The Role of Galectin-3 in Acute Myocardial Infarction: A Narrative Literature Review

Haviz Reddy[1*], Akmal M. Hanif[2], Taufik Rizkian[2], Wahyudi[2]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Cardiovascular Division, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

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*Corresponding author:
Haviz Reddy

E-mail address:
havizreddy@gmail.com

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A B S T R A C T

Galectin-3 (Gal-3) is a protein, namely a lectin, that binds to beta galactosides. Gal-3 has been shown to be related to the process of fibrosis, classification of atherosclerosis, and cardiac remodeling. Gal-3 regulation is known to be involved in the process of atherogenesis. Low-density lipoprotein (LDL) Oxidation increases Gal-3 expression in vascular smooth muscle cells. Gal-3 also induces fibroblasts and vascular smooth muscle cells to proliferate and produce fibrosis-related proteins in the extracellular matrix. Inhibition of Gal-3 can reduce the atherosclerotic process and reduce the progression of plaque formation. Gal-3 also induces fibroblasts and vascular smooth muscle cells to proliferate and produce fibrosis-related proteins in the extracellular matrix. Inhibition of Gal-3 can reduce the atherosclerotic process and reduce the progression of plaque formation. Several clinical trials have focused on the role of Gal-3 in acute myocardial infarction patients showing that Gal-3 is upregulated. In these patients. This literature review aims to describe the role of Gal-3 in acute myocardial infarction.

1. Introduction

Coronary heart disease (CHD) is a disease with a high prevalence in the world. Although management and several biomarkers can be used for early diagnosis and predicting prognosis in patients with coronary heart disease, coronary heart disease events such as acute myocardial infarction (AMI) are still accompanied by high morbidity and mortality.[1] The prevalence of acute myocardial infarction is approaching 3 million people worldwide.[2] In patients with acute myocardial infarction, as many as 70% of fatalities are due to occlusion of an atherosclerotic plaque.[2] Rupture of the atherosclerotic plaque induces an inflammatory cascade of monocytes and macrophages, thrombus formation, and platelet aggregation. This causes decreased oxygen delivery through the coronary arteries, which results in decreased oxygenation of the myocardium. Mitochondria in myocardial cells are unable to produce ATP, thereby inducing a cascade of ischemia, endocardial apoptosis, or myocardial infarction.[2]

Galectin-3 (Gal-3) is a protein, namely a lectin, that binds to beta galactosides. Gal-3 has been shown to be related to the process of fibrosis, classification of atherosclerosis, and cardiac remodeling. Gal-3 regulation is known to be involved in the process of atherogenesis. Low-density lipoprotein (LDL)

Oxidation increases Gal-3 expression in vascular smooth muscle cells. Gal-3 also induces fibroblasts and vascular smooth muscle cells to proliferate and produce fibrosis-related proteins in the extracellular matrix. Inhibition of Gal-3 can reduce the atherosclerotic process and reduce the progression of plaque formation.[1] Several clinical trials have focused on the role of Gal-3 in acute myocardial infarction patients showing that Gal-3 is upregulated in these patients.[3-6] This literature review aims to describe the role of Gal-3 in acute myocardial infarction.

Galectin-3

Galectin-3 is a member of the 32–35 kDa β-galactoside binding lectin. Galectin-3 is primarily expressed and secreted by macrophages but is also expressed in fibroblasts, mast cells, and neutrophils. Galectin-3 is the only lectin found in mammals. Galectin-3 is expressed in the cytoplasm, nucleus, and cell membranes, thereby allowing it to play an important role in modulating inflammatory and immunological responses. Galectin-3 regulates various biological processes through its carbohydrate recognition domain using a carbohydrate-independent mechanism.[7]

Galectin-3 functions by binding to different ligands, for example, to inflammatory factors (interleukin [IL]-4, CD45, and CD98) to promote inflammation and cell apoptosis or to the extracellular matrix to promote fibrosis. Galectin-3 takes part in various pathophysiological steps in regulating inflammation, fibrosis, immunity, and cancer metastasis. Inflammation and fibrosis play an indispensable role in myocardial remodeling. Studies by Calvier demonstrated that galectin-3 is a central component in the development of myocardial and vascular fibrosis, possibly by activating myofibroblast-mediated transforming growth factor (TGF)-β and stimulating matrix production.[8]

Plasma galectin-3 is one of the currently studied biomarkers. Galectin-3 is a β-galactoside-binding lectin expressed in monocytes, which has an important role in inflammation, immunity, and

cancer and is involved in the pathogenesis of atherosclerosis, diabetes, and asthma. Galectin-3 is a β-galactoside-binding lectin family consisting of 250 amino acids with ≥1 carbohydrate-recognition domain (CRD) expressed everywhere and is involved in inflammation and fibrosis in the heart and kidney. Galectins have been identified in mammals with a total of 15 galectins and are divided into three forms: 1) The galectin prototype with a single CRD (dimeric); 2) Galectin repeated with two CRDs (tandem); 3) Galectins of the chimera type with a single CRD, connected to a long and flexible N-terminal domain (1-3).[9,10]

Galectin-3 is the only chimera-type galectin. Human galectin-3 is a 35-kDa protein encoded by the LGALS3 gene on chromosome 14. The N-terminal domain of galectin-3 is sensitive to proteolysis by matrix metalloproteinases and participates in interactions with other intracellular proteins. The first twelve amino acids of galectin-3 are required for nuclear secretion and translocation. The C-terminal CRD of galectin plays a role in its interaction with N-acetylactosamine-containing glycoconjugates. Galectin-3 binds both dependent and independent proteins to carbohydrates.[9,10]

Galectin-3 is expressed in human tissues, including all types of immune cells (macrophages, monocytes, dendritic cells, eosinophils, mast cells, natural killer cells, and activated T and B cells), epithelial cells, and endothelial cells. Galectin-3 expression in regulated tissue development more during embryogenesis and childhood compared to adulthood. During the early stages of embryogenesis, the expression pattern is more specific, mainly located in the epithelium, kidney, chondrocytes, and liver.[9,11]

Galectin-3 is mostly located in the cytoplasm and migrates to the nucleus (Figure 1)**.** These markers are also secreted onto the cell surface and into biological fluids. The function of galectin-3 is affected by where it is located. Galectin-3 in the cytoplasm is important for cell survival due to its interaction with certain survival-associated proteins, including B-2 cell

lymphoma (Bcl-2) and active guanosine-5'-triphosphate (GTP)-binding K-Ras. Galectin-3 in the nucleus promotes pre-mRNA splicing and regulates gene transcription, whereas galectin-3 in the extracellular modulates cell-cell interactions, including epithelial cells and the extracellular matrix. Therefore, galectin-3 is essential in various biological activities, including cell growth, cell proliferation, differentiation, apoptosis, pre-mRNA splicing, transformation, angiogenesis, inflammation, fibrosis, fibrogenesis, and host defense. Research shows that galectin-3 is involved in the pathogenesis of remodeling, cardiovascular fibrosis, and ventricular dysfunction, as well as in various autoimmune and inflammatory processes.[9,11,12]

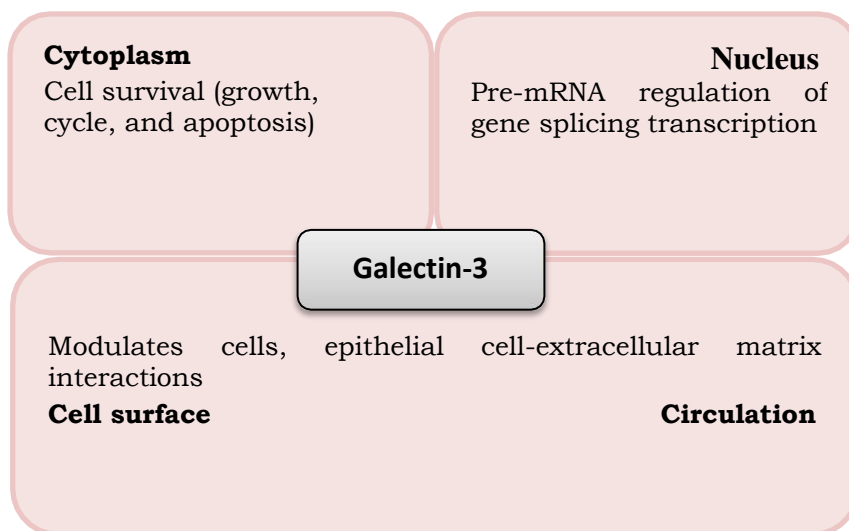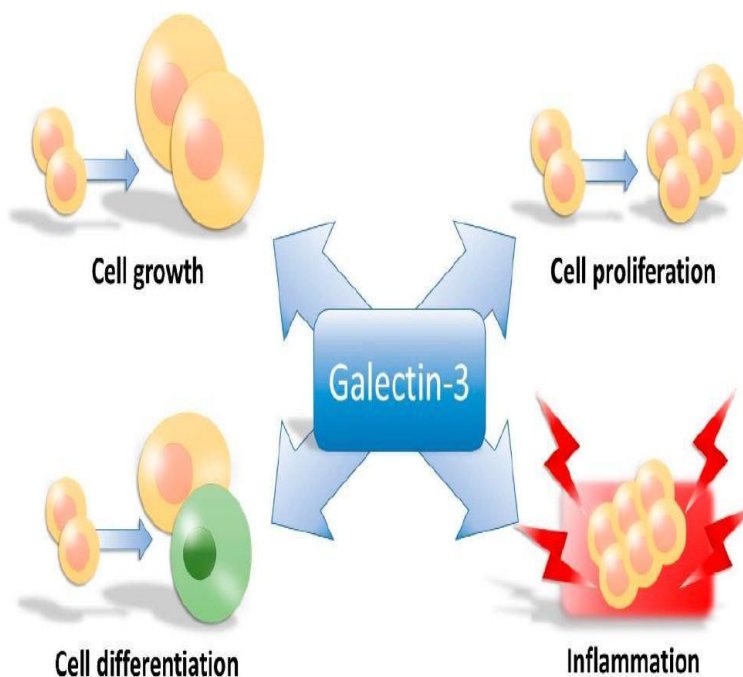

Figure 1. Galectin-3 function.[9]

Figure 2. Effects of galectin-3 on cells.[11]

Increases or decreases in galectin-3 expression levels were observed in various diseases, including heart, kidney, liver, cancer, and infections. Galectin-3 is a stable biomarker and is not associated with age, body mass index, or gender. Galectin-3 shows no circadian variation and increases slightly after exercise and returns to normal levels after 1-3 hours. Therefore, galectin-3 can be used in the diagnosis and prognosis of various types of diseases and can also serve as a therapeutic target to treat diseases.[9]

Role of galectin-3 in acute myocardial infarction

Various studies have shown that galectin 3 in serum increases after acute myocardial infarction (AMI) and decreases significantly within 5 days after acute onset. Galectin 3 is said to have a role involved in the remodeling process of the ventricles and determining the prognosis of AMI. Previous research found that Gal-3 was statistically correlated with left ventricular ejection fraction (LVEF). In AMI patients, the negative correlation between Gal-3 and LVEF was statistically significant, but there was a high degree of heterogeneity. After a relatively long myocardial infarction, there is a statistically significant negative correlation between gal3 and LVEF, and there is a low degree of heterogeneity. The negative correlation between gal3 and infarct size was not significant. There is a high degree of heterogeneity. The Lei T study also demonstrated that higher Gal-3 levels were associated with an increased cause of death in MI patients during a follow-up period of between 30 days and 5.4 years. There is evidence to suggest that Gal-3 may be used to predict poor prognosis and LVEF in patients with myocardial infarction but does not significantly correlate with infarct size after myocardial infarction.[1] According to Di Tano et al., Galectin-3 has been shown to be involved in ventricular remodeling and predicts earlier prognosis after the onset of AMI.[13]

Galectin-3 is a major inflammatory signal and promoter, which can increase neutrophil superoxide production, stimulate rupture of the cellular respiratory chain, and trigger oxidative stress reactions that lead to increased uptake of ox-LDL by vascular endothelial cells, macrophages, and smooth muscle cells, which ultimately cause foam cell proliferation and increase atherosclerosis. In a case-control study by Aksan et al., Galectin-3 levels in patients with coronary heart disease were shown to be significantly higher than in the control group. It was found that serum galectin-3 levels were positively correlated with the severity of coronary artery stenosis, the number of vessels involved, and serum C-reactive protein levels.[14]

The study conducted by Sanchez-Mas et al. studied the expression of galectin-3 in the myocardium in a rat model of myocardial infarction (MI).[15] After permanent ligation of the left anterior descending coronary artery, the rats were euthanized at 1, 2, 4, 12, and 24 weeks post-MI. This study demonstrated that galectin-3 expression was upregulated at the site of infarction, reaching a maximum at 1-week post-MI, which was then followed by a gradual decline over the following weeks. Besides galectin-3, various extracellular matrix and fibrotic markers such as collagen I, collagen III, and TIMP-1 also experienced increased expression. Although there was also an increase in galectin-3 in the non-infarcted area, maximal levels did not appear until 24 weeks.[16]

Fibrosis is a fundamental component of the detrimental structural remodeling in the myocardium that is triggered by multiple risk factors (such as those in AMI). Galectin-3 stimulates myofibroblast proliferation and procollagen-1 deposition, which ultimately contribute to cardiac fibrosis, structural remodeling, and diomyocyte dysfunction.[13] In addition, another study stated that patients with acute coronary syndromes with higher galectin-3 expression levels showed decreased LVEF compared to AMI patients with lower galectin-3 levels.[17]

Interestingly, galectin-3 has different and controversial roles in the early and late phases of AMI. This contributes to the reparative process in the infarct area in the early phase, which is important for

the maintenance of LVEF. In later phases, galectin-3 may trigger the transition from inflammation and acute triggering to chronic cardiac fibrosis, leading to adverse ventricular deformation and, ultimately, heart failure and decreased LVEF. With the aim of exploring the important contribution of galectin-3 to cardiac fibrosis and remodeling, several recent studies assessing the pharmacological inhibition of galectin-3 have suggested that this may be a method for the prevention of heart failure.[18]

One study found that patients with anterior ST-elevation myocardial infarction (STEMI) and left anterior descending artery occlusion treated with primary percutaneous coronary intervention (PCI) had increased serum galectin-3 levels during hospitalization and were associated with an increased risk of LV remodeling.[9] In addition, increased galectin-3 expression levels were associated with higher rates of atrial fibrillation (AF) after initial onset and were the most effective independent predictor of clinical deterioration in AMI patients without heart failure receiving prior PCI therapy within 30 days of baseline onset. Galectin-3 levels are also associated with reinfarction after initial AMI.[7]

Serum galectin-3 levels vary significantly after STEMI over a short period of time and are associated with reperfusion time.[7] Galectin-3 expression levels are positively and significantly associated with certain inflammatory factors in AMI patients. Galectin-3 is positively and significantly associated with certain biomarkers, including matrix metalloproteinase 3, monocyte chemoattractant protein-1, and interleukin (IL)-8, which are involved in extracellular matrix turnover. However, galectin-3 was positively associated with AMI size and left ventricular (LV) remodeling in patients with a history of AMI.[19]

Serum galectin-3 levels were also found to be significantly higher in outpatient patients with poor cardiovascular status for 3 months. Compared with known biomarkers (e.g., troponin and BNP), galectin-3 was found to have a stronger predictive value for MACE based on ROC analysis. On the outcomes Initially, the study of Mosleh et al. showed that

patients who were hospitalized for >48 hours also had significantly higher serum galectin-3 levels than patients with shorter lengths of stay.[20] Although baseline variables and other comorbidities may have contributed to the prolonged hospitalization, galectin-3 may be used to identify diseased patient populations that are at higher risk for an outcome poor clinical after AMI.[19]

Based on the results of Al-Salam et al.'s study in rats, Gal-3 levels increased significantly and were associated with decreased levels of pro-apoptotic proteins, cytochrome c, Bax, annexin V, caspase-3.[21] The antiapoptotic activity of Gal-3 is mediated by a significant increase in the protein beta-catenin, NF kappa-B, and Akt-1. Al-Salam concluded that an increase in Gal-3 levels in the first 24 hours of the onset of AMI could regulate antiapoptotic mechanisms that will determine the course of the disease or prognosis.[21]

Clinical use of galectin-3 as a heart disease biomarker

Recent studies suggest that galectin-3 has the potential to be a new marker of heart disease and a prognostic indicator for heart failure patients. Clinical studies have shown that serum and myocardial Galectin-3 levels in patients with HF reflect an inflammatory condition of the heart and may be considered a useful biomarker for cardiac inflammation and fibrosis, depending on the pathophysiological mechanism of HF. In the general population, high plasma Galectin-3 concentrations correlate with the clinical outcome of heart failure. Elevated serum levels are associated with adverse clinical events in both patients with acute and chronic heart failure in whom the ejection fraction is maintained or reduced.[22]

Clinical significance and application of galectin-3

Recommendations regarding the clinical assessment and analytical perspective of new biomarkers in the diagnosis and management of heart failure were prepared by the National Academy of

Clinical Biochemistry (NACB). Within these criteria, a new biologic marker must be able to recognize the fundamental causes of heart failure, assess its severity, and estimate the risk of disease progression. The American College of Cardiology Foundation (ACC)/American Heart Association (AHA) guidelines recommend the use of Gal-3 as a biomarker for the assessment of myocardial fibrosis in heart failure, but the European Society of Cardiology (ESC) does not recommend the clinical use of Gal-3.[22]

Galectin-3 in heart failure

Galectin-3, as a biomarker of fibrosis and inflammation, has been implicated in the development and progression of heart failure and can predict increased morbidity and mortality. Two recent meta-analyses demonstrated that increased galectin-3 expression levels were associated with death in acute and chronic heart failure, whereas another systematic review demonstrated that galectin-3 was effective for predicting all-cause and cardiovascular mortality. Primarily under the influence of certain clinical factors, including estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), and N-terminal pro-B-type natriuretic peptide (NT-proBNP).[9]

A prospective cohort study with 26-month follow-up revealed that galectin-3 expression level was an independent predictor of death at 26 months in patients with chronic heart failure and that a galectin-3 level of more than 21 ng/mL was associated with increased mortality. In heart failure patients with coronary heart disease, serum galectin-3 levels are elevated and are an independent predictor of all-cause mortality and rehospitalization. Galectin-3 levels are strongly associated with outcomes in heart failure patients with preserved ejection fraction (HFpEF) compared with heart failure patients with reduced ejection fraction (HFrEF). Galectin-3 is also associated with HF severity and exhibits dynamic changes during mechanical unloading, and predicts survival rates after left ventricular assist device (LVAD) use.[9]

Galectin-3 in coronary heart disease and myocardial infarction

In patients with aortic valve stenosis, serum and myocardial galectin-3 expression levels are positively related to the degree of fibrosis and relative wall thickness, which are important indicators of geometric remodeling. Galectin-3 in valve interstitial cells obtained from aortic stenosis patients induces the expression of inflammatory, fibrotic and osteogenic markers.[22] Fibrotic and osteogenic in valve interstitial cells undergoing osteoblast differentiation, suggesting their potential function in calcification in aortic stenosis. One study demonstrated that galectin-3 was not associated with aortic stenosis severity or functional status and did not provide prognostic information about the occurrence of aortic stenosis-associated stenosis.[20]

In patients with coronary artery disease, serum galectin-3 levels showed a significant positive relationship with coronary artery disease severity, as determined by the Gensini score and a number of diseased vessels, and increased serum galectin-3 levels reflected increased degrees of myocardial fibrosis.[8] In contrast, in patients with the acute coronary syndrome, serum galectin-3 levels showed a significant positive relationship with the Gensini score; However, not with the number of diseased vessels. In addition, acute coronary syndrome patients with higher galectin-3 expression levels showed decreased LVEF and eGFR.[21]

Galectin-3 in other heart diseases

Galectin-3 expression levels are increased in patients with AF, especially in persistent AF. Galectin-3 expression independently predicts the recurrence of atrial tachyarrhythmia after a single ablation procedure. In addition, galectin-3 was independently associated with new-onset AF, with atrial remodeling, and with left atrial volume indices in AF patients.[19,21]

Increased galectin-3 expression levels were observed in patients with pulmonary arterial hypertension. The galectin-3 elevation is associated with several indices of right ventricular function and

morphology and is predictive of impaired right ventricular function. In patients with hypertrophic cardiomyopathy, the expression level of galectin-3 is increased and is associated with an increased degree of left ventricular hypertrophy. However, it was not associated with decreased myocardial left ventricular diastolic and systolic function. Galectin-3 is associated with myocardial replacement fibrosis as assessed by late gadolinium enhancement in patients with non-ischemic dilated cardiomyopathy.[20]

Future clinical use of galectin-3 as a biomarker

Endomyocardial biopsy is widely used as a diagnostic tool for patients with heart disease, such as myocarditis and other cardiomyopathies, which are often difficult to diagnose with conventional radiological imaging methods. Histological examination of endomyocardial biopsy is still the gold standard for the final diagnosis, of myocarditis and other cardiomyopathies, such as cardiac fibrosis, despite continuous advances in diagnostic and therapeutic approaches.[14] Human biopsies are usually obtained under different conditions, for example, varying time periods between biopsy and processing and variations in disease onset or severity. In contrast, serum Gal-3 levels reflect myocardial Gal-3 expression or cardiac fibrosis using state-of-the-art animal models for time pathway histological examination. It is possible that the differences between experimental data and clinical findings are due to the wide variability in clinical settings with differences in sample collection and disease stage. As experimental animal data clearly indicate that serum Gal-3 may be an early diagnostic biomarker for cardiac degeneration or fibrosis in acute myocarditis, further studies are needed to investigate whether the findings also apply to cardiac degeneration or fibrosis in humans. Gal-3 can be used as a predictive biomarker for early stages or new attacks of heart failure, especially if it is only the first single pathological factor. In addition, Gal-3 can also be used as an additional indicator to detect a worse prognosis, mortality, and readmission.[22]

2. Conclusion

Galectin-3 is a stable biomarker and is not related to age, body mass index, or gender can be used to predict the prognosis of AMI and predict left ventricular function in the diseased population after the onset of AMI.

3. References

1. Lei T, Kan C, Zhihua H. Correlation between galectin-3 and adverse outcomes in myocardial infarction patients: A meta-analysis. Cardiology Research and Practice, Hindawi. 2020; (20): 2–7.

2. Mechanic OJ, Grossman SA. Acute myocardial infarction. Treasure Island (FL): StatPearls Publishing. 2020; 1(20): 1-10.

3. Ciaccio A, et al. Predictive value of galectin-3 for the occurrence of coronary artery disease and prognosis after myocardial infarction and its association with carotid IMT values in these patients: a mid-term prospective cohort study. Atherosclerosis. 2016; (246): 309–17.

4. MusiałDymicka-Piekarska M, et al. Impact of percutaneous coronary intervention on biomarker levels in patients in the subacute phase following myocardial infarction: the occluded artery trial (OAT) biomarker ancillary study. BMC Cardiovasc Disord, 2013; (13): 91.

5. Winter MP, et al. Soluble galectin-3 is associated with premature myocardial infarction. European Journal of Clinical Investigation. 2016; 46(5): 386–91.

6. Sasso GB, et al. Short-term changes in gal 3 circulating levels after acute myocardial infarction. Archives of Medical Research. 2016; 7 (47): 521–5.

7. Yu L, Ruifrok WP, Meissner M, Bos EM, van Goor H, et al. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. Circ Heart Fail. 2013; 6: 107-17.

8. Calvier L, Miana M, Reboul P, Cachofeiro V, Martinez-Martinez E, et al. Galectin-3 mediates aldosterone-induced vascular fibrosis. Arterioscler Thromb Vasc Biol. 2013; 33: 67-75.

9. Dong R. Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). Int J of Mol Med. 2018; 41: 599-614.

10. Oliveira FL, Gatto M, Bassi N, et al. Galectin-3 in autoimmunity and autoimmune diseases. Exp Biol Med (Maywood). 2015; 240: 1019-1028.

11. Ruvolo PP. Galectin-3 as a guardian of the tumor microenvironment. Biochim Biophys Acta. 2016; 1863(3): 427-37.

12. Meijers WC, Lopez-Andrés N, de Boer RA. Galectin-3, cardiac function, and fibrosis. Am J Pathol. 2016; 186(8): 2232-4.

13. Di Tano G, Caretta G, De Maria R, et al. Galectin-3 predicts left ventricular remodelling after anterior-wall myocardial infarction treated by primary percutaneous coronary intervention. Heart. 2016; 1–7.

14. Aksan G, Gedikli Ö, Keskin K, Nar G, İnci S, et al. Is galectin-3 a biomarker, a player-or both-in the presence of coronary atherosclerosis? J Investig Med. 2016; 64: 764-70.

15. Sanchez-Mas J, Lax A, Asensio-Lopez MC, Fernandez-Del Palacio MJ, Caballero L, et al. Galectin-3 expression in cardiac remodeling after myocardial infarction. Int J Cardiol. 2014; 172: e98-101.

16. Agnello L, Bivona G, Lo Sasso B, Scazzone C, Bazan V, et al. Galectin-3 in acute coronary syndrome. Clin Biochem. 2017; 50(13-14): 797–803.

17. George M.Value of pentraxin-3 and galectin-3 in acute coronary syndrome: A short-term prospective cohort study. Ther Adv Cardiovasc Dis. 2015; 9: 275–84.

18. Stegmayr J. Extracellular and intracellular small-molecule galectin-3 inhibitors. Sci Rep. 2019; 9(1): 2186.

19. Singsaas EG, Manhenke CA, Dickstein K. Circulating galectin-3 levels are increased in patients with ischemic heart disease but are not influenced by acute myocardial infarction. Cardiology. 2016; 134: 398–405.

20. Mosleh W, Chaudhari MR, Sonkawade S. The therapeutic potential of blocking galectin-3 expression in acute myocardial infarction and mitigating inflammation of infarct region: A clinical outcome-based translational study. Biomark Insights. 2018; 13: 1177271918771969.

21. Al-Salam S, Hashmi S, Jagadeesh. Galectin-3: A cardiomyocyte antiapoptotic mediator at 24-hour post myocardial infarction. Cellular Physiology and Biochemistry. 2020; 54(2): 287-302.

22. Hara A. Galectin-3 as a next-generation biomarker for detecting early stage of various diseases. Biomolecules. 2020; 10(3) 389.