Original Article

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Biochemistry Section

Assessment of Relationship between Galectin-3 and Biochemical Parameters in Peritoneal Dialysis Patients with Left Ventricular Hypertrophy

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ABSTRACT

Introduction: Cardiovascular complications are considered as the main cause of mortality in patients with End-Stage Renal Disease (ESRD). Cardiovascular Disease (CVD) includes disorders of the Left Ventricular Hypertrophy (LVH) of the heart which is the most frequent cardiac alteration in ESRD. Galectin-3 (GAL-3), a β-galactoside-binding protein has been proposed to be a new clinical biomarker that reflects cardiac fibrosis in patients with Heart Failure (HF).

Aim: To evaluate the relationship between GAL-3 and biochemical parameters in Peritoneal Dialysis (PD) patients with and without LVH.

Materials and Methods: This cross-sectional study enrolled 45 patients (25 women and 20 men) with ESRD who were categorised as having CVD with (n=12) or without (n=33) LVH. Demographic, biochemical and clinical characteristics of 45 patients were analysed. The relationship of plasma GAL-3 levels was analysed with the biochemical parameters for both the groups of patients. For comparison between groups, Student unpaired t-test was used for the data of normal distribution while Mann-Whitney test was used for data of non-Gaussian distribution. Pearson's correlation test was performed to examine various correlations.

Results: Significantly high number (83.3%) of female patients were observed in ESRD with LVH. The groups did not differ significantly in their demographic, and biochemical and clinical parameters. There was significant increase in Left Ventricular End-Diastolic Diameters (LVEDD), Left Ventricular (LV) mass and LV mass index in patients with LVH as compared to the patients without LVH. The levels of GAL-3 showed slight increase (91±23.98 ng/mL) levels in LVH patients as compared to the patients without LVH (83.68±32.8 ng/mL). Exponential positive correlation between serum levels of GAL-3 and creatinine in ESRD patients without LVH (r=0.563, p=0.001). GAL-3 also showed positive correlations with urea without (r=0.563, p=0.001) as well as and uric acid (r=0.416, p=0.0178) for ESRD patients without LVH. However, GAL-3 showed no association with uric acid and urea (r=0.04487, p=0.896; r=0.2383, p=0.48) in ESRD patients with LVH.

Conclusion: GAL-3 positively correlated to the biochemical parameters in ESRD patients. Patients with LVH only showed positive correlation between GAL-3 and creatinine. Moreover, GAL-3 could not be used as the biomarker because it did not correlate with established diagnostic parameter like LV mass and LV mass index. Hence, in this study GAL-3 is not a potential clinical biomarker for the progression of cardiovascular complications in ESRD patients. Overall, these data reflect the need for further investigation of GAL-3 to HF in patients with ESRD.

Keywords: Cardiovascular disease, Chronic kidney disease, End stage renal disease, Heart failure

INTRODUCTION

Galectin-3 is a 31 KDa β-galctoside-binding protein produced by macrophages and other cells. It has been shown to play a role in the regulation of inflammation and fibrosis [1]. In addition, Galectin-3 has been recently reported as a biomarker for HF [2].

ESRD affects individuals throughout the world and is now recognised as a major public health problem [3,4]. The crude prevalence of ESRD in Saudi Arabia is 4% of the general population and it is estimated that the incidence of ESRD has also increased [5]. The diagnosis of ESRD requires a measured decrease in kidney function, with a Glomerular Filtration Rate (GFR) of less than 60 mL/min per 1.73 m^2 and/or kidney damage for three months or more. Kidney damage refers to pathologic abnormalities evidenced by biopsy or imaging as well as alterations in urinary sediment or proteinuria (proteinuria/creatinuria >200 mg/g, albuminuria/creatinuria >30 mg/g) [6]. ESRD is the final common pathway for all renal diseases; may occur due to ischemia, hypoxia, proteinuria, hypertension and in presence of predisposing factors (smoking, diabetes, hyperlipidemia) [7-9].

ESRD has many adverse outcomes which need to be monitored and managed. A wide variety of diseases including CVD and obesity are associated with ESRD and haemodialysis [10]. Recently, a medical term, 'Cardiorenal Syndrome' (CRS), was coined to describe acute to chronic clinical overlapping of kidney and heart dysfunctions [11]. Dialysis and Renal Replacement Therapy (RRT) is required in end-stage disease. Dialysis is a common alternative due to limited availability of organ donors [12,13].

Dialysis may involve haemodialysis or PD. It is well established that patients with ESRD have a high incidence of CVD compared to the general population. Moreover, CVD is considered the major cause of morbidity in ESRD patients [14]. This association has not been fully understood and cannot be adequately explained by changes in the traditional risk factors [15]. The ESRD is also known as irreversible advanced Chronic Kidney Disease (CKD) where there is permanent loss of kidney function causing extreme mortality rates [6,16]. Continuous Ambulatory Peritoneal Dialysis (CAPD) helps in treating ascites and is a suitable alternative to dialysis [17].

LVH is considered one of major independent predictor of CVD and one of typical feature of ESRD. The most common cause of LVH is hypertrophy which results from an increased preload due to hypervolemia and an increased afterload due to peripheral resistance. There is a high prevalence of CVD (40%)

and ventricular hyperthrophy (70%) in patients on RRT [10,18]. Moreover, dialysis patients have three-fold increase risk of HF and high rate of mortality due to LVH [19]. A faster diagnosis is important to prevent CVD complications. Also, the etiology must be understood so that appropriate therapy is started [20,21]. As GAL-3 has been reported a clinical biomarker in HF, it would be interesting to evaluate the role of GAL-3 in ESRD patients with and without LVH. The aim of this study was to understand the role of GAL-3 in ESRD patients undergoing PD in terms of renal function testing.

MATERIALS AND METHODS

Study Population

This cross-sectional study enrolled 45 patients (25 women and 20 men) with ESRD attending the nephrology clinic at King Fahad Specialist Hospital, Qassim, Saudi Arabia from January to December 2016. The research protocol was approved by Regional Research Ethics Committee- Qassim (number: 1252/33/45). Written informed consent was obtained from all participants before enrollment in the study.

Inclusion criteria: Among 72 patients, only 45 patients fulfilled the inclusion criteria, which were lack of permanent heart rhythm disorders, no diastolic-systolic dysfunction, no moderate to severe valvular disease (diagnosed with echocardiography) and absence of active inflammatory or infectious disease based on clinical evaluation and laboratory testing.

Exclusion criteria: Patients were excluded from the study if they had CVDs such as myocardial infarction, angina pectoris, valvular heart disease, hypertrophic dilated cardiomyopathy.

All patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) received four exchanges per day using standard dialysis bags (8 L/day). Information on patient's demographics and clinical parameters was obtained from medical records and also from patients themselves using a case report form.

Galectin-3 Measurements

Blood samples were collected after an overnight fast and immediately centrifuged at 3000 rpm for 15 minutes at 4°C. The samples were then stored at -70°C until being assayed. Galectin-3 levels were measured by immunoassay using ARCHITECT i2000SR (Abbott Diagnostics, Abbott Park, IL, USA) according to the manufacturer instructions. All samples were assayed in duplicate and the values were represented as mean±SD.

Patients Demographics, Risk Factors and Clinical Analysis

Patient demographics were recorded upon enrolment to the hospital. Risk factors such as BMI, Systolic and Diastolic Blood Pressures (SBP and DBP), Total Cholesterol (TC), Triglycerides (TGs), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C) and the ratio of TGs/HDL, hypertension, urea, uric acid and creatinine were estimated. Echocardiographic measurements were performed in accordance with the American Society of Echocardiography (ASE) guidelines [22].

STATISTICAL ANALYSIS

The statistical significance of the difference between the means of two groups of samples was assessed by the data which was expressed as mean±SD. For comparison between the groups, Student unpaired t-test was used for the data of normal distribution while Mann-Whitney test was used for data of non-Gaussian distribution. Pearson's correlation test was performed to examine various correlations. Differences were considered to be significant when the p-value was less than 0.05 ($p<0.05$).

RESULTS

Demographic, risk factors and clinical characteristics of the 45 patients are summarised in [Table/Fig-1]. Patients were classified into two groups accordingly; with LVH (n=12) and without LVH (n=33). The mean age of the patients with LVH was 41±18 years and the patients without LVH was 37±17. In patients with LVH, 83.3% were females, however, in patients without LVH 45.45% were females. The groups did not differ significantly in their BMI, SBP, DBP, TC, TGs, HDL-C, LDL-C and in the ratio of TGs/HDL [Table/Fig-1].

Variables	Patients with LVH (n:12)	Patients without LVH (n:33)	p-value
Age (years)	41±18	37±17	0.324
Gender	10 F/2 M	15 F/18 M	
BMI	25±5.8	24±5.6	0.650
SBP (mmHg)	148.7±16.8	137±37.52	0.126
DBP (mmHg)	81.7±8.82	82.6±37.53	0.899
Galectin-3 (ng/mL)	91±23.98	83.68±32.80	0.632
TC (mmol/L)	4.03±2.80	3.75±1.85	0.756
TGs (mmol/L)	0.87±0.51	1.32±1.3	0.084
HDL-C (mmol/L)	0.99±0.87	0.85±0.36	0.612
LDL-C (mmol/L)	2.71±1.94	2.35±1.4	0.579
TGs/HDL ratio	1.13±0.57	1.95±2.2	0.062
Non HDL-C (mmol/L)	3.05±2.20	2.9±1.72	0.844
Uric Acid (µmol/L)	343±55.38	377.3±94.4	0.156
Urea (mmol/L)	17.17±6.88	19.54±6.42	0.40
Creatinine (µmol/L)	977.3±423.8	1013±342.1	0.805
LVEDD (mm)	50±6.2	41±5.25	0.001
PWT (mm)	10.55±1.81	12.05±12.34	0.598
EF (%)	51.6±15.56	58.97±2.7	0.180
LV mass (g)	198.5±35.56	123.7±41.47	<0.0001
LV mass index (g/m^2)	125.5±20.84	76.06±16.2	<0.0001

[Table/Fig-1]: Demographic and clinical characteristics of patients.
BMI: Body mass index; EF: Ejection fraction; LV: Left ventricular; LVEDD: Left ventricular end diastolic diameter; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PWT: Posterior wall thickness; TC: Total cholesterol; TGs: Triglyceride; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; Non-HDL-C: Non-high density lipoprotein cholesterol and TGs/HDL-C: Triglyceride/high density lipoprotein cholesterol ratio

There was also no significant difference in both the groups for uric acid, urea and creatinine in the blood levels [Table/Fig-1]. However, there was moderate increase in LVEDD, LV mass and LV mass index in patients with LVH as compared to the patients without LVH. The patients with LVH showed slight increase (91±23.98 ng/mL) in the level of GAL-3 as compared to the patients without LVH (83.68±32.8 ng/mL) however, this increase was not significant [Table/Fig-1].

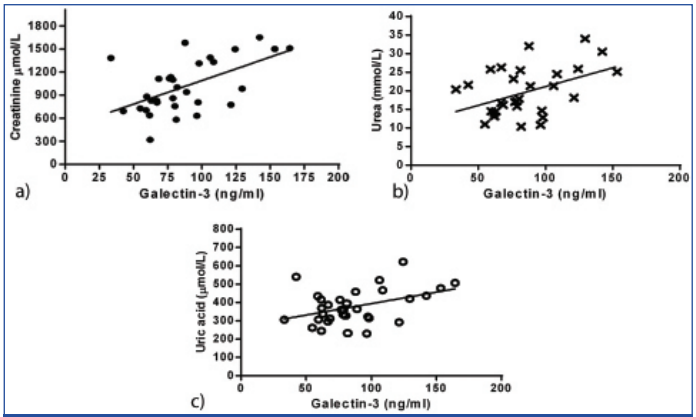
Correlations were analysed in all ESRD patients between GAL-3 and risk factors mentioned in this study. In all ESRD patients without LVH, GAL-3 showed an exponential positive correlation with creatinine ([Table/Fig-2a]; r=0.563, p=0.001), urea ([Table/Fig-2b]; r=0.446, p=0.0119) and uric acid ([Table/Fig-2c]; r=0.439, p=0.0246).

In contrast, serum levels of GAL-3 with LVH patients showed no correlation with urea ([Table/Fig-3a]; r=0.2383, p=0.4804) and uric acid ([Table/Fig-3b]; r=0.04487, p=0.896). Further analysis about this correlation revealed that only LVH group had GAL-3 association with creatinine ([Table/Fig-3c]; r=0.6624, p=0.026).

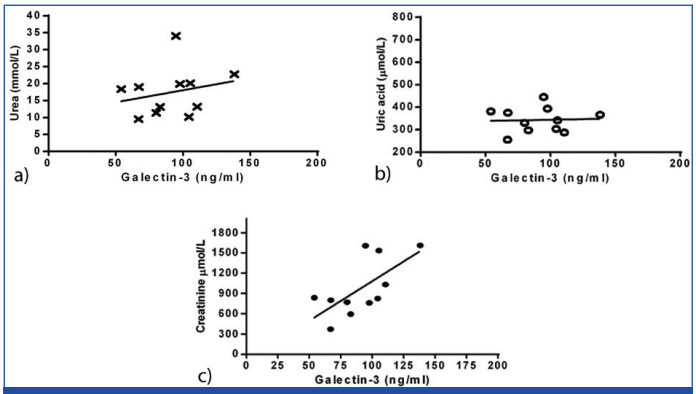
There was no significant difference in serum levels of GAL-3 among ESRD on PD either with LVH or without LVH. However, in LVH patients, higher galaectin-3 levels were associated with higher LVEDD [Table/Fig-4].

DISCUSSION

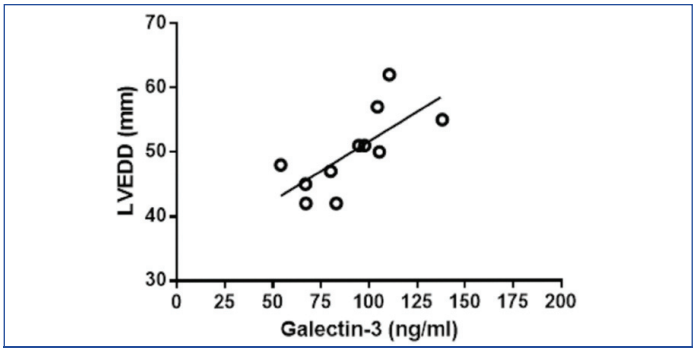
Gal-3 is a novel biomarker produced by activated macrophages, and is associated with myocardial fibrosis and progression of HF [16]. It



[Table/Fig-2]: Correlation of Galectin-3 versus creatinine (a) (r=0.563, p=0.001), urea (b) (r=0.446, p=0.0119) and uric acid (c) (r=0.416, p=0.0178) in all ESRD patients without LVH.



[Table/Fig-3]: Correlation of Galectin-3 versus urea (a) (r=0.239, p=0.480), uric acid (b) (r=0.045, p=0.896) and creatinine (c) (r=0.439, p=0.0246) in all ESRD patients with LVH.



[Table/Fig-4]: Correlation of Galectin-3 versus LVEDD (r=0.709, p=0.0145) in ESRD patients with LVH.

is already known that patients with ESRD have a high incidence of CVD compared to the general population [14]. LVH is considered one of major independent predictor of CVD and one of typical feature of ESRD. Hence, to understand the association between Gal-3 and ESRD patients with and without LVH, the level of serum Gal-3 was screened in these patients. In this study, demographic, risk factors and clinical characteristics of ESRD patients were also analysed. Patients with LVH included a higher number of females as compared to males. It is well established that women have lower incidence of CVD as compared to men, more specifically coronary artery diseases and acute coronary syndrome [23,24]. However, HF, stroke and atrial fibrillation are more often seen in elderly women [25-27], with an increase in prevalence of hypertension [28,29]. LV and LVH are more prevalent in hypertensive women with subclinical cardiac damage [30].

However, in patients without LVH, no remarkable difference in the ratio of male and female patients was observed (p-value not significant (0.282)). Both the groups did not differ significantly in their BMI, SBP, DBP, TC, TGs, HDL-C, LDL-C and in the ratio of TGs/HDL. Although slight higher values of Uric acid, urea and creatinine were observed in ESRD patients without LVH, however, the differences were moderately increased in LVEDD, LV mass and LV mass index in patients with LVH as compared to the patients without LVH. GAL-3 also contributes in the progression of cardiovascular remodeling along with many inflammatory and autoimmune diseases [31-34]. Increased levels of GAL-3 were detected in most of CVD patients and its prognostic values for various clinical outcome were investigated extensively [35]. It has been reported that high expression of GAL-3 levels was related with mortality in acute and chronic HF [36,37]. Increased levels of GAL-3 were estimated using immunoassay in LVH patients as compared to the patients without LVH. However, this increase was not significant. Moreover, patients with and without LVH exhibited positive correlation between GAL-3 and creatinine.

In contrast, GAL-3 did not show any association with urea and uric acid in ESRD patients with LVH. Furthermore, in ESRD patients without LVH, GAL-3 showed positive correlation with creatinine, urea and uric acid. This is further ascertained by a previously published systematic review which indicated that galectin-3 is ineffective in predicting all-cause mortality and cardiovascular mortality, particularly under the influence of certain clinical factors including eGFR, Left Ventricular Ejection Fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) [38]. In a previous study, patients with acute decompensated HF exhibited increased GAL-3 expression levels which were associated with impaired ventricular-arterial coupling, elevated pulmonary artery pressures and severe systolic dysfunction [39]. Changes in LV structure and function associated with chronic HF are linked to serum levels of GAL-3 [40].

There was no significant difference in serum levels of GAL-3 among ESRD patients on PD either with or without LVH. However, in LVH patients, higher galaectin-3 levels were associated with higher LVEDD.

Limitation(s)

The study sample was limited. Additionally, the data presented in this study are cross-sectional and clear causation of relationship between GAL-3 and other clinical parameters cannot be determined.

CONCLUSION(S)

In conclusion, GAL-3 levels were reported to be a predictor of therapeutic response to ESRD patients. The GAL-3 levels in plasma are inversely related to the renal function of patients mainly without LVH. Hence, GAL-3 is not found to be a substantial clinical biomarker for the progression of cardiovascular complications in ESRD patients. Overall, these data reflect the need for further investigation of GAL-3 to HF in patients with ESRD.

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