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LABORATORY STUDY

The association of serum-free light-chain levels with markers of renal function

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Abstract

Background: The kidney is often affected in plasma cell dyscrasias, usually due to the effects of nephrotoxic monoclonal-free light chains. Renal failure due to a monoclonal gammopathy may be detected by the highly sensitive serum-free light-chain (sFLC) ratio yet missed by electrophoretic assays. The aim of this study was to assess sFLC levels in relation to markers of renal function. *Methods*: Five-hundred thirteen patients were included in this study. sFLC levels were measured by Freelite® (The Binding Site Group Ltd, Birmingham, UK) assay using the BNII nephelometer (Siemens Diagnostics, Germany). Kappa/lambda (κ/λ) sFLC ratio was calculated. Serum creatinine levels were analyzed by modified Jaffe method in Cobas 8000 analyser. GFR was estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Patients were assigned to two groups depending on their eGFR values: $\leq$60 mL/min/1.73 m^2 (Group 1, $n = 103$) and >60 mL/min/1.73 m^2 (Group 2, $n = 410$). Data were expressed as median and min–max. All the statistical analyses were done with SPSS version 20.0 and a significance level of 0.05 was considered. *Results*: Serum κ-FLC median value was 36.4 (5.62–16,000) mg/L, serum λ-FLC was 21.7 (4.91–8770) mg/L, κ/λ sFLC ratio was 1.33 (0.01–3258) and serum creatinine was 1.56 (0.63–7.21) mg/dL in Group 1. Both λ sFLC and κ/λ sFLC ratios were correlated with eGFR ($r = -0.318$, $r = 0.198$, $p < 0.05$, respectively). We did not find any significant correlation between κ/λ sFLC ratio and eGFR in Group 2. *Conclusions*: We examined the association between sFLC concentrations and renal function. Our preliminary findings suggest that serum λ-FLC might be considered as a useful marker for predicting renal function. Prospective studies are needed to clarify the usefulness of these parameters for identifying renal failure due to a monoclonal gammopathy.

Keywords

Kappa sFLC, lambda sFLC, renal function, serum-free light chains, sFLC ratios

History

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Introduction

Free light chains (FLCs) are produced during excess immunoglobulin synthesis and are removed from the serum by the kidneys.[1] Abnormal concentrations of sFLC may result from a number of clinical situations including reduced renal clearance, or monoclonal plasma cell proliferative disorders. The molecular weight of both of the light chains is ~22.5 kDa. But the lambda (λ) light chain is covalently bound as a dimer while the kappa (κ) light chain is a monomer. These differences lead to different glomerular filtration rates of the light chains. FLCs were filtered through the glomeruli in the kidney nephrons and then metabolized after reabsorbtion in the proximal tubules. Under normal conditions, very little FLCs were excreted in the urine because of the short half-life of sFLC which are cleaned quickly by renal tubular reabsorption and then is rapidly metabolized in the proximal tubule.[2–6] A decrease in the GFR is associated with an increase in sFLC levels.

The kidney is frequently affected in plasma cell dyscrasias, due to the nephrotoxic effects of FLCs. Monoclonal-free light chains (FLCs) generally cause rapid progressive renal failure in patients with multiple myeloma. Serum from patients with either polyclonal hypergammaglobulinemia or renal impairment often have elevated κ-FLC and λ-FLC due to increased synthesis or reduced renal clearance. However, the κ/λ FLC ratio (rFLC) usually remains normal in these conditions. A significantly abnormal rFLC should only be due to a plasma proliferative (or lymphoproliferative) disorder that secretes excess FLC and disturbs the normal balance between κ and λ secretion.[5–12]

The development of a sensitive immunoassay for serum-free light-chain (sFLC) determination has improved the diagnosis of monoclonal gammopathy. However, metabolism of FLC largely depends on renal function which could lead to misinterpretation of results. Previous work, however, has demonstrated that, in patients with renal failure, the FLC ratio can be increased above normal with no other evidence of monoclonal proteins suggesting that in this population, the

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Table 1. Patient demographic and biochemical data.

	Median (min–max)	
	Group 1 (GFR ≤ 60, $n = 103$)	Group 2 (GFR > 60, $n = 410$)
Age (years)	69 (40–85)	60 (19–83)
Creatinine (mg/dL)	1.56 (0.63–7.21)	0.77 (0.29–1.74)
eGFR (mL/min)	40 (8–60)	93 (61–135)
Free kappa (mg/L)	36.4 (5.62–16,000)	20.8 (5.34–16,000)
Free lambda (mg/L)	21.7 (4.91–8770)	16.4 (4.91–1700)
κ/λ ratio	1.33 (0.01–516.02)	1.24 (0.01–2851.41)

range should be extended (reference range 0.37–3.1). The aim of this study was to assess the relationship between sFLC levels and renal function.

Materials and methods

This retrospective study was conducted with patients over 18 years at Medical Faculty Hospital of Akdeniz University. The study included 513 patients that came to the hospital during the year 2013. Blood samples were taken from patients by centrifugation at 4000 rpm for 5 min. The obtained serum was stored at −80 °C until the analysis. sFLC levels were measured by Freelite® (The Binding Site Group Ltd, Birmingham, UK) assay using the BNII nephelometer (Siemens Diagnostics, Marburg, Germany). In addition, κ/λ sFLC ratio was calculated. The normal serum reference ranges that were used have been reported as κ 3.3–19.4 mg/L, λ 5.71–26.3 mg/L and κ/λ ratio 0.26–1.65. But, in patients with renal impairment, it is recommended to interpret the results of the κ/λ ratio with a modified reference range of 0.37–3.1.

Serum creatinine levels were analyzed by modified Jaffe method in Cobas 8000 analyser (Roche, Mannheim, Germany). GFR was estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[13] Patients were assigned to two groups depending on their eGFR values. Group 1 has 103 patients with chronic renal failure (GFR ≤ 60 mL/min/1.73 m^2) and Group 2 has 410 patients without renal impairment (GFR > 60 mL/min/1.73 m^2). Data were expressed as median and min–max.

Statistical analysis

All statistical analyses were done with SPSS version 20.0 (Chicago, IL) and Spearman's rho correlation test was used for correlation analysis. Statistical significance was set at a p value of <0.05.

Results

Patient demographic and biochemical data are shown in Table 1. Mean age of patients was 62 (19–85) years. Among the 513 patients, eGFR values of 103 patients were found as ≤60 mL/min/1.73 m^2. Although the sFLC concentrations and κ/λ ratios were observed higher in Group 1 patients, these findings did not show any significance.

Correlation analysis showed that there was a positive correlation between λ sFLC and creatinine in Group 1 patients ($p = 0.008$, $r = 0.260$) and a negative correlation between eGFR ($p = 0.001$, $r = -0.318$). We found that κ/λ ratio was negatively correlated with creatinine ($p = 0.007$, $r = -0.263$), and positively with eGFR ($p = 0.046$, $r = 0.198$). Table 2 shows the significant correlation in Group 1 patients.

Table 2. Spearman correlation coefficients for λ sFLC, κ/λ ratio, creatinine and eGFR in Group 1 patients.

	Creatinine	eGFR (mL/min)
λ sFLC	0.260**	−0.318**
κ/λ ratio	−0.263**	0.198*

Notes: Correlations are significant at the *0.05 level and **0.001 level.

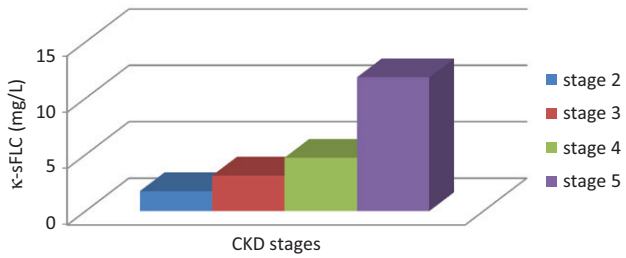

Figure 1. Serum kappa-free light-chain concentrations in Group 1 patients. Kappa sFLC increased dramatically in CKD stages ($p < 0.05$).

In Group 2, there was a positive correlation between age and sFLC levels (for κ $p = 0.001$, $r = 0.169$ and for λ $p = 0.004$, $r = 0.140$, respectively). A positive correlation was found between κ sFLC and creatinine ($p = 0.011$, $r = 0.126$), while κ sFLC was negatively correlated with eGFR ($p = 0.005$, $r = -0.137$). We did not find any significant correlation between κ/λ sFLC ratio and eGFR in Group 2 patients.

Serum parameters were also assessed according to CKD stages in Group 1 patients. For this reason, KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification were used.[14] eGFR values were classified as 60–89 mL/min as Stage 2, 30–59 mL/min as Stage 3, 15–29 mL/min as Stage 4 and <15 mL/min as Stage 5. As shown in Figures 1 and 2, both κ and λ sFLCs rose progressively through CKD stages ($p < 0.05$). κ/λ sFLC ratios were decreased dramatically in CKD stage 5 ($p < 0.05$) (Figure 3).

Discussion

Elevated polyclonal FLCs in serum result from increased polyclonal production, reduced renal clearance or a

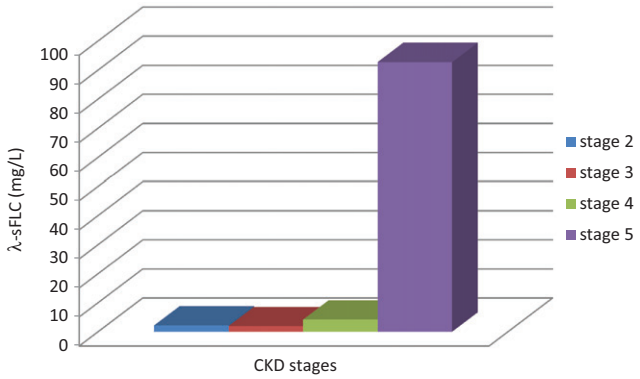

Figure 2. Serum lambda-free light-chain concentrations in Group 1 patients. Serum-free lambda light chains increased progressively with each CKD stage ($p < 0.05$).

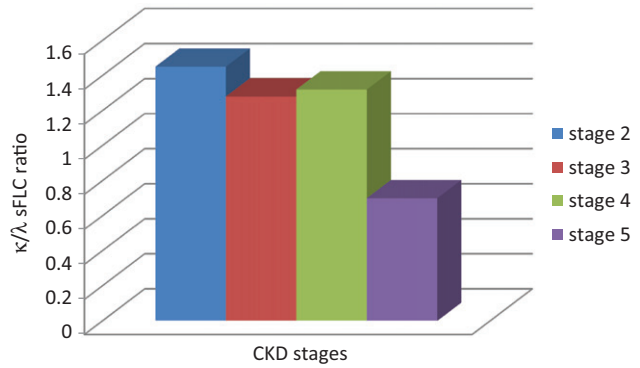

Figure 3. Serum-free kappa/lambda ratio in Group 1 patients. Serum-free kappa/lambda ratio decreased dramatically in CKD stage 5 ($p < 0.05$).

combination of both mechanisms. Reduced clearance of sFLCs results from impaired renal GFR.[6] There are limited data concerning the use of FLC assays in patients with renal disease. Preliminary analysis of follow-up data from a prospective cohort of 1394 patients with CKD indicated that summation of free κ plus free λ concentrations was prognostic for all causes of mortality and change in GFR.[15] Hutchison et al. suggested that the combined FLC concentrations had greater prognostic value than the creatinine-based CKD staging system. The principal causes of death associated with high FLC concentrations were cardiovascular disease, infections and cancer.[6–15]

Nowrousian et al.[16] were found to increase the serum and urinary FLC concentrations with renal failure in their study. Serum FLC concentrations may change in different renal pathologies, especially renal patients with diabetes may show higher concentrations. On the other hand, most patients with chronic inflammatory diseases and associated renal impairment have high concentrations of polyclonal FLCs, but with substantially normal κ/λ ratio.[17–20] The clinical study of elevated sFLCs in renal impairment are unclear. Reports have suggested that the elevated FLCs lead to reductions in immune function and therefore should be classified as uremic toxins.[6] In line with these studies, we investigated whether there is a difference between sFLC levels in patients with and without kidney disease and compared the results with eGFR values. Although the sFLC concentrations and κ/λ ratios were observed higher in Group 1 patients, these findings did not show any significance in our study. However, our findings suggested that only λ sFLC levels were shown to be more significantly correlated with renal function.

κ-FLC is generated twice as fast as λ-FLC, but λ-FLC forms dimers and doubles its molecular weight and slows the renal clearance.[21] Thus, in the patients with kidney disease, FLC increases in serum due to the decrease in the urinary excretion because of reduced renal clearance. The reason for this may be – λ created larger molecules than κ due to the λ formed dimers and pass into the bloodstream with a decrease in urinary excretion.

In this study, we have examined the relationship between sFLC levels and renal function. It is important to observe that κ/λ ratios slightly decreased in patients according to CKD stages. These findings may indicate that λ sFLC levels increase with progression of kidney disease. Therefore, λ sFLC monitoring may be a useful predictor for the determination of decline in GFR. On the other hand, there are limited data concerning the reference ranges of sFLC in patients with renal disease. More detailed studies are needed for the assessment of these different reference ranges and the predicting role of sFLCs in renal disease.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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