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An overview about galectin-3 and its relationship with cardiovascular diseases

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Abstract

Inflammation is one of the cornerstones of atherosclerosis. Galectin-3 (Gal-3) acts on the stages of the inflammatory process. Gal-3 is a candidate for being a valuable marker for heart failure (HF) and coronary artery disease (CAD). Further studies are needed for the diagnosis and follow-up of CAD. In the literature, the relationship between Gal-3 and CAD has not been researched sufficiently. We aimed to write a review by referring to recent studies about Gal-3 in the etiopathogenesis of CAD, its prognostic significance, and its contribution to the treatment regimen.

Keywords: Atherosclerosis, Galectin-3, İnflammation, Heart failure, Coronary artery disease

Introduction

Inflammation is one of the cornerstones of atherosclerosis and an important cause of stroke and cardiovascular disease (CVD) [1]. Galectin-3 (Gal-3), one of the soluble galactoside-binding lectins, induces phagocytosis and proliferation of vascular smooth muscle cells and accelerates atherogenesis [2]. Gal-3 is a predictor of mortality in coronary artery disease (CAD) [3]. Elevated Gal-3 expression causes the development of cardiovascular diseases. We aimed to review Gal-3's impact on CAD.

Fibroblasts, endothelial cells, neutrophils, monocytes/macrophages, dendritic cells, and inflammatory cells are involved in the release of Gal-3. Gal-3 affects inflammation stages such as neutrophil adhesion, monocyte/macrophage chemoattraction, apoptotic neutrophils opsonization, and activation of mast cells [4, 5]. It has a significant correlation with CAD, and it is an important bioxmarker to predict heart failure and CV events [6, 7].

The Gal-3 expression is low in the myocardial cells, but some pathological conditions notably upregulate this expression. Gal-3 influences the entry of macrophages into myocardial cells in hypertrophy. In the hypertrophic rat heart, Gal-3 is a potent mitogenic agent for active myocardial macrophages and fibroblasts with binding sites in the fibroblasts and extracellular matrix. This finding shows that Gal-3 acts in tissue fibrogenesis. Also, it increases the production of collagen by contributing to the differentiation of cardiac fibroblasts to myofibroblasts [5, 8, 9].

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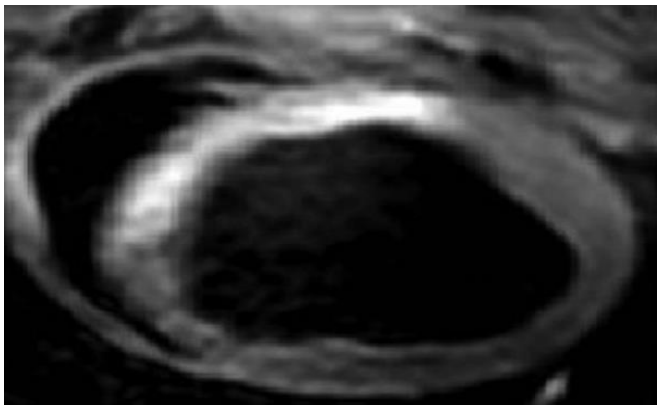
Gal-3 in heart failure (HF)

Increasing Gal-3 levels may reflect the degree of myocardial fibrosis, determined by cardiac magnetic resonance (CMR). Increased Gal-3 levels may indicate left ventricular (LV) diastolic dysfunction (Figure 1) [10, 11]. Gal-3 has recently been added to the class of useful prognostic markers as an important predictor of HF [12]. Hashmi and Al-Salam et al. reported transcriptional translational Gal-3 expression in the early stage of the ischemic left ventricular myocardium [13].

Figure 1: Galectin-3 and myocardial fibrosis



Coromilas et al. [14] demonstrate that Gal-3 can be used as a useful biomarker to assess prognosis in patients with HF with a left ventricular assist device. Gal-3 is a marker of inflammation that is not affected by acute cardiac volume or pressure increase compared to BNP. The role of Gal-3 in heart transplant follow-up may be better understood through more studies. In a cohort study, Rieth et al. [15] found a positive correlation between high Gal-3 and systolic dysfunction.

Gal-3 was highly detected in myofibroblasts as an independent determinant of myocardial fibrosis [16]. Liu et al. [17] showed that the inhibition of the transforming growth factor-β (TGF-β)/signal protein 3 (Smad3) pathway by AC-SDKP also regressed the Gal-3-activated profibrotic process and improved cardiac remodeling. Thus, the interaction of gal-3 and TGF-β/Smad3 protein signal transduction pathway proved to cause myocardial remodeling. Another study showed that suppression of Gal-3 reduces type I collagen synthesis and accumulation [18]. Decreasing Gal-3 expression effectively reduces oligomyositis fibrinolysis. In addition, Gal-3 triggers cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction [19].

The reliability of this result was confirmed after the elimination of various confounding variables affecting the prognosis in patients with normal ejection fraction (EF). Gal-3 may cause LV hypertrophy in hypertrophic cardiomyopathy (HCM) [20]. It may be useful for identifying major adverse cardiac events (MACE) in HCM.

Gal-3 in diabetes mellitus (DM)

Gal-3 levels may increase in type 2 DM [21]. Despite insufficient evidence, Gal-3 is thought to cause microvascular and macrovascular complications in type 2 DM [22]. It may be a potential biomarker for myocardial and structural lesions in patients with Type 2 DM complicated with hypertension [23]. Gal-3 was also proven to have an important role in the physiopathogenesis of diabetic nephropathy [24]. It was negatively correlated with glycosylated hemoglobin levels, and its level was significantly decreased with metformin treatment. Thus, it may play a role in the development and progression of diabetes [25].

Experiments showed that recombinant Gal-3 given exogenously may cause insulin resistance *in vitro*. Its mechanism may rely on a possible inhibition of insulin signaling by binding of gal-3 to the insulin receptor [26]. The induction of insulin resistance by gal-3 may also be related to its proinflammatory role in lipid-related metabolic disorders [27]. Pang et al. [28] claimed that gal-3 has an active role in glucose intolerance and obesity in mice.

Gal-3 in myocardial infarction (MI)

Some researchers assumed that Gal-3 has an active role in the formation of atherogenesis. Furthermore, it transports modified lipoproteins in the proinflammatory pathway in atherosclerosis [29]. Gal-3 levels may increase in MI. A higher Gal-3 was proven to be a strong predictor of MACE at 30 days follow-up [30].

Gal-3 is an essential marker for determining atherosclerotic plaque burden and stability [31]. Higher Gal-3 levels were observed in macro-calcified plaques [32]. The inhibition of gal-3 probably prevents the atherosclerotic process. The inhibition of Gal-3 may be a new therapy regimen in atherosclerosis by providing plaque stabilization [33].

Mayr et al. [34] demonstrated the relationship between post-MI left ventricular dysfunction and Gal-3. The association of Gal-3 with increased formation of oxidized low-density lipoprotein cholesterol (LDL-C) and vascular smooth muscle cell activation was demonstrated. This relationship predisposes to atherosclerotic plaque formation and MI [35].

Winter et al. [36] argued that increased Gal-3 is a potent factor for MI recurrence. Also, Aksan et al. [37] demonstrated that Gal-3 is a successful agent in determining the severity of CAD. Gleissner et al. [38] showed that increased levels of the Gal-3 binding protein (Gal-3BP) were related to long-term mortality. Based on these findings, it may be assumed that Gal-3BP levels could be a marker of inflammatory and metabolic stress rather than a reflection of coronary atherosclerotic plaque instability.

Gal-3 in atrial fibrillation (AF)

In the Framingham Heart Study (FHS), 3450 patients were followed 10 years. In a 10-year follow-up, it was observed that the incidence of AF increased with high serum Gal-3 [39]. Gal-3 value was higher in patients with AF than those with sinus rhythm [40]. Gal-3 was also correlated with AF duration and left atrial diameter [41], and significantly higher in the presence of spontaneous echo contrast (SEC) and left atrial thrombus [42].

After radiofrequency ablation, Gal-3 and left atrial diameter were independent risk factors for recurrent AF [43]. The interaction of Gal-3 with AF is thought to be via atrial remodeling and myocardial fibrosis. This mechanism could shed light on future research [44].

Gal-3 in Kawasaki disease (KD)

Numano et al. [45] found high Gal-3 in KD with a giant coronary aneurysm. Gal-3 may be a clinical marker for myocardial and vascular fibrosis in KD, with precise imaging techniques and measurement of procollagen fragments. Gal-3 therapy may provide functional improvement in myocardial cells in KD.

Conclusion

The role of Gal-3 in determining atherosclerotic plaque burden and CAD severity is still debated in the current scientific world. Increased Gal-3 levels in CAD suggest that it is part of the atherosclerotic inflammatory process. Today, Gal-3 is considered as a new marker associated with HF and other CV events according to different clinical trials. Presumably, the inhibition of Gal-3 will be useful in preventing atherosclerosis. Strategies to diminish the gal-3 function may provide a different perspective in the treatment of atherosclerotic diseases.

References

1. Askin L, Tanrıverdi O. An Overview of Clinical Studies on Endocan and Cardiovascular Disease. Erciyes Med J. 2021;43(3):233-6. doi: 10.14744/etd.2020.09699.
2. Blanda V, Bracale UM, Di Taranto MD, Fortunato G. Galectin-3 in Cardiovascular Diseases. Int J Mol Sci. 2020;21(23):9232. doi: 10.3390/ijms21239232.
3. Maiolino G, Rossitto G, Pedon L, Cesari M, Frigo AC, Azzolini M, et al. Galectin-3 predicts long-term cardiovascular death in high-risk patients with coronary artery disease. Arterioscler Thromb Vasc Biol. 2015;35(3):725-32. doi: 10.1161/ATVBAHA.114.304964.
4. Henderson NC, Sethi T. The regulation of inflammation by galectin-3. Immunol Rev. 2009;230(1):160-71. doi: 10.1111/j.1600-065X.2009.00794.x.
5. Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JP, Schroen B, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation. 2004;110(19):3121-8. doi: 10.1161/01.CIR.0000147181.65298.4D.
6. Kusaka H, Yamamoto E, Hirata Y, Fujisue K, Tokitsu T, Sugamura K, et al. Clinical significance of plasma galectin-3 in patients with coronary artery disease. Int J Cardiol. 2015;201:532-4. doi: 10.1016/j.ijcard.2015.08.099.
7. Chen A, Hou W, Zhang Y, Chen Y, He B. Prognostic value of serum galectin-3 in patients with heart failure: a meta-analysis. Int J Cardiol. 2015;182:168-70. doi: 10.1016/j.ijcard.2014.12.137.
8. Reifenberg K, Lehr HA, Torzewski M, Steige G, Wiese E, Küpper I, et al. Interferon-gamma induces chronic active myocarditis and cardiomyopathy in transgenic mice. Am J Pathol. 2007;171(2):463-72. doi: 10.2353/ajpath.2007.060906.
9. Yu L, Ruifrok WP, Meissner M, Bos EM, van Goor H, Sanjabi B, et al. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. Circ Heart Fail. 2013;6(1):107-17. doi: 10.1161/CIRCHEARTFAILURE.112.971168.
10. Lepojärvi ES, Piira OP, Pääkkö E, Lammentausta E, Risteli J, Miettinen JA, et al. Serum PINP, PIIINP, galectin-3, and ST2 as surrogates of myocardial fibrosis and echocardiographic left venticular diastolic filling properties. Front Physiol. 2015;6:200. doi: 10.3389/fphys.2015.00200.
11. McCullough PA. Practical experience using galectin-3 in heart failure. Clin Chem Lab Med. 2014;52(10):1425-31. doi: 10.1515/cclm-2014-0278.
12. Meijers WC, Januzzi JL, deFilippi C, Adourian AS, Shah SJ, van Veldhuisen DJ, et al. Elevated plasma galectin-3 is associated with near-term rehospitalization in heart failure: a pooled analysis of 3 clinical trials. Am Heart J. 2014;167(6):853-60.e4. doi: 10.1016/j.ahj.2014.02.011.
13. Hashmi S, Al-Salam S. Galectin-3 is expressed in the myocardium very early post-myocardial infarction. Cardiovasc Pathol. 2015;24(4):213-23. doi: 10.1016/j.carpath.2014.12.001.
14. Coromilas E, Que-Xu EC, Moore D, Kato TS, Wu C, Ji R, et al. Dynamics and prognostic role of galectin-3 in patients with advanced heart failure, during left ventricular assist device support and following heart transplantation. BMC Cardiovasc Disord. 2016;16:138. doi: 10.1186/s12872-016-0298-z.
15. Rieth AJ, Jung C, Gall H, Rolf A, Mitrovic V, Hamm CW, et al. Association of galectin-3 with changes in left ventricular function in recent-onset dilated cardiomyopathy. Biomarkers. 2019;24(7):652-658. doi: 10.1080/1354750X.2019.1642959.
16. Ho JE, Liu C, Lyass A, Courchesne P, Pencina MJ, Vasan RS, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. J Am Coll Cardiol. 2012;60(14):1249-56. doi: 10.1016/j.jacc.2012.04.053.
17. Liu YH, D'Ambrosio M, Liao TD, Peng H, Rhaleb NE, Sharma U, et al. N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. Am J Physiol Heart Circ Physiol. 2009;296(2):H404-12. doi: 10.1152/ajpheart.00747.2008.
18. Calvier L, Miana M, Reboul P, Cachofeiro V, Martinez-Martinez E, de Boer RA, et al. Galectin-3 mediates aldosterone-induced vascular fibrosis. Arterioscler Thromb Vasc Biol. 2013;33(1):67-75. doi: 10.1161/ATVBAHA.112.300569.
19. Lax A, Sanchez-Mas J, Asensio-Lopez MC, Fernandez-Del Palacio MJ, Caballero L, Garrido IP, et al. Mineralocorticoid receptor antagonists modulate galectin-3 and interleukin-33/ST2 signaling in left ventricular systolic dysfunction after acute myocardial infarction. JACC Heart Fail. 2015;3(1):50-58. doi: 10.1016/j.jchf.2014.07.015.
20. Yakar Tülüce S, Tülüce K, Çil Z, Emren SV, Akyıldız Zİ, Ergene O. Galectin-3 levels in patients with hypertrophic cardiomyopathy and its relationship with left ventricular mass index and function. Anatol J Cardiol. 2016;16(5):344-8. doi: 10.5152/AnatolJCardiol.2015.6191.
21. de Boer RA, Edelmann F, Cohen-Solal A, Mamas MA, Maisel A, Pieske B. Galectin-3 in heart failure with preserved ejection fraction. Eur J Heart Fail. 2013;15(10):1095-101. doi: 10.1093/eurjhf/hft077.
22. Pugliese G, Iacobini C, Ricci C, Blasetti Fantauzzi C, Menini S. Galectin-3 in diabetic patients. Clin Chem Lab Med. 2014;52(10):1413-23. doi: 10.1515/cclm-2014-0187.
23. Seferovic JP, Lalic NM, Floridi F, Tesic M, Seferovic PM, Giga V, et al. Structural myocardial alterations in diabetes and hypertension: the role of galectin-3. Clin Chem Lab Med. 2014;52(10):1499-505. doi: 10.1515/cclm-2014-0265.
24. Tan KCB, Cheung CL, Lee ACH, Lam JKY, Wong Y, Shiu SWM. Galectin-3 is independently associated with progression of nephropathy in type 2 diabetes mellitus. Diabetologia. 2018;61(5):1212-1219. doi: 10.1007/s00125-018-4552-z.
25. Weigert J, Neumeier M, Wanninger J, Bauer S, Farkas S, Scherer MN, et al. Serum galectin-3 is elevated in obesity and negatively correlates with glycosylated hemoglobin in type 2 diabetes. J Clin Endocrinol Metab. 2010;95(3):1404-11. doi: 10.1210/jc.2009-1619
26. Li P, Liu S, Lu M, Bandyopadhyay G, Oh D, Imamura T, et al. Hematopoietic-Derived Galectin-3 Causes Cellular and Systemic Insulin Resistance. Cell. 2016;167(4):973-984.e12. doi: 10.1016/j.cell.2016.10.025.
27. Johnson AMF, Hou S, Li P. Inflammation and insulin resistance: New targets encourage new thinking: Galectin-3 and LTB4 are pro-inflammatory molecules that can be targeted to restore insulin sensitivity. Bioessays. 2017;39(9):10.1002/bies.201700036. doi: 10.1002/bies.201700036.
28. Pang J, Rhodes DH, Pini M, Akasheh RT, Castellanos KJ, Cabay RJ, et al. Increased adiposity, dysregulated glucose metabolism and systemic inflammation in Galectin-3 KO mice. PLoS One. 2013;8(2):e57915. doi: 10.1371/journal.pone.0057915.
29. Iacobini C, Menini S, Ricci C, Scipioni A, Sansoni V, Cordone S, et al. Accelerated lipid-induced atherogenesis in galectin-3-deficient mice: role of lipoxidation via receptor-mediated mechanisms. Arterioscler Thromb Vasc Biol. 2009;29(6):831-6. doi: 10.1161/ATVBAHA.109.186791.
30. Tsai TH, Sung PH, Chang LT, Sun CK, Yeh KH, Chung SY, et al. Value and level of galectin-3 in acute myocardial infarction patients undergoing primary percutaneous coronary intervention. J Atheroscler Thromb. 2012;19(12):1073-82. doi: 10.5551/jat.12856.
31. Gullestad L, Ueland T, Kjekshus J, Nymo SH, Hulthe J, Muntendam P, et al. The predictive value of galectin-3 for mortality and cardiovascular events in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Am Heart J. 2012;164(6):878-83. doi: 10.1016/j.ahj.2012.08.021.
32. Falcone C, Lucibello S, Mazzucchelli I, Bozzini S, D'Angelo A, Schirinzi S, et al. Galectin-3 plasma levels and coronary artery disease: a new possible biomarker of acute coronary syndrome. Int J Immunopathol Pharmacol. 2011;24(4):905-13. doi: 10.1177/039463201102400409.
33. Menini S, Iacobini C, Ricci C, Blasetti Fantauzzi C, Salvi L, Pesce CM, et al. The galectin-3/RAGE dyad modulates vascular osteogenesis in atherosclerosis. Cardiovasc Res. 2013;100(3):472-80. doi: 10.1093/cvr/cvt206.
34. Mayr A, Klug G, Mair J, Streil K, Harrasser B, Feistritzer HJ, et al. Galectin-3: relation to infarct scar and left ventricular function after myocardial infarction. Int J Cardiol. 2013;163(3):335-337. doi: 10.1016/j.ijcard.2012.06.087.
35. Gao Z, Liu Z, Wang R, Zheng Y, Li H, Yang L. Galectin-3 Is a Potential Mediator for Atherosclerosis. J Immunol Res. 2020;2020:5284728. doi: 10.1155/2020/5284728.
36. Winter MP, Wiesbauer F, Alimohammadi A, Blessberger H, Pavo N, Schillinger M, et al. Soluble galectin-3 is associated with premature myocardial infarction. Eur J Clin Invest. 2016;46(5):386-91. doi: 10.1111/eci.12605.
37. Aksan G, Gedikli Ö, Keskin K, Nar G, İnci S, Yıldız SS, et al. Is galectin-3 a biomarker, a player-or both-in the presence of coronary atherosclerosis? J Investig Med. 2016;64(3):764-70. doi: 10.1136/jim-2015-000041.
38. Gleissner CA, Erbel C, Linden F, Domschke G, Akhavanpoor M, Doesch AO, et al. Galectin-3 binding protein plasma levels are associated with long-term mortality in coronary artery disease independent of plaque morphology. Atherosclerosis. 2016;251:94-100. doi: 10.1016/j.atherosclerosis.2016.06.002.
39. Ho JE, Yin X, Levy D, Vasan RS, Magnani JW, Ellinor PT, et al. Galectin 3 and incident atrial fibrillation in the community. Am Heart J. 2014;167(5):729-34.e1. doi: 10.1016/j.ahj.2014.02.009.
40. Sonmez O, Ertem FU, Vatankulu MA, Erdogan E, Tasal A, Kucukbuzcu S, et al. Novel fibro-inflammation markers in assessing left atrial remodeling in non-valvular atrial fibrillation. Med Sci Monit. 2014;20:463-70. doi: 10.12659/MSM.890635.
41. Gurses KM, Yalcin MU, Kocyigit D, Canpinar H, Evranos B, Yorgun H, et al. Effects of persistent atrial fibrillation on serum galectin-3 levels. Am J Cardiol. 2015;115(5):647-51. doi: 10.1016/j.amjcard.2014.12.021.
42. Kocyigit D, Gurses KM, Yalcin MU, Canpinar H, Canpolat U, Evranos B, et al. Serum galectin-3 level as a marker of thrombogenicity in atrial fibrillation. J Clin Lab Anal. 2017;31(6):22120. doi: 10.1002/jcla.22120.
43. Clementy N, Benhenda N, Piver E, Pierre B, Bernard A, Fauchier L, et al. Serum Galectin-3 Levels Predict Recurrences after Ablation of Atrial Fibrillation. Sci Rep. 2016;6:34357. doi: 10.1038/srep34357.
44. Clementy N, Piver E, Bisson A, Andre C, Bernard A, Pierre B, et al. Galectin-3 in Atrial Fibrillation: Mechanisms and Therapeutic Implications. Int J Mol Sci. 2018;19(4):976. doi: 10.3390/ijms19040976.
45. Numano F, Shimizu C, Jimenez-Fernandez S, Vejar M, Oharaseki T, Takahashi K, et al. Galectin-3 is a marker of myocardial and vascular fibrosis in Kawasaki disease patients with giant aneurysms. Int J Cardiol. 2015;201:429-37. doi: 10.1016/j.ijcard.2015.07.063.

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