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GALECTIN 3: NEW MARKER FOR MONITORING CLINICAL HEART FAILURE

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ABSTRACT

Introduction: Galectin-3 is a structurally unique member of a family of multifunctional beta-galactoside-binding lectins that are important in the regulation of inflammation, immunity, and cancer. Goals. A study has been carried out in 36 apparently healthy patients without known heart disease and in 52 patients who mainly suffered from heart failure (HF). **Material and methods:** Patient samples have been processed with a chemiluminescent immunoassay (CMIA) (Abbott Diagnostics) on an Architect. The assay is based on two monoclonal antibodies (87B5 and M3 / 38) specific for galectin-3. The increase in galectin-3 has been associated with fibroblast proliferation, a key component in the establishment of cardiac restructuring. The determination of BNP and cardiac troponin I was carried out on a Univel Dxi600 autoanalyzer (Beckman Coulter). **Results:** The mean levels of galectin-3 obtained in the group of healthy patients was 25.3±17.3 ng / ml, while the mean levels of the 52 patients with chronic heart failure was 27.9±24.8 ng /ml. While the mean levels of BNP in the group of healthy patients was 91.4±71.7 pg /ml, while the mean levels of the 52 patients with chronic heart failure 257.3±195.8 pg /ml. And the mean values of Troponin I in the group of healthy patients was 0.031 ± 0.026 ng /ml, and in the group of patients with HF it was 0.043 ± 0.037 ng / ml. **Conclusions:** We found statistically significant differences when comparing the mean levels of galectin-3 in the group of healthy patients with those with chronic heart failure ($p < 0.05$) and also in the mean BNP values compared to the group with chronic HF ($p < 0.05$). The different studies carried out on galectin-3 show that the concentrations are useful in a large number of cardiovascular diseases. The majority to evaluate the investigation of the correlation with other risk factors and the prognostic utility in different clinical endpoints in patients with chronic HF. Studies have been carried out in patients with acute decompensated HF, acute coronary artery disease, and healthy populations. In all of them, galectin-3 showed a prognostic utility for mortality, the development of chronic HF, the development of cardiovascular diseases, or rehospitalization.

KEYWORDS: Galectin-3, heart failure.

INTRODUCTION

Galectins constitute a family of proteins conserved through evolution that are capable of deciphering specific glycocodes in complex macromolecules located on cell membranes or in the extracellular matrix (ECM). This behavior is possible through a phylogenetically intact 135 amino acid domain from lower mammalian invertebrates, called the carbohydrate recognition domain (DRC), which interacts with the structure (Gal beta1 -> 4 GlcNAc) n.[1-5]

Within galectins, galectins 1 and 3 are members of the group of galectins known as the proto type. They behave as homodimers composed of two identical carbohydrate recognition domains that recognize simple disaccharide carbohydrate structures, in the context of complex glycoconjugates.[2,6-10]

Galectin-3 is a member of the beta-galactosidase family of lectins, which has a structure of 30 KDa and plays an important regulatory role in inflammation, immunity, and cancer (Figure 1).

Is a protein secreted by activated macrophages that activates fibroblasts and myofibroblasts that form collagen and citratricial tissue.[6-9]

The DCR of galectin-3 is S-shaped and is further constituted by a protein amino-terminal domain as shown in Figure 1. It functions as a receptor for ligands containing poly-N-acetyl-lactosamine. It is normally found in the epithelium of different organs and in inflammatory response cells such as macrophages, dendritic cells and Kupffer cells.[10,11]

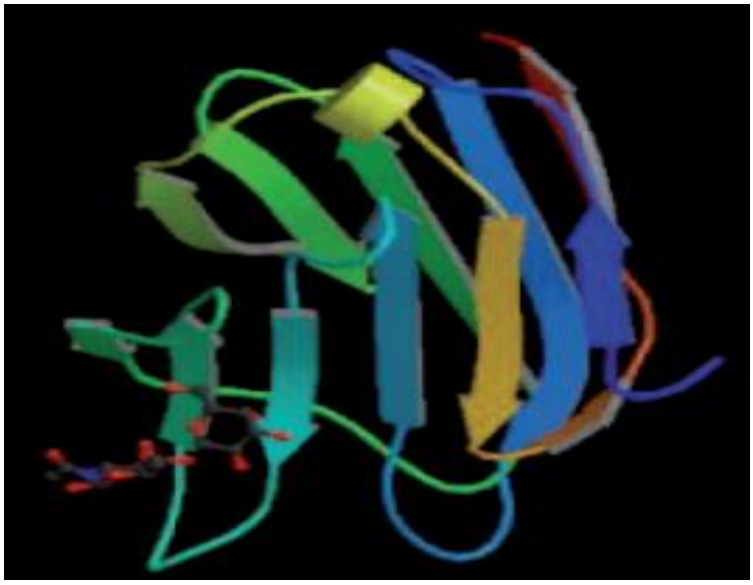

Figure 1: Structure of human galectin-3. It is a 26-30 KD protein synthesized by a gene found on chromosome 14q21.3.

Galectin 3 has both intracellular and extracellular functions. In relation to its intracellular functions, it has been identified as a component of heterogeneous ribocucleoproteins and as a factor in messenger RNA splicing. Likewise, it participates in the control of the cell cycle and reduces apoptosis of T cells, probably through interaction with members of the Bcl-2 family.[5,7] Galectin 3 is secreted by monocytes, macrophages, and epithelial cells. As an extracellular molecule, it activates monocytes, macrophages, mast cells, neutrophils and lymphocytes and intervenes in cell-cell interactions, as well as between cell and extracellular matrix. It promotes neurite outgrowth, induces endothelial cell differentiation and angiogenesis, and functions as a chemoattractant for monocytes and endothelial cells.[1,10] In acute episodes, it has been observed that galectin-3 has the ability to activate the enzyme NADPH oxidase and thus stimulate the generation of superoxide radicals and induce the respiratory burst in neutrophils.[4] Galectin-3 has revealed completely antagonistic properties to those described for Gal-1, regarding the regulation of programmed cell death mechanisms.[5] Gal-3 cDNA transfection in T cell lines managed to rescue cells from Fas L-induced apoptosis. The linkage of this protein to a protective effect of apoptosis opens the way to a new paradigm. Gal-1 and Gal-3 would represent a family of proteins similar to that of Bcl-2, in which the related members, despite the great similarity in their primary structure, present antagonistic effects on cell death programs, such as Bcl- 2, Bcl-xL vs Bax, Bak. Likewise, the interaction between Gal-1 and Gal-3 would allow establishing a balance between proliferation, differentiation and cell death.

OBJECTIVES

A study was carried out in 36 apparently healthy patients without known heart disease and in 52 patients who mainly suffered from HF, in order to evaluate the Architect Galectin-3 technique and compare it with other markers such as B-type natriuretic peptide (BNP).

MATERIAL AND METHODS

The study was carried out in 36 patients apparently, of whom 18 were men and 18 women, aged between 45 and 75 years, and without known heart disease and in 52 patients who mainly suffered from heart failure, of which 30 were males and 22 females with an age range similar to the healthy control group. Patient samples have been processed with a chemiluminescent immunoassay (CMIA) (Abbott Diagnostics) on an Architect. The assay is based on two monoclonal antibodies (87B5 and M3/38) specific for galectin-3. The increase in galectin-3 has been associated with fibroblast proliferation, a key component in the establishment of cardiac restructuring.[3-10] The determination of BNP and cardiac troponin I was carried out on a Univel Dxi600 autoanalyzer (Beckman Coulter).

RESULTS AND DISCUSSION

The mean levels of galectin-3 obtained in the group of healthy patients was 25.3 ± 17.3 ng / ml, while the mean levels of the 52 patients with chronic heart failure was 27.9 ± 24.8 ng / ml. While the mean levels of BNP in the group of healthy patients was 91.4 ± 71.7pg/ml, while the mean levels of the 52 patients with chronic heart failure 257.3 ± 195.8 pg/ml. And the mean values of Troponin I in the group of healthy patients was 0.031 ± 0.026 ng / ml, and in the group of patients with HF it was 0.043 ± 0.037 ng/ml.

Figure 2 graphically shows the mean values of cardiac Troponin I, Galectin and BNP.

Figure 3 shows the regression line obtained when comparing the cardiac Troponin I and Galectin 3 values

of the patients under study (y = 0.794 x + 0.0108 (n = 52) (p <0.05).) Figure 3. Regression line obtained by comparing the cardiac Troponin I and Galectin 3 values of the study patients. y = 0.794 x + 0.0108 (p <0.05).

Figure 4 shows the regression line obtained when comparing the BNP and Galectin 3 values of the study patients y = 0.7143 x + 10.75 (p <0.05). Figure 4. Regression line obtained when comparing the BNP and Galectin 3 values of the study patients y = 0.7143 x + 10.75 (n = 52) (p <0.05).

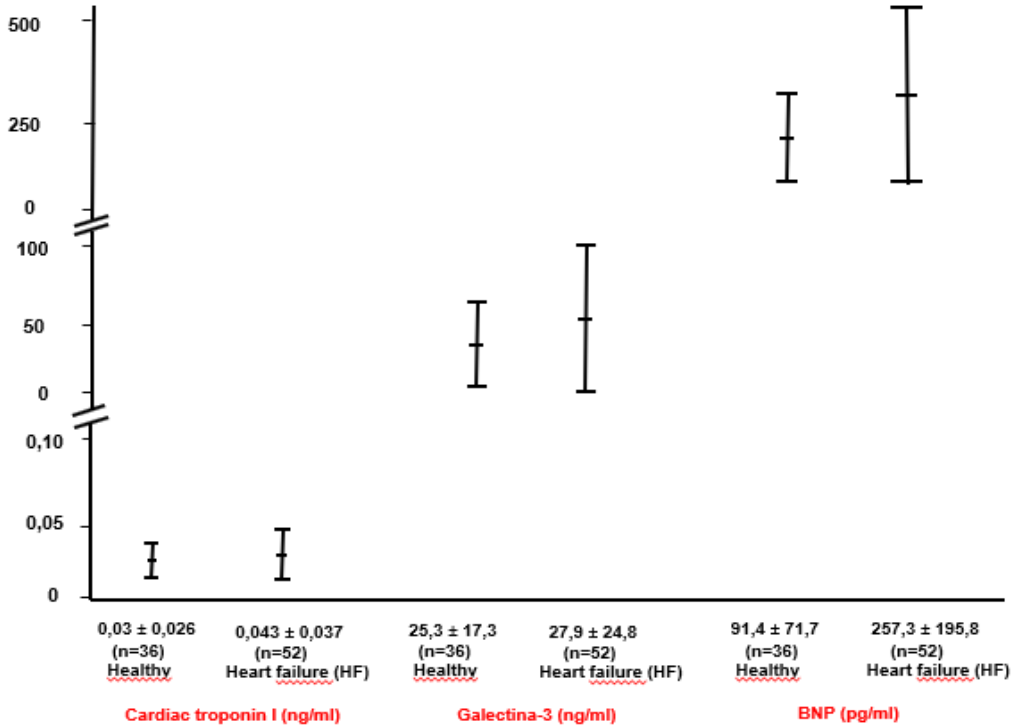

Figure 2: Main expression of galactin-3 associated with fibrosis and inflammation processes (Vergaro G, Del Franco A, Giannoni A, Padeletti L, Passino C, Emdin M. Galectin-3 and myocardial fibrosis in nonischemic dilated cardiomyopathy. International Journal of Cardiology. 2015; 184: 96-100)

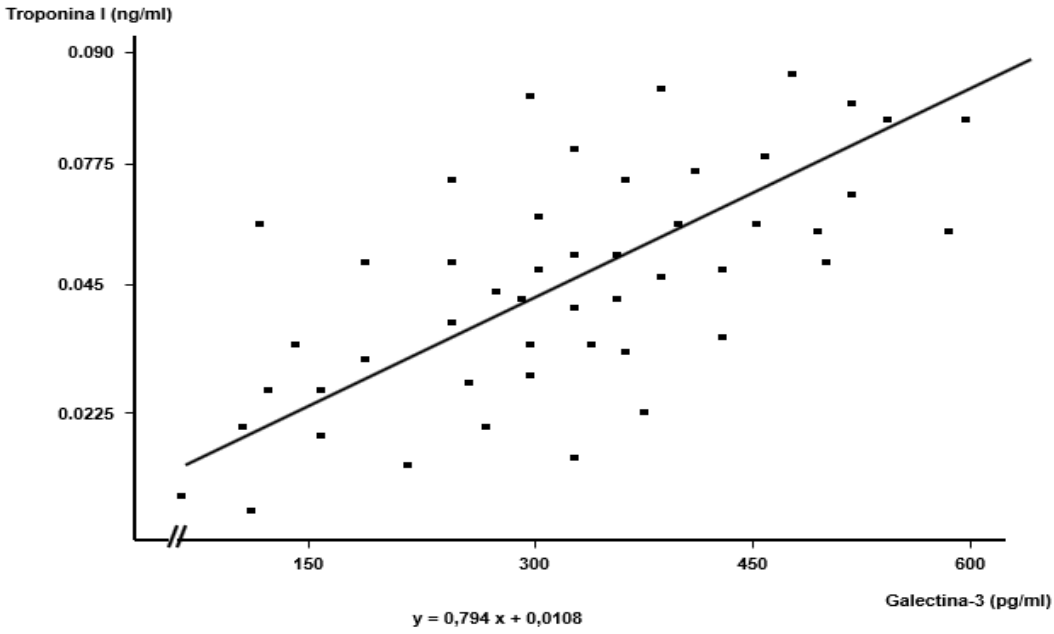

Figure 3: Regression line obtained by comparing the cardiac Troponin I and Galectin 3 values of the study patients. y = 0.794 x + 0.0108 (p <0.05).

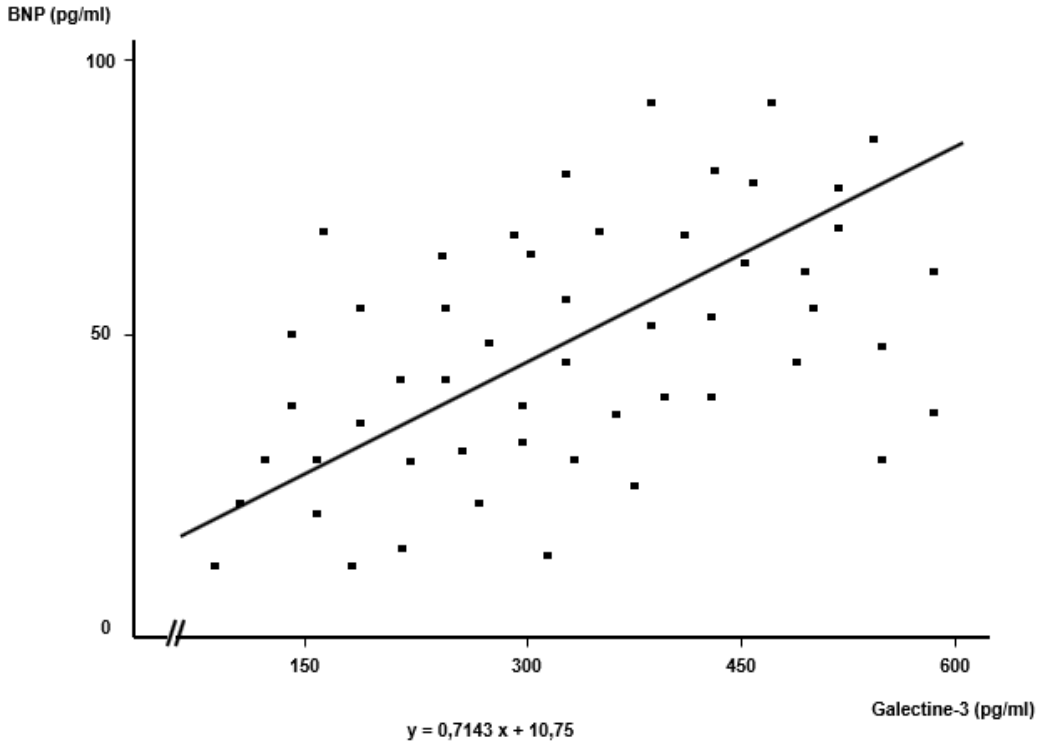

Figure 4: Regression line obtained when comparing the BNP and Galectin 3 values of the study patients y = 0.7143 x + 10.75 (n = 52) (p <0.05).

DISCUSSION

The expression of galactin-3 has been associated with fibrosis and inflammation processes that contribute to the development and progression of heart failure (Figure 5). Thus, galectin-3 defines a distinct form of heart failure characterized by progressive fibrosis. Myocardial galectin-3 concentrations direct fibroblast activation and lead to cell proliferation and interstitial fibrosis (Figure 6).[9]

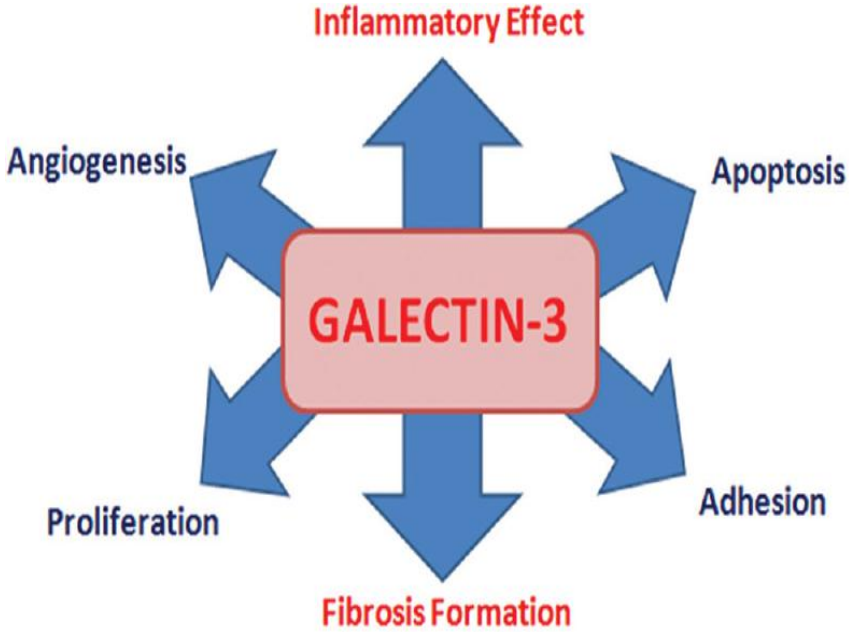

Figura 5: Principal expresión de la galactina-3 asociada con los procesos de fibrosis e inflamación (-Vergaro G, Del Franco A, Giannoni A, Padeletti L, Passino C, Emdin M. Galectin-3 and myocardial fibrosis in nonischemic dilated cardiomyopathy. International Journal of Cardiology. 2015; 184: 96-100).

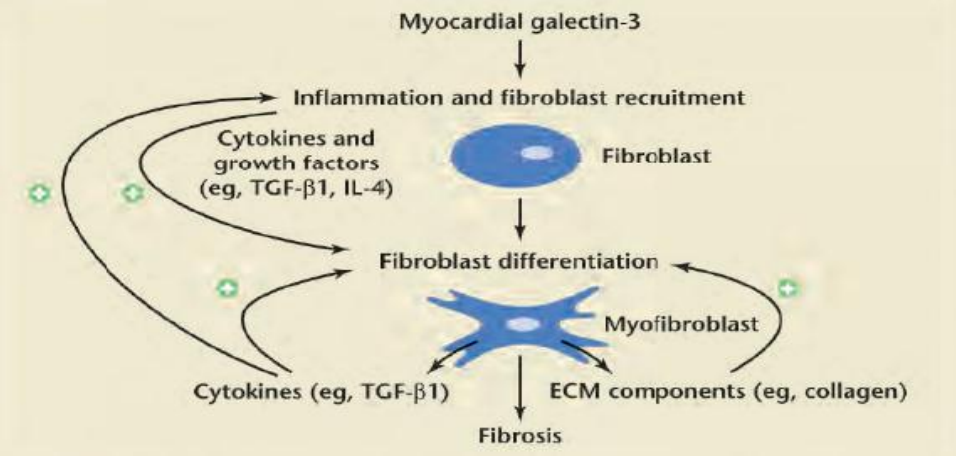

Figure 6: Mechanism of myocardial galectin-3 regulation. (ECM: extracellular matrix, IL: interleukin, TGF: transforming growth factor). Taken from 9.

The clinical evolution and monitoring of the prognosis in patients diagnosed with chronic heart failure can be done with the help of the galectin-3 assay. According to BG Medicine, which developed the test, the galectin-3 rates of patients affected by heart failure are about 30% higher. These patients tend to develop proliferative cardiac fibrosis. The availability of a galectin-3 test, which allows the identification of these high-risk patients, constitutes another important advance towards obtaining a more efficient and appropriate therapy for patients suffering from heart failure. In fact, there are already several cooperation agreements, among other diagnostic laboratories, that wish to offer the test, based on the ELISA technique, on their respective platforms.[4-8] The commercial company BG Medicine indicates a cut-off value of 17.8 ng/ml for galectin-3. Patients with protein concentrations above this value have a higher risk of hospitalization and mortality than patients with heart failure with galectin-3 values below 17.8 ng / ml. Up to the level of galectin-3 equal to 25.9 ng/ml, there is a gray area in which caution is required when interpreting the results. However, since galectin-3 is not specific to the heart and apart from heart failure, elevated levels of galectin-3 are also found in some types of cancer (and in other fibrotic pathologies.

Architect's Galectin-3 Assay (Abbott Laboratories) is a chemiluminescent microparticle assay (CMIA) for testing serum and plasma with EDTA. That allows to process patient samples daily by being fully automated in front of the microtitter plate. However, it remains to be determined how best to use it on a day-to-day basis. The correlation of the Architet test with that of the original commercial house (ELISA BG Medicine) is very good, presenting correlation coefficients r> = 0.90 for samples in the interval between 4.0 and 114.0 ng / ml.[10] Baseline galectin-3 concentrations in patients with chronic heart failure are significantly and independently associated with a higher risk of mortality and of hospitalization and subsequent rehospitalizations (> 26 ng/ml) than those of low-risk patients (<18 ng / ml).[7,8] (Figure 7).

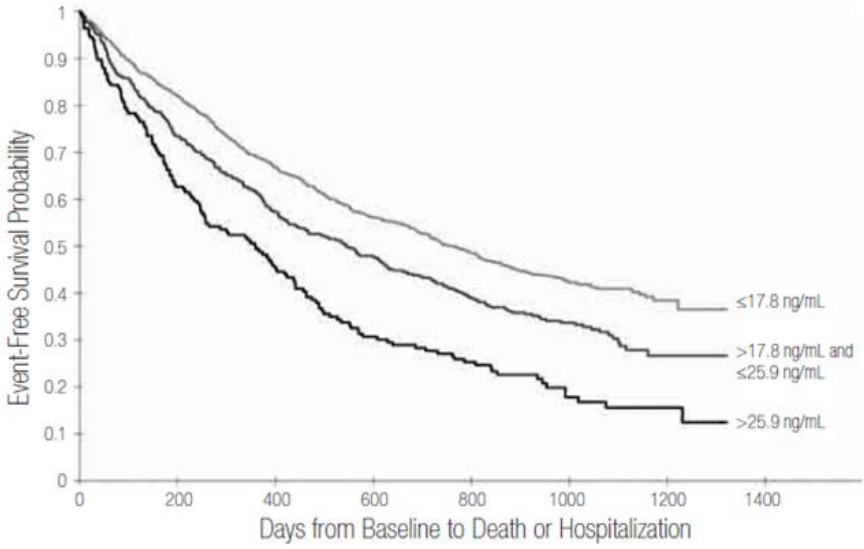

Figure 7: Clinical implications and increase in Galectin-3.

Although there are already extensive studies on the application of galectin-3, it should be asked, what does the analysis of galectin-3 contribute in daily practice. Considering that the manufacturer of the test admits that the conclusions that can be obtained from the analysis should be taken with caution, the clinician is impelled to communicate to the patient with an elevated index of galectin-3, little more than it poses a greater risk high that his heart failure progresses unfavorably.[11-14] Since the galectin-3 index remains fairly constant during the evolution of the disease, the parameter is limited to diagnose heart failure, unlike natriuretic peptides. Likewise, it is independent of decompensation episodes and heart failure therapy, so it is also not useful for pharmacological monitoring.[12-14] In spite of everything, in the future, galectin-3 could play an important role in the administration of therapy, because its determinations make it possible to know which patients are susceptible to receiving more intensive therapy or surveillance. One might think not only of heart failure patients, but especially those who are at increased risk. Also in the application of continuous remote monitoring, it could be stratified by the galectin-3 index. Although the best thing would be for new therapies to appear on the market that would introduce greater added value, especially in heart failure patients with a high galectin-3 index. This, although it is not ruled out, has not yet materialized.[12,15-17]

Different studies were carried out to observe the prognostic utility of galectin-3 in more than 1500 patients with chronic heart failure.[10-12] The patients had a follow-up of varying lengths from 18 months to 6.5 years, with clinical endpoints such as causes of death, causes of hospitalization, cardiovascular mortality, and rehospitalization for heart failure. An increase in galectin-3 concentration was associated with poorer prognoses in all three studies. Increased concentrations of natriuretic peptides were found to be associated with increased galectin-3 concentrations. Elevated concentrations of both biomarkers at the same time had more prognostic value than those of a single marker.[10-12]

The COACH study (Coordinating Study on Outcomes of Advising and Counseling in Heart Failure) investigated heart failure patients with both reduced ejection fractions (HFEFF) or with preserved ejection fraction (HFECF).[17] The importance of prognosis was greater in patients with preserved ejection fraction, which are more difficult to diagnose and treat.

Patients who came to the emergency department for evaluation of possible acute decompensated heart failure were included in the PRIDE study (Pro-BNP Investigation of Dyspnea in the Emergency Department). Patients were followed for 60 days for endpoints of death and recurrent heart failure. At 60 days, the median galectin-3 concentration was higher in patients who died than in those who survived. The combination of galectin-3 with PN was the best prediction for prognosis in patients with acute heart failure.[18]

The prognostic utility of galectin-3 was studied in patients with acute coronary insufficiency in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy) clinical trial. At discharge of the patients, galectin-3 and BNP concentrations were measured. Elevated galectin-3 concentrations were associated with the possibility of developing heart failure followed by acute coronary failure even after adjusting for major clinical risk factors.[19] Patients with high levels of galectin-3 and BNP have an increased chance of developing heart failure, which may serve for stratification of the risk of heart failure after acute coronary failure.

Galectin-3 has also been evaluated in the general population in the PREVEND study (Prevention of Renal and Vascular End-stage Disease) and its associations with all causes of mortality during a follow-up period with a median of 10 years. High galectin-3 concentrations were associated with increased mortality.[20] The utility of galectin-3 measurement in samples from the Framingham Heart Study offspring cohort was also evaluated. In this study, galectin-3 concentrations were associated with an increased risk for new heart failure and all-cause mortality in this population.[21]

The CORONA (Controlled Rosuvastatin Multinational Trial in HF) study investigated the use of statins in patients with heart failure and the primary clinical endpoints of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as well as all causes of mortality. Patients with low galectin-3 concentrations had a lower risk of mortality and death from cardiovascular accident.[22] Other studies in patients on statin treatments versus placebo patients showed that patients with galectin-3 concentrations < 19.0 ng/ml benefited from statin treatment, while patients with concentrations > 19.0 ng/ml. ml did not derive any benefit from treatment.[22] In our study, we have found statistically significant differences when comparing the mean levels of galectin-3 in the group of healthy patients with those with chronic heart failure ($p < 0.05$) and also in the mean BNP values compared to the group with chronic HF ($p < 0.05$).

CONCLUSIONS

Those performed with galectin-3 show that the concentrations are useful in a large number of cardiovascular diseases. The majority to evaluate the investigation of the correlation with other risk factors and the prognostic utility in different clinical endpoints in patients with chronic HF. Studies have been carried out in patients with acute decompensated HF, acute coronary artery disease, and healthy populations. In all of them, galectin-3 showed a prognostic utility for mortality, the development of chronic HF, the

development of cardiovascular diseases, or rehospitalization.

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