Research Article

Galectin 3, a Non-Informative Prognostic Biomarker for Heart Failure in Chronic Hemodialysis Patients

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Abstract

Introduction: Galectin 3 (Gal-3) is a lectin protein, involved in several biological processes such as cell growth, differentiation, signaling, division and apoptosis. Furthermore, Gal-3 is a novel prognostic biomarker for chronic heart failure. N-Terminal (NT)-pro hormone BNP (NT-proBNP) is another heart failure biomarker since it is secreted from the atria and the ventricles of patients with heart failure and increased significantly in symptomatic and asymptomatic patients suffering from left ventricular dysfunction. The Patients with End-Stage Renal Disease (ESRD) have an increased risk of all-cause mortality.

Objective: The overall aim of the present paper was the study of Gal-3 secretion and its possible prognostic factor alone or associated in asymptomatic hemodialysis patients.

Patients and design: A prospective, observational and longitudinal cohort study has been conducted on 145 asymptomatic uremic patients that were under hemodialysis program for two years. Blood samples were taken, and several biological parameters and heart failure biomarkers such as NT-proBNP and Gal-3 were measured.

Results: NT-proBNP and Gal-3 values were increased in all the studied population where the cumulative mortality rate and the mean survival were 11.7% and 22.57 months, respectively. Univariate Cox analysis revealed prognostic values of NT-proBNP and Gal-3 of 5.01 (IC95%=1.08-23.18, P=0.04) and 1.00 (IC95%=0.97-1.02, P=0.99), respectively. However, NT-proBNP prognostic value became statistically non- significant after adjustment 3, 39 (IC95%=0.64-17.70, P=0,148).

Conclusion: While high levels were recorded in hemodialysis patients, Gal-3 cannot be used as prognostic biomarker for overall mortality rate, independently or in association with NT-proBNP.

Keywords:

Biomarker; Gal-3; NT-proBNP; Chronic hemodialysis; Prognostic score

Introduction

Galactin3 (Gal-3) is 26-36 Kda molecular weight protein, belonging to lectin family where 15 members have been yet identified in mammalians. Gal-3 bind specifically to β-galactosides at a well-conserved carbohydrate recognition domain.

Furthermore, Gal-3 form dimers and oligomers through a proline and glycine-rich N-terminal domain. It has also a high affinity for lactose and N-Acetyllactosamine (LacNAc) as the other galectins, but it has a broad oligosaccharide profile including the polylactosaminoglycans found in extracellular matrices and cells surface.

Gal3 is genetically expressed in different tissues by several cell types including macrophages and polarized epithelial cells. The protein is detectable inside, outside and on the surface of the cell. Gal-3 is involved in many biological processes such as cell-cell and cell- extracellular adhesion matrix, cell division, differentiation, signaling, apoptosis, normal growth regulation, tumor growth and metastasis.

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Possible implication in inflammation and fibrosis, mainly cardiac fibrosis was reported. Gal-3 is secreted in large quantities by activated macrophages recruited to the myocardium in response to acute or chronic cardiac inflammation to activate the quiescent fibroblasts into myofibroblasts secreting collagen, a valuable myocardial healing element [1].

While Gal-3 is a novel prognostic biomarker for the heart failure, it has no interest in the diagnosis process since it does not allow the distinction between acute and chronic heart failure, nor the distinction between preserved and decreased ejection heart failure. In a study conducted on patients with acute heart failure, high levels of Gal-3 were predictive of mortality at 60 days from relapse of congestive flare. Furthermore, patients with Gal-3 values over 17.8 mg/ml significantly tended to be rehospitalized for heart failure aggravation 1 to 4 months after discharge. Likewise, a study conducted on 115 patients with acute dyspnea suffering from heart failure revealed that Gal-3 levels over 15 mg/ml compared to the echocardiography indices were strongly predictive (63%) for mortality at 4 years.

Unlike NT-proBNP, Gal-3 level remains persistent in 55 patients at the end-stage of heart failure after ventricular assistance. The maximum normal threshold level for Gal-3 is fixed in most studies at 17.8 mg/ml among which high risk of mortality and rehospitalization is possible. N-Terminal (NT)-pro hormone BNP (NT-proBNP) is another heart failure biomarker since it is secreted from the atria and the ventricles of patients with heart failure and increased significantly in symptomatic and asymptomatic patients suffering from left ventricular dysfunction. The normal threshold level of NT-proBNP was fixed at 125 mg/ml. Hemodialysis is a non-physiological technique where the used dialysis fluids rise often biocompatibility issues, in addition to the dialysis membranes which are less efficient than the glomerular filter. Despite its contribution to comfort and survival of patients, hemodialysis is considered as major risk factor of mortality which is 20 times compared to the general population of equal age. In hemodialysis patients, cardiovascular complications mainly coronary disease (40%) and ventricular hypertrophy (75%) are considered as the leading causes of death. According to chronic renal failure is associated with systolic and/or diastolic alteration of the myocardium, described as type 4 cardiorenal syndrome. The aim of the present study was monitoring Gal-3 level and its possible prognostic value in chronic asymptomatic hemodialysis patients [2].

Patients and methods

An observational longitudinal and prognostic cohort study has been conducted on 145 asymptomatic uremic patients at end-stage chronic renal failure and receiving emergency hemodialysis using FRESENIUS 4008S generator and Helixone-type dialysis membrane. All the patients were recruited at four hemodialysis units: CHU Hussein Dey, Koléa hospital; Dar el Beida hospital, and private hemodialysis unit, Algiers, Algeria. The experimental study started in April 2014 and extended for 35 months. Ambulatory dialysis patients over the age of 18 and chronic hemodialysis patients for more than 6 months were included in the study. However, patients previously experienced cardiovascular issues such as acute coronary syndrome, coronary bypass surgery, peripheral arterial disease and amputation were excluded from the study. Blood samples in Ethylenediaminetetraacetic acid (EDTA) and heparin tubes were taken before the onset of dialysis session and plasma were directly processed or stored at -60°C until further analysis. Biochemical makers namely, hemoglobin measured by ABX micros 60Horiba, urea, creatinine, ultra-sensitive C-Reactive Protein (us-CRP), triglycerides, total cholesterol, High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, Alkaline Phosphatase (ALP) and Albumin were performed on Cobas Interga® 400plus, and calcium, phosphorus were measured on Xpand Siemens. NT-proBNP assay was performed on Cobas e411Roche while Gal-3 was performed on Vidas PC Biomerieux. Taking into consideration the biological assessment, all patients were supervised during 24 months for possible detection of cardiovascular complications mainly, myocardial infarction, angina pectoris, heart failure, stroke, coronary angioplasty with or without stenting and death [3].

Statistical analysis

The statistical analysis has been conducted using SPSS 22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The Shapiro-Wilk test was used for the normal distribution analysis of quantitative variables. Quantitative variables with normal or Gaussian distribution were presented as mean ± standard deviation (m ± SD). Quantitative variables with "non-normal" distribution were presented as median M with the Interquartile Range IQR [IQ1-IQ3]. Qualitative variables were presented as a percentage. The Mann Whitney U test was used for the comparison of two non- Gaussian distribution means. A chi-squared test was used for the comparison of two percentages. The Cox proportional-hazards model was used to determine the association of a candidate heart failure biomarker with mortality. Testes were considered significant at $P<0.05$.

Results

Median age of the studied population was 50 years (18-87 years). A male predominance was observed in the recruited population with a sex ratio of 1.23. Their average Body Mass Index (BMI) was 22.25 ± 4.09 kg/m^2 (14-35 Kg/m^2). Among the hemodialysis patients, 64% were hypertensive while 19% were diabetic (Table 1). The main etiologies of end-stage renal failure were diabetic nephropathy (17%), nephroangiosclerosis (12%) and polycystic kidney disease (9%). Unfortunately, in 38% of the patients, the etiology remains unknown.

Table 1: Clinical and biological characteristics of asymptomatic chronic hemodialysis patients.

Parameters	Patients (n)	Normal thresholds
BMI Kg/m^2	22.25 ± 4.09 (131)	18.5-25
Urea g/L	1.14 ± 0.28 (145)	0.15-0.45
Creatinine mg/L	89.61± 26.71 (145)	04-12
Uric acid mg/L	55.36 ±12.47 (145)	20-70
Triglycerides g/L	1.36 [0.85-1.72] (145)	0.5 -1.5
Total cholesterol g/L	1.56 ± 0. 35 (145)	1.5-2.00
cHDL g/L	0.36 [0.31-0.44] (145)	>0.40
cLDL g/L	0.83 [0.65-0.99] (139)	<1.30
No cHDL g/L	1.18 ± 0,36 (145)	<1.60
CRP hs mg/L	3.70 [2.00- 6.40] (145)	<1
Albumin g/L	41.63 [39.74-44.19] (145)	35-50

Gal-3 median was 74 mg/ml (54.35-94.45 mg/ml) which is five times above her threshold level (17.8 mg/ml) (Table 1). The minimum registered level was 18.7 mg/ml against 100 mg/ml for the maximum level, while 49% of patients (n=71) had Gal-3 levels above 75 mg/ml. Same statements were registered for NT-proBNP where 100% of the hemodialysis patients bellow 75 years presented values above the normal threshold level (125 p While Gal-3 level was not significantly correlated with all the considered demographic and biological parameters, non-diabetic subjects with a dialysis duration of 122 months had average levels of 75 mg/ml against 63 mg/ml for diabetic subjects with dialysis duration of 69 months (P=0.025) (Table 2 and Figure 1). NT-proBNP showed significant negative correlations with BMI, hemoglobin, PTH, and ALP levels.

Table 2: Spearman's correlation between NT-proBNP, Galectin 3 and demographic and biological characteristics.

Parameters	R de spearman	
	NT- proBNP	Galectin 3
Age (years)	NS	NS
Gender (male/female)	NS	NS
Duration of dialysis (months)	NS	NS
NT-proBNP pg/ml	1	NS
Galactin 3 ng/ml	NS	1
CRP hs mg/L	NS	NS
25OH total vitamin D ng/ml	NS	NS
PTH pg/ml	0	NS
ALP U/L	-0.175	NS
Total cholesterol g/l	-0.243	NS
Triglycerides g/l	-0.329	NS

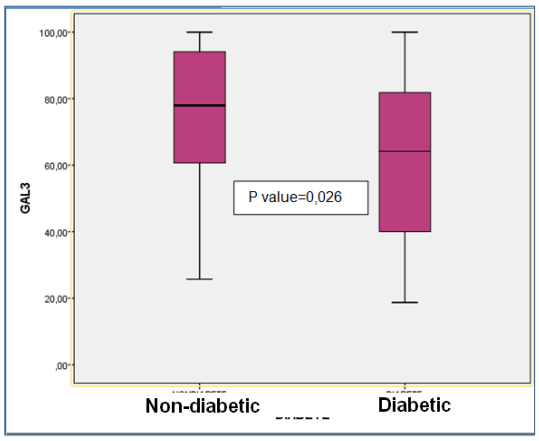

Figure 1: Distribution of Galectin 3 levels in diabetic and non-diabetic asymptomatic chronic uremic patients.

During the two years of the study, six patients became blinds while one person had a stroke and 17 deaths were recorded during this period. Among the dead people, 11 had cardiac arrest; one had ovarian carcinoma, one post-infectious syndrome, one post-stroke AVC, while the origin of death was unknown in three cases. The cumulative mortality was 5.5% (n=8/145) and 6.4% (n=9/139) during the first and second year, respectively. The two-year prevalence of mortality was 11.7% with a death rate of 5.31 per 1000 patients per month. The overall survival mean of the studied population was 22.57 months (95% CI=21.86-23.28 months). The Mann-Whitney U test (Table 3) of the biological and clinical characteristics shown that the deceased hemodialysis patients were older (76 vs 49 years, P<0.001)), with low albumin levels (38 vs 42.11 g/l, P<0.001), 25OH vitamin D deficiency (14.90 vs 20.81 ng/ml, P<0.05) and higher levels of NT-proBNP (35000 vs 7703 pg/ml, P<0.05).

Univariate Cox analysis revealed significant risk of mortality (hazard risk HR=5.00) when NT-proBNP levels exceed 29971 p overall survival mean of the studied population was 22.57 months (95% CI=21.86-23.28 months). The Mann-Whitney U test (Table 3) of the biological and clinical characteristics shown that the deceased hemodialysis patients were older(76 *vs* 49 years, P<0.001)), with low albumin levels (38 *vs* 42.11 g/l, P<0.001), 25OH vitamin D deficiency (14.90 *vs* 20.81 mg/ml, P<0.05) and higher levels of NT-proBNP (35000 *vs* 7703 mg/ml, P<0.05).

Table 3: Univariate Cox hazard risk (HR) analysis of N-terminal (NT)-pro hormone BNP (NT- proBNP) and Galectin 3 (Gal-3) in the overall mortality rate.

NT proBNP pg/ml	HR (IC95%)	P
NTproBNP <2847	Reference	0.051
NTproBNP 2848-8132	2.03 (0.37-11.10)	0.413
NTproBNP 8133-29971	0.98 (0,13-6.97)	0.986
NTproBNP >29971	5.008 (1.08-23.18)	0.039
Gal-3	1.00 (0.97-1.02)	0.986

Discussion

Considering a normal threshold level of 17.8 mg/ml for the prognosis of chronic heart failure, the Gal-3 levels measured in plasma collected from asymptomatic chronic hemodialysis patients were alarming in all the studied population with a median of 74 mg/ml. Reported similar findings where the Gal-3 median level was 70.6 mg/ml, without urinary excretion of Gal-3. Likewise, in a study conducted on 1168 diabetic hemodialysis patients and 2579 coronary angiogram patients, negative correlation between Gal-3 level and Glomerular Filtration Rate (GFR) was reported, with an average of 54 mg/ml in dialysis patients compared to 11-14 mg/ml in the general population. Studying an animal model with progressive renal fibrosis, Gal-3 was highly secreted by macrophages, a key element in the pathogenesis of renal fibrosis, through the activation of renal fibroblasts. The increased level of Gal-3 is a major risk factor for chronic renal failure (HR=2.22, 95%CI=1.89-2.60). However, this association was attenuated after adjustment of urinary albumin/creatinine ratio and GFR. Using immunohistochemistry, the gene expression of Gal-3 in normal kidney was confirmed in distal tubuli but not in the glomerular sections, however Gal3 positive infiltration cells were reported in the glomeruli of diabetic nephropathy patients. Furthermore, the number of glomerular Gal-3 positive infiltration cells was associated with increased uremic excretion of proteins in all patients and with decreased renal functions in diabetic nephropathy patients [4].

In the presented study, mortality prevalence of 11.7% and average survival time of 22.57 months were reported. These statements are close to those reported by Cherifi where the overall mortality was 10%. According to Gal-3 was an independent prognostic factor for mortality in chronic hemodialysis patients with adjusted HR of 5.40 where mortality prevalence was 23%. The small sample size was the major limitations of the present study which would affect the prognostic factors' analysis. In a study conducted on 173 asymptomatic hemodialysis patients, NT-proBNP and Gal-3 combination was a prognostic marker of mortality and cardiovascular complications, unlike our study where only mortality was retained, Interestingly, Gal-3 level was prognostic factor for cardiovascular complication and overall mortality in patients with chronic renal failure. Other studies confirmed that Gal-3 was not a significant prognostic factor in hemodialysis patients [5].

Conclusion

In the present pilot study, high levels of Gal-3 were reported in chronic hemodialysis patients. However, it cannot be used as a prognostic marker of overall mortality independently or in combination with NT-proBNP. Further studies on larger population are required to validate the above statements.

References

1. Amin HZ, Amin LZ, Wijaya IP. Galectin-3: A novel biomarker for the prognosis of heart failure. Clujul Med. 2017;90(2):129-132.
2. Krzeslak A, Lipinska A. Galectin-3 as a multifunctional protein. Cell Mol Biol Lett. 2004;9(2):305-328.
3. Hrynchyshyn N, Jourdain P, Desnos M, Diebold B, Funck F. Galectin-3: A new biomarker for the diagnosis, analysis and prognosis of acute and chronic heart failure. Arch Cardiovasc Dis. 2013;106(10):541-546.
4. van Kimmenade RR, Januzzi Jr JL, Ellinor PT, Sharma UC, Bakker JA, Low AF, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, andapelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol. 2006;48:1217-1224.
5. 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.

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