturb the proMMP to alter its structure and permit activity without loss of the 10 kD prodomain. Other exogenous MMP activators include oxidants such as HOCI and ONOO-, which activate proMMPs by reacting with the cysteine in the propeptide. This activation process can also take place in vivo, under inflammatory conditions. On the other hand, the major endogenous MMP inhibitor in serum is α 2-macroglobulin and in tissues are the TIMPs.

MMP-9 expression in post-MI cardiac remodeling

MMP-9 activates several chemokines, including CXCL5, CXCL6 and CXCL8 and contributes to the release of cell surface receptors (e.g. tumor necrosis factor- α receptor) to alter the local microenvironment. MMP-9 also has several inflammatory response elements, including activator protein-1, specificity protein-1, and NF- κ B sites that makes it highly responsive to inflammatory stimuli. A striking increase in MMP-9 activity is found at days 1 to 4 in the infarct region and this increase corresponds with neutrophil and macrophage infiltration. Mukherjee et al. demonstrated that MMP-9 promoter transcripts with a β -galactosidase reporter show MMP-9 promoter activity at day 3 post-MI that peaked at day 7. The earlier initial increase in MMP-9 protein levels seen at day 1 post-MI is due to the release of pre-formed MMP-9 from infiltrating neutrophils, where it is stored in gelatinase granules.⁸

MMP-9 is a biomarker for cardiac remodeling

The most consistent biomarkers associated with LV remodeling were related to ECM turnover or neurohormonal activation. Among the biomarkers, MMP-9, collagen peptides, and B-type natriuretic peptide were prominent biomarkers that predicted adverse LV remodeling after MI. Of note, several polymorphisms have been evaluated within the MMP-9 gene and have been shown to influence gene expression. Specifically, the C1562T allele associated with increased MMP-9 plasma concentrations, whereas the R279Q polymorphism had no effect on plasma levels but associated with future CV events. The 279 amino acid where these polymorphisms occur resides in the catalytic domain of the MMP-9 enzyme, suggesting that MMP-9 activity levels may be higher in patients with the R279Q polymorphism.⁸

CONCLUSION

Galectin-3 is a fairly stable biomarker. It can be detected even before the onset of heart failure occurs. Heart failure is one of the complications of AMI as well as one of the major cardiovascular parameter. One study showed that elevated levels of Galectin-3 that persisted up to 3-6 months of the follow-up period in patients with heart failure were associated with a poorer prognosis. Many studies explain that the role of Galectin-3 is strong in cardiac remodeling/fibrosis and the occurrence of heart failure. Inhibition of Galectin-3 with a pharmacological agent has been shown can prevent cardiac fibrosis process, particularly in patients with advanced heart failure. Since its discovery as a gene product induced by cardiomyocyte stretch in vitro, ST2 has emerged as a dominant player with IL-33 in modulating ventricular function and remodeling via effects on apoptosis, inflammation and myocardial fibrosis. Clinically, measurement of sST2 appears promising as a biomarker for remodeling and outcome across the AHA HF Stages. Circulating levels of sST2 are strongly related to short and longterm post-discharge mortality in acute coronary syndromes and acute and chronic HF, as well as markers of cardiac structure, and function. Ongoing research examining a role for serial assessment of sST2 concentrations in chronic HF will establish whether this biomarker has incremental utility beyond standard HF management. Current preclinical and clinical documentation strongly support MMP-9 as a panel member in the biomarker list to diagnose or treat the pathophysiology of post-MI ventricular remodeling and congestive heart failure. Immune cells such as neutrophils or macrophages modify many processes in the MI response, and future research focused on biochemical and structural approaches to examine the ECM will likely provide new information on the remodeling process. Based on the evidence provided, further prospective studies are required to assess the prognostic value of MMP-9 for post-MI remodeling, particularly in comparison with traditional markers.

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