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The Correlation of Serum Galectin-3 Level with the Staging of Chronic Kidney Disease Coexistent with Diabetes Mellitus and with Hypertension

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Abstract

Background: Chronic Kidney Disease (CKD), characterized by significant proteinuria and reduction of estimated Glomerular Filtration Rate (eGFR), usually developed in coexistence with Diabetes Mellitus (DM) and Hypertension (HTN). Galectin-3, known as a proinflammatory and profibrogenic mediator, was thus utilized in evaluating the correlation with CKD staging and the relationship to CKD coexistent with DM and with HTN in this hospital-based case-control study.

Methods: Participants who had no known profibrotic disorders with or without CKD were eligible for the investigation. The clinical data such as coexistent DM or HTN were required, and the serum galectin-3 and creatinine were measured with calculation of eGFR for analysis.

Results: A total of 104 participants were enrolled, including 65 CKD patients and 39 non-CKD subjects. Compared with the non-CKD group, the serum galectin-3 level was significantly increased in the CKD group (16.8±6.5 vs. 32.9±18.2 ng/mL, $P<0.001$). The serum galectin-3 level was significantly correlated with the serum creatinine concentration ($r=0.630$, $P<0.001$) and inversely with the eGFR ($r=-0.613$, $P<0.001$). Furthermore, the serum galectin-3 expression was seemingly higher in the CKD patients in coexistence with DM (33.8±18.1 vs. 30.9±18.7 ng/mL, $P=0.547$) and with HTN (33.9±19.2 vs. 26.9±10.1 ng/mL, $P=0.265$) than those without, respectively.

Conclusion: The serum galectin-3 concentration was remarkably elevated in CKD patients compared with those who had no CKD. The level of serum galectin-3 was also significantly correlated with the serum creatinine concentration as well as inversely correlated with the eGFR. The results indicated that serum galectin-3 level was significantly associated with the progression of CKD, which was not affected by the coexistent DM or HTN.

Keywords: Chronic Kidney Disease (CKD); Diabetes Mellitus (DM); Estimated Glomerular Filtration Rate (EGFR); Galectin-3; Hypertension (HTN)

Introduction

Chronic Kidney Disease (CKD), meaning progressive kidney damage accompanied by deteriorating renal function with the presence of significant proteinuria and reduction of estimated Glomerular Filtration Rate (eGFR), has become one of the major public health issues globally [1,2]. CKD has been reported to be associated with substantial morbidities and increased all-cause mortalities [3-6]. Besides, Diabetes Mellitus (DM) and Hypertension (HTN) have been recognized as major risk factors of developing CKD with more rapid progression, and both have been reported to be the leading causes of end-stage renal disease in which kidney transplant and hemodialysis therapy are required [7,8]. According to the literature review, it was reported that 20.6 to 39.6% of patients who had DM and 27.5 to 57.5% of patients who had HTN developed CKD [9-14]. Therefore, early diagnosis and treatment for DM and HTN in CKD may retard the disease progression and reduce complication rate.

Galectin-3, a 32 to 35 kDa binding protein with β- galactoside, is predominantly expressed by the epithelium, endothelium and activated macrophage. It was also reported that galectin-3 could be implicated in tissue fibro genesis and inflammatory process [15,16]. In previous studies, galectin-3 was utilized to evaluate the outcomes in patients with cardiovascular diseases such as cardiac hypertrophy and acute heart failure [17,18]. Recent studies indicated that galectin-3 could be independently associated with progressive renal impairment [19,20]. However, the role of galectin-3 in CKD patients who had coexistent DM or HTN remained to be disclosed. In this study, we aimed to investigate the correlation of serum galectin-3 concentration with the staging of CKD and the association of serum galectin-3 level with renal function impairment in CKD patients who had coexistent DM or HTN.

Materials and Methods

Subjects

All blood specimens were obtained for analysis after the participants or one member of their family provided the written informed consent in the study. This investigation involved with 104 participants who were examined in the Outpatient Department of Nephrology, Far Eastern Memorial Hospital (FEMH), from March to December 2015. The clinical data were reviewed in detail via the electronic medical record, including patient age, gender, CKD staging (if the patient was diagnosed as CKD), and history of DM, HTN, cancer, Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), viral hepatitis and cirrhosis. One subject who had an eGFR of 60 mL/min per 1.73 m2 and more or had no proteinuria for at least 3 months was regarded as the non-CKD group, according to the Modification of Diet in Renal Disease (MDRD) study equation [eGFR = 186 x (serum creatinine)-1.154 x age-0.203 x (0.742, if female) x (1.212, if African American)] [21]. The CKD patient who had persistent proteinuria and an eGFR less than 60 mL/min per 1.73 m2 for more than 3 months was assigned to the CKD group. Additionally, those who had experienced acute kidney injury in recent 3 months or had established diagnosis of diseases associated with tissue fibrosis such as cancer, CHF, COPD, viral hepatitis or cirrhosis were excluded from the study. The study was approved by the research ethics review committee of FEMH and was supervised by the data safety monitoring board.

Biochemical Analysis and Galectin-3 Assay

The serum was separated from the whole blood specimens and preserved at -80°C until analysis. The serum creatinine level was measured by the Jaffe's method using an automated chemistry analyzer (Hitachi 911, Roche, Minnesota, USA) with calculation of eGFR on the basis of MDRD equation as described above. Besides, the concentration of serum galectin-3 was determined by an enzyme linked fluorescent assay system (VIDAS®bioMérieux, Marcy-l'Etoile, France) according to manufacturer's instructions [22].

Statistical Analysis

Statistical analysis was performed using SPSS (version 19.0; SPSS Inc., Chicago, USA) statistical software. All data were presented as the mean±standard deviation. The data were analyzed and compared by unpaired and two-tailed student's t- test, and multiple comparisons were performed by one-way Analysis of Variance (ANOVA). The Pearson's correlation coefficient was also calculated to estimate the correlation of two variables. The P value less than 0.05 was considered as statistically significant.

Results

The demographic characteristics of the subjects with and without CKD were listed in (Table 1).

Variables	Non-CKD group	CKD group	P value
Age (year)	66.7±12.2	66.5±12.0	0.932
Gender (male/female)	13/26	40/25	
Coexistent disorders			
Diabetes mellitus (n)	18	43	
Hypertension (n)	16	55	
Serum creatinine (mg/dL)	0.78±0.19	2.81±1.95	<0.001
eGFR (mL/min per 1.73 m2)	84.0±11.3	29.0±15.4	<0.001

Serum glucose (mg/dL)			
Diabetes mellitus	158.3±48.4	151.1±63.3	0.668
Non-diabetes mellitus	97.2±6.9	99.9±11.3	0.364
Serum galectin-3 (ng/mL)	16.8±6.5	32.9±18.2	<0.001
Data were presented as the mean±standard deviation. CKD: Chronic Kidney Disease; eGFR: estimated Glomerular Filtration Rate.			

Table 1: The demographic features of subjects with and without chronic kidney disease.

A total of 104 participants, including 65 CKD patients and 39 non-CKD subjects, were registered in the study. Of these participants, 61 had established diagnosis of DM under oral antihyperglycemic therapy or insulin treatment with regular follow-up of blood glucose and glycated hemoglobin levels, and 71 had HTN under antihypertensive agent use with periodical record of blood pressure. Among the 65 CKD patients, 29 were stage 3, 24 were stage 4, and still 12 were stage 5 without hemodialysis or peritoneal dialysis. Compared with the non-CKD group, the serum creatinine (0.78±0.19 vs. 2.81±1.95 mg/dL, P<0.001) and galectin-3 levels (16.8±6.5 vs. 32.9±18.2 ng/mL, P<0.001; (Figure 1).

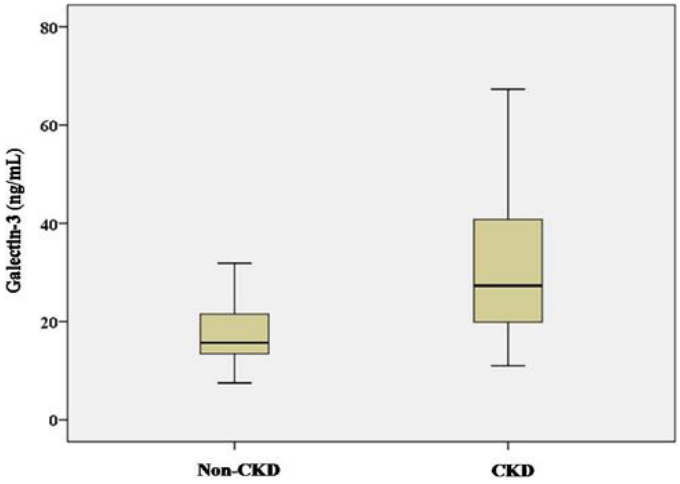

Figure 1: The serum galectin-3 level in the subjects without Chronic Kidney Disease (CKD) and patients with CKD. The serum galectin-3 concentration was significantly higher in the CKD patients than the non-CKD subjects (32.9±18.2 vs. 16.8±6.5 ng/mL, P<0.001).

were significantly increased and the eGFR was significantly decreased (84.0±11.3 vs. 29.0±15.4 mL/min per 1.73 m2, P<0.001) in the CKD group. Our data revealed that the serum galectin-3 level was significantly correlated with the serum creatinine concentration (r=0.630, P<0.001) and inversely with the eGFR (r=-0.613, P<0.001). Additionally, the change observed among all participants in the study from the non-CKD subjects to stage 3, 4 and 5 CKD patients was shown in (Figure 2).

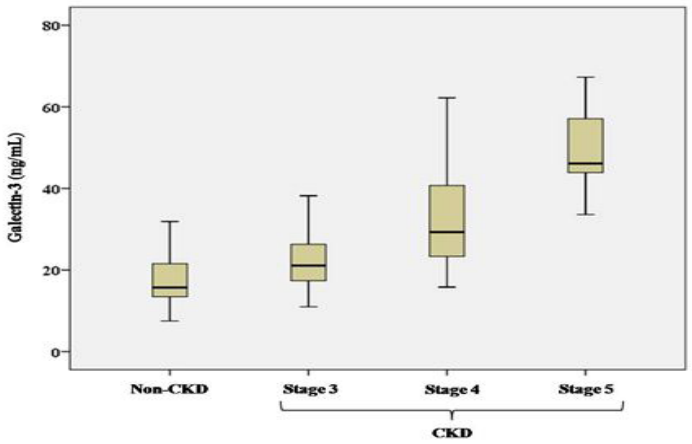

Figure 2: The serum galectin-3 level in the subjects without Chronic Kidney Disease (CKD) and patients with CKD. The serum galectin-3 concentrations were 24.3±15.8, 34.6±18.4 and 48.9±10.1 ng/mL in stage 3, 4 and 5 CKD, respectively; and the serum galectin-3 expression was significantly increased with CKD stage progression (P=0.023).

The serum galectin-3 concentrations were 24.3±15.8, 34.6±18.4 and 48.9±10.1 ng/mL in stage 3, 4 and 5 CKD, respectively, indicating that the level of serum galectin-3 was significantly increased with CKD progression (P=0.023). As shown in (Figure 3),

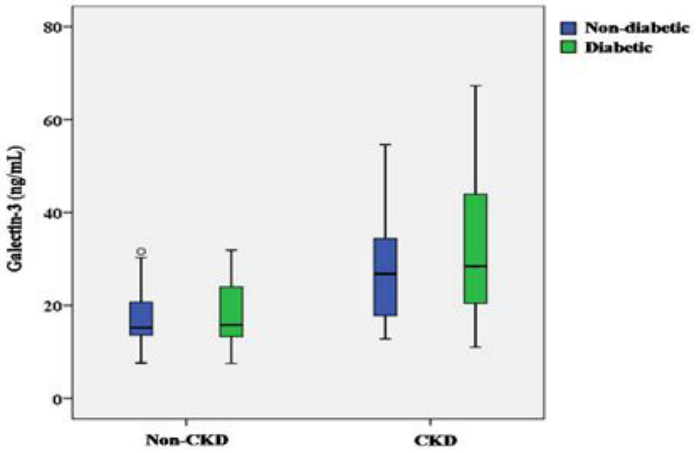

Figure 3: The serum galectin-3 concentration in the subjects without Chronic Kidney Disease (CKD) and patients with CKD who had coexistent Diabetes Mellitus (DM) or not. The serum galectin-3 concentration was slightly higher in the CKD patients with coexistent DM than those without, and no statistical significance was identified (33.8±18.1 vs. 30.9±18.7 ng/mL, P=0.547).

the serum galectin-3 concentration was slightly higher in the CKD patients with coexistent DM than those without (33.8±18.1 vs. 30.9±18.7 ng/mL, P=0.547). Furthermore (Figure 4).

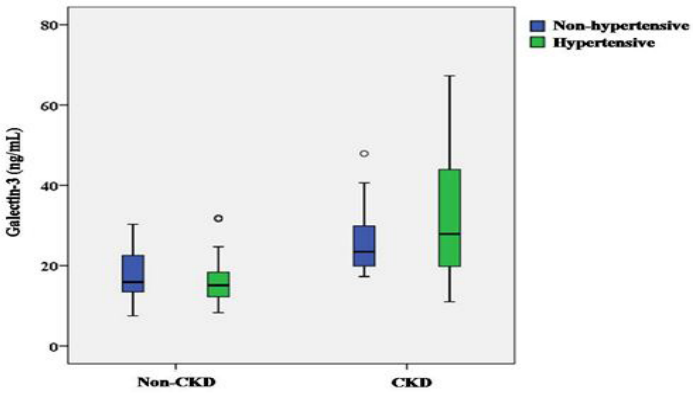

Figure 4: The serum galectin-3 concentration in the subjects without Chronic Kidney Disease (CKD) and patients with CKD who had coexistent Hypertension (HTN) or not. The serum galectin-3 concentration was higher in the CKD patients with coexistent HTN than those without, but there was no statistical significance (33.9±19.2 vs. 26.9±10.1 ng/mL, P=0.265).

revealed that the level of serum galectin-3 was seemingly higher in the CKD patients with coexistent HTN than those without (33.9±19.2 vs. 26.9±10.1 ng/mL, P=0.265).

Discussions

Our main finding indicated that the concentration of serum galectin-3 was significantly higher in the CKD patients than in the non-CKD subjects. Additionally, the serum galectin-3 level was significantly correlated with the serum creatinine concentration as well as inversely correlated with eGFR, indicating the correlation of serum galectin-3 level with the staging of CKD. Our results also revealed that the concentration of serum galectin-3 was higher in the CKD patients who had coexistent DM or HTN than the non-CKD subjects with DM or HTN, though no statistical significance was found. There was a significant correlation between the serum galectin-3 level and age as well as risk factors of cardiovascular disease, including tobacco use, hypercholesterolemia, HTN and DM [23]. The increased expression in serum galectin-3 preceded the development of a spectrum of diseases, including heart failure, pneumonia, sepsis and renal diseases [24]. It was also reported that serum galectin-3 level was inversely correlated with the eGFR in humankind, and elevated serum galectin-3 expression could be associated with increased risk of incident CKD and all-cause mortality, rather than the risk of incident proteinuria [19,23]. Over these decades, the role of galectin-3 in inflammation and fibrosis had been clarified, but the detailed mechanism remained to be elucidated. According to the literature review, galectin-3 is mainly synthesized and secreted by the activated macrophages and plays a pivotal role in the modulation of inflammatory and fibrogenic pathways in renal tissue injury [25].

In the renal tissue of non-CKD subjects, galectin-3 was identified in the distal tubules instead of the glomeruli. Interestingly, the galectin-3 expression was remarkably enhanced in the glomeruli accompanied with increased macrophages in the tubules of DM-associated renal disease rather than other types of nephropathy [26]. Besides, upregulation of galectin-3 was observed in the rodent model of diabetic nephropathy [27]. The galectin-3 overexpression could subsequently exert direct effects on tissue modeling via the Advanced Glycosylation End Product (AGE) receptor-mediated signaling pathway by modulating the function of the AGE receptor complex, which could be a key regulator in the pathogenesis of end-organ damage [28]. In contrast, still another study indicated that galectin-3 ablation progressed diabetic glomerulopathy as the accumulation of AGE in the renal tissues was identified in the galectin-3/AGE receptor knockout animal model [29,30]. The role of galectin-3 could be complex and tissue/disease-specific in the pathogenesis, for which further research is needed.

It was also reported that the renal galectin-3 expression was markedly enhanced in the HTN-derived nephropathy [31]. In a rodent model of HTN, it was observed that the deterioration of renal function was accompanied with increased expression of proinflammatory markers such as interleukin-6 and monocyte chemoattractant protein-1, and profibrotic mediators like α-smooth muscle actin and tissue inhibitor of metalloprotein-1 in the kidney [31]. Furthermore, it was observed that inhibition of galectin-3 effectively retarded the progression of hypertensive nephropathy via the suppression of inflammatory cytokines and profibrotic factors, suggesting the role of galectin-3 as a therapeutic target in the HTN-related renal disease.

There are several limitations in our study. First of all, the methodology of creatinine measurement in the study was the Jaffe's method instead of the Isotope Dilution Mass Spectrometry (IDMS), which may lead to overestimation of serum creatinine and therefore underestimation of eGFR. Secondly, since the calculation of eGFR was based on the MDRD equation in the study, the value of eGFR could be less accurate in those who had a slightly higher serum creatinine level or a serum creatinine concentration within the reference range. Besides, the detection of serum galectin-3 concentration only was not specific for renal system and could potentially reflect other profibrotic situations, leading the association to be disclosed with certain bias. Although participants with known fibrotic diseases such as cancer, COPD, CHF, viral hepatitis and cirrhosis were not eligible for the study, the profibrotic conditions could not be totally excluded in cases that diagnosis of such profibrotic disorders had not been established. Furthermore, the lack of follow-up investigation at the progression of CKD and its related comorbidities as well as the periodical measurements of serum galectin-3 concentration accompanied with the limited case number were also limitations in our study.

To summarize, the serum galectin-3 expression was remarkably elevated in CKD patients compared with those who had no CKD. The serum galectin-3 level was also significantly correlated

with the serum creatinine concentration and inversely correlated with the eGFR. Besides, the serum galectin-3 level was seemingly higher in the CKD patients in coexistence with DM or with HTN than those who had DM or HTN without nephropathies. These results indicated that serum galectin-3 level was significantly associated with the progression of CKD, which was not affected by the coexistent DM or HTN.

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