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Prevalence and clinical significance of abnormal serum kappa/lambda light chain ratio in patients with chronic kidney disease

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KEY WORDS

chronic kidney disease, free light chains, multiple myeloma, nephrotic syndrome, proteinuria

ABSTRACT

INTRODUCTION A range of malignant diseases (both solid organ tumors and hematogenous malignancies) may manifest as proteinuria/nephrotic syndrome. Multiple myeloma (MM) typically involves the kidneys and proteinuria, and chronic kidney disease (CKD) may also be the first manifestation of MM.

OBJECTIVES The aim of the study was to evaluate the prevalence and clinical significance of abnormal serum free kappa/lambda light chain ratio in patients referred to a renal center for a diagnostic workup for proteinuria or CKD of an unknown origin (or both).

PATIENTS AND METHODS Free light chain tests were performed in 92 consecutive patients (mean age, 63 ±13.9 years; women, 38%; men, 62%) using FreeLite kits. In addition, serum creatinine, calcium, and albumin levels as well as estimated glomerular filtration rate (eGFR) were measured and blood count and proteinuria were assessed. In 39 patients, kidney biopsy was also performed. Nephrotic syndrome was found in 38% of the patients; nonnephrotic proteinuria, in 39.1%; and isolated reduction of eGFR (without proteinuria), in 22.9%.

RESULTS MM was confirmed in 5 patients (5.43%; all patients had a highly abnormal kappa/lambda ratio). After the exclusion of the subjects with MM, the abnormal kappa/lambda ratio was found in 37 patients (42.5%); MM was excluded in all patients after careful hematological evaluation, including bone marrow biopsy in 12 cases. The percentage of the abnormal kappa/lambda ratio was high regardless of the proteinuria level, eGFR, or the type of glomerulopathy diagnosed by kidney biopsy. The kappa/lambda ratio did not correlate with age, proteinuria, or eGFR.

CONCLUSIONS Our results suggest that an abnormal kappa/lambda ratio (in most cases higher than normal) is a common and, most likely, nonspecific finding in patients with proteinuria or CKD of an unknown origin (or both).

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INTRODUCTION Proteinuria is the key feature of primary and secondary glomerular disease. The diagnosis of primary glomerulopathy is to a large extent based on the exclusion of several systemic (extrarenal) disorders that may also involve the kidney. These include, among others, metabolic diseases (with diabetes as the leading one), amyloidosis, autoimmune and infectious diseases, and malignancies. Therefore, an extensive diagnostic workup is needed in patients with proteinuria (especially elderly patients and those with comorbidities) to identify the cause of glomerular involvement secondary to other diseases or—after the exclusion of these causes—to consider the glomerular disease as primary.[1]

Several malignancies may be associated with different types of glomerular disease. One of the best known associations is a link between certain types of cancer (including breast, bowel, and bronchial cancer) and membranous nephropathy.

TABLE 1 Demographic and clinical characteristics of the study group (n = 92)

Parameter	Value
age, y	63 ±13.9
sex, male/female	57 (62) / 35 (38)
diabetes	28 (30.4)
hypertension	63 (68.5)
coronary artery disease	13 (14.1)
renal syndromes on admission	
nonnephrotic proteinuria	35 (38)
nephrotic syndrome	36 (39.1)
CKD of unknown origin	21 (22.8)

Data are presented as number (percentage) of patients or mean ± standard deviation.

Abbreviations: CKD, chronic kidney disease

In fact, at least in case reports, most (if not all) of the existing malignancies were described to coexist with glomerulopathy. The cause–effect relationship between malignancy and glomerular disease is difficult to establish: a neoplasm may precede glomerular manifestation and possibly trigger proteinuria; a simple coincidence between kidney disease and malignancy is possible (without any pathophysiological relationship); and, finally, glomerular disease (in particular, its immunosuppressive treatment) may predispose to malignancy during follow-up.[2]

There is no standard algorithm to search for malignancy in patients with proteinuria. Several authors recommend the "common-sense" approach, which includes: colonoscopy, gastroduodenoscopy (especially in patients over 50 years of age), mammography (in patients over 40 years of age), chest radiography, a digital rectal examination to assess the size of the prostate, and a urological consultation. Other tests, imaging procedures, and consultations may be necessary in the case of suggestive clinical data.[1]

Multiple myeloma (MM) is the second most common hematological malignancy with an annual incidence in Europe and United States of about 4 to 6 cases per 100 000 population, commonly involving the kidneys. The cause–effect relationship between MM and renal disease is well established: monoclonal light chains interact with several nephron structures, which results in a range of kidney manifestations.[3] The assessment of serum and urine levels of free light chains (FLC) with the kappa/lambda ratio is considered a milestone in the detection of clonal plasma cell proliferation. This diagnostic method allowed to identify patients with MM at earlier stages before such classic manifestations as osteolytic bone lesions, advanced renal failure, or significant anemia (together known as CRAB) develop. However, the value of FLC assessment as part of routine differential diagnosis in patients with proteinuria of unknown origin has not been studied. To the best of our knowledge, no study has investigated the prevalence of an abnormal kappa/lambda ratio in patients referred to a renal center for the diagnosis of proteinuria or chronic kidney disease (CKD) of unknown origin (or both) and are not suspected of MM on admission.

The aim of the study was to analyze the prevalence of the abnormal kappa/lambda ratio and its clinical significance in patients referred to a renal center because of proteinuria or CKD of an unknown origin (or both).

PATIENTS AND METHODS The initial study group consisted of 126 consecutive patients with proteinuria or CKD of unknown origin (or both) referred to a renal center for further diagnostic workup, including kidney biopsy. Nephrotic syndrome was defined as 24-hour proteinuria of 3.5 g or more; nonnephrotic proteinuria, as 24-hour urine protein loss ranging between 0.3 and 3.5 g (regardless of estimated glomerular filtration rate [eGFR]), and CKD of unknown origin, as isolated (ie, without proteinuria) reduction of eGFR to less than 60 ml/min/1.73 m^2. Serum free kappa and lambda light chains were assayed in all patients fulfilling the above criteria. We excluded patients with a prior diagnosis of renal disease and those with known or suspected MM or other hematological or solid organ malignancy. Subjects with confirmed secondary glomerular nephropathy (related to diabetes, lupus, or antineutrophil cytoplasmic antibody-associated small-vessel vasculitis), patients with CKD stage 5 (eGFR of less than 15 ml/min/1.73 m^2) at the time of the study, or kidney transplant recipients were also excluded. The final study group consisted of 92 patients. Their demographic and clinical characteristics (including major comorbidities) are shown in TABLE 1. In all patients, standard biochemical parameters were measured, including serum sodium, potassium, creatinine, urea, calcium, total protein, and albumin levels (Cobas C 6000 Analyser, Roche Diagnostics, Basel, Switzerland). In this analyzer, serum creatinine concentrations are measured using the Jaffe method. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease formula. Urinalysis with quantitative proteinuria and peripheral cell counts were also performed in all subjects (LAURA, Erba – Lachema, Brno, Slovakia and Sysmex XT 1800i, Norderstedt, Germany, respectively). FLCs were assayed using FreeLite kits (Binding Site, San Diego, California, United States) and Cobas C 6000 Analyser. Depending on clinical indications, patients were also subjected to bone marrow or kidney biopsy.

RESULTS In 5 patients (5.43%), the kappa/lambda ratio was lower than normal, and in 37 (39.1%), it exceeded the reference value; after the exclusion of 5 patients with MM (see below), the respective numbers were 4 (4.6%) and 33 (37.9%). All patients with an abnormal kappa/lambda ratio were formally evaluated by a hematologist, which resulted in 17 bone marrow biopsies. In 12 cases, bone marrow biopsies were considered nonspecific (ie, did not fulfill the criteria of any

TABLE 2 Comparison of the kappa/lambda ratio and other clinical parameters between patients with and without multiple myeloma

Parameter	Reference range	MM+ n = 5	MM– n = 87
age, y	NA	67 ±11.8	63 ±13.89
kappa/lambda ratio	0.26–1.65	see below[b]	1.92 ±3.13
serum creatinine, mg/dl	0.5–0.9	1.57 ±0.98	1.68 ±0.81
eGFR[a], ml/min/1.73 m^2	>60	51.42 ±29.58	49.4 ±25.9
calcium, mg/dl	8.6–10.2	9.0 ±3.19	9.06 ±0.92
phosphate, mg/dl	2.7–4.5	3.64 ±0.9	3.70 ±0.7
albumin, g/24 h	32.0–52.0	29.38 ±8.82	29.5 ±9.7
urine protein, g/24 h	0.0–0.3	3.62 ±8.63	3.27 ±3.94
nephrotic syndrome	N/A	3 (3.3)	33 (35.9)
Hb, g/dl	12.0–16.0	11.9 ±2.04	11.9 ±2.18
PLT count, µl^{-1}	150–400	280 ±62.3	261 ±99.4

Data are presented as a number (percentage) of patients or mean ± SD.

a detailed distribution of ranges shown in TABLE 4
b 5 individual values were: 0.02, 199.4, 387, 968, and 12 479

Abbreviations: eGFR, estimated glomerular filtration rate; Hb, hemoglobin; NA, not available; PLT, platelet; SD, standard deviation

TABLE 3 Serum free kappa/lambda ratio in the study group (n = 87, after exclusion of patients with multiple myeloma) depending on renal syndrome on admission

Renal syndrome	n (%)	Urine protein g/24 h mean ± SD	Kappa/lambda ratio mean ± SD	Above normal range n (%)	Below normal range n (%)
nephrotic syndrome	33 (37.9)	7.35 ±3.57	1.64 ±2.08	11 (33.3)	3 (9.1)
nonnephrotic proteinuria	33 (37.9)	1.26 ±0.85	1.48 ±0.55	12 (36.4)	1 (3)
CKD of unknown origin	21 (24.1)	0.035 ±0.078	3.07 ±5.62	10 (47.6)	0

Abbreviations: see TABLES 1 and 2

TABLE 4 Serum free kappa/lambda ratio in the study group (n = 87, after exclusion of patients with multiple myeloma) depending on glomerular filtration rate

eGFR, ml/min/1.73 m^2	n (%)	eGFR, ml/min/1.73 m^2	K appa/lambda ratio	Above normal range n (%)	Below normal range n (%)
>90	7 (8)	103.4 ±11	1.28 ±0.56	1 (14.3)	0
60–90	17 (19.5)	77.3 ±6.76	2.84 ±6.35	4 (23.5)	2 (11.8)
30–60	37 (42.5)	45.21 ±9.03	1.47 ±0.55	13 (35)	1 (2.7)
15–30	26 (30)	22.52 ±4.32	2.13 ±2.22	15 (57.7)	1 (3.85)

Abbreviations: see TABLE 2

hematological pathology); the diagnosis of MM was established in 5 cases (5.43%). The clinical and biochemical characteristics of the patients with respect to the diagnosis of MM (we included parameters that are particularly important in patients suspected of MM) are shown in TABLE 2. The values of the kappa/lambda ratio according to renal syndrome on admission and eGFR (after the exclusion of 5 patients with MM) are presented in TABLES 3 and 4. In 39 of 92 patients, kidney biopsy was performed. The distribution of histopathological diagnoses with the respective values of the kappa/lambda ratio and proteinuria is shown in TABLE 5. In 7 subjects, both bone marrow and kidney biopsies were performed (only in 1 patient, MM was found in bone marrow and MM nephropathy in the kidney). The kappa/lambda ratio (after the exclusion of subjects with MM) did not show significant correlations with age, serum creatinine, eGFR, calcium, 24-hour proteinuria, or blood count.

DISCUSSION MM is a hematological malignancy that is frequently observed (and sometimes

TABLE 5 Kappa/lambda ratio according to diagnosis on kidney biopsy (n = 37; after exclusion of 2 patients with multiple myeloma)

	n (%)	Kappa/lambda ratio	Above normal range n (%)	Below normal range n (%)	Proteinuria, g/24 h	eGFR, ml/min/1.73 m^2
FSGS	8 (21.6)	1.43 ±0.72	3 (37.5)	1 (12.5)	4.17 ±2.92	54.9 ±32.4
IgAN	7 (18.9)	1.53 ±0.54	4 (57.1)	0.0	4.5 ±3.9	43.2 ±19.6
MN	8 (21.6)	1.3 ±0.68	2 (25)	0.0	7.08 ±4.6	70.8 ±17.7
MCN	4 (10.8)	4.05 ±5.06	1 (25)	0.0	5.0 ±2.77	63.8 ±34.8
pauci-immune crescentic GN	2 (5.4)	2.42 ±0.28	2 (100)	0.0	0.0 ±0.0	58.5 ±27.4
AA amyloidosis	3 (8.1)	0.79 ±0.68	1 (33.3)	1 (33.3)	7.5 ±7.05	56.7 ±20.8
other[a]	5 (13.5)	1.23 ±0.3	1 (20)	0.0	5.17 ±5.58	67.8 ±29.4

a mesangioproliferative pattern of injury (2 cases); non-specific lesions (3 cases)

Abbreviations: FSGS, focal/segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, IgA nephropathy; MCN, minimal change nephritis; MN, membranous nephropathy; others, see TABLE 2

overlooked) by specialists other than hematologists (orthopedists, neurologists and neurosurgeons, nephrologists, etc.) owing to its multisystemic involvement and manifestations. Patients with MM are referred to a renal center because they frequently have decreased eGFR and proteinuria—renal involvement on diagnosis is present in more than 50% of the patients.[3] We were able to confirm 5 cases of MM among 92 patients (5.43%) referred to our department for diagnosis of proteinuria or CKD of unknown origin. Importantly, we did not suspect MM in any of those patients before we started our diagnostic procedures. A direct comparison of our data with other studies is difficult because we did not identify a study using a similar methodological approach in the literature. Most of large kidney biopsy registries do not report MM nephropathy as a separate diagnosis; it can be found only in a few reports, with a prevalence of 1% to 3%. This percentage may be higher when elderly patients or special indications for biopsy are considered.[4-7] Given the fact that almost all types of renal involvement may be identified in the course of MM (including minimal change disease, membranoproliferative pattern, different forms of tubulointerstitial injury, etc.), MM-related nephropathy may be concealed by these and other histopathological diagnoses or classified as "other".[8,9] The percentage of patients suffering from MM in our group roughly corresponds with these data, although only 1 subject in our study had biopsy-proven MM-related nephropathy. Of note, the proportion of particular diagnoses based on kidney samples in our patients is generally in agreement with large biopsy registries—membranous nephropathy as a leading diagnosis, followed by focal/segmental glomerulosclerosis and IgA nephropathy, might be expected in subjects at a mean age of more than 60 years.

None of our patients (including 5 patients with confirmed MM) was suspected of hematogenous malignancy on referral to our department. Our results are in line with data reported by other authors. Li et al.[10] analyzed the prevalence of renal involvement among patients with non-Hodgkin lymphoma in large renal pathology archives and found that only 10% of the patients subjected to kidney biopsy for proteinuria of unknown origin were aware of their hematological condition at the time of the biopsy. Kowalewska et al.[11] reported that 20% of patients who were diagnosed with a renal manifestation of different lymphoplasmatic neoplasms on renal biopsy were aware of the malignancy at the time of the biopsy. Lymphoplasmacytic neoplasm-related glomerular involvement was found by these authors only in 0.5% of all biopsies in their database. These data indicate that although renal involvement in MM is common and reaches 50% of the cases, the prevalence of this pathology in renal biopsy registries (which include all patients who undergo biopsy for any reason) is relatively low.

We did not identify any studies that examined the prevalence of an abnormal kappa/lambda ratio in an unselected group of patients referred for a diagnostic workup for proteinuria or CKD of unknown origin (or both). The absolute values of the kappa/lambda ratio in patients with MM were significantly lower (1 patient, 0.02) or higher (4 patients, 199.4, 387, 968, and 12 479) than normal. However, these patients did not differ from the remaining patients in terms of eGFR, serum calcium levels, hemoglobin levels, or platelet count. More interestingly, most patients without MM were characterized by an abnormal (in most cases, above normal) kappa/lambda ratio (although the absolute values were relatively low). The ratio tended to increase with higher CKD stages and was highly prevalent in all types of renal pathology found on renal biopsy. Since careful hematological assessment (with bone marrow biopsy in some cases) excluded the presence of any hematological malignancy in 37 patients (88.1%) with an abnormal kappa/lambda ratio, we may conclude that the abnormal kappa/lambda ratio, although common, appears to be harmless and of no clinical significance.

FLC testing has become a standard diagnostic method in the evaluation of patients suspected of

MM. The percentage of an abnormal serum kappa/lambda ratio varies between 90% and 100% in patients with MM and is significantly higher compared with patients with monoclonal gammopathy of undetermined significance (30%–45%). The Myeloma Working Group statement on clinical utility of FLC assay in MM does not provide any particular out-of-range (cut-off) value for the kappa/lambda ratio that could be considered more specific or sensitive for the diagnosis of MM.[12] Sthaneshwar et al.[13] demonstrated that a cut-off value of 2.0 has high sensitivity and specificity for confirming MM. As it was shown in another study on sensitivity of light chain assessment in the diagnosis of MM, in the majority of MM patients the kappa/lambda ratio exceeds 100, but there are still patients with confirmed disease and the ratio slightly above the reference range.[14] On the other hand, the lowest ratio in a series of patients with MM evaluated in another study was 36.[15] It seems that any abnormal value of the kappa/lambda ratio may indicate the presence of MM and a need for further diagnostic workup, although the higher the ratio, the higher the probability of finding MM.[16]

In our study, no correlation was found between the kappa/lambda ratio, age, and eGFR. An association between the absolute serum kappa and lambda light chain levels and age has been reported in the literature. Data on the relationship between the kappa/lambda ratio and age are conflicting: it was not observed in a number of studies, while in other studies, the correlation was lost after an adjustment for eGFR.[15,17] In fact, advanced renal failure results in the accumulation of light chains owing to their prolonged half-life; since physiological ability of the kidneys to clear the kappa light chain faster than the lambda light chain is lost, the kappa chain may be accumulated in higher amounts with a slight increase in the kappa/lambda ratio solely due to a markedly reduced eGFR. Nevertheless, the kappa/lambda ratio exceeding 3 is unlikely to be associated only with reduced eGFR.[18] Abnormal kappa/lambda ratio continues to be a sensitive marker of monoclonal gammopathy also in subjects with seve re renal failure who require dialysis, although in those patients specificity of an assay increased when the kappa/lambda ratio increased from a range of 0.26 to 1.65 to a higher range of 0.37 to 3.1.[19]

A high percentage of patients with an abnormal kappa/lambda ratio in our study may result from 2 possible mechanisms: accumulation of FLC secondary to various degrees of reduction in eGFR and unspecific systemic stimulation of the immune system in the course of glomerular disease.

In summary, our study demonstrated that measuring serum FLC levels and calculating the kappa/lambda ratio may help diagnose MM in patients with proteinuria or CKD of unknown origin (or both) who were not initially suspected of this malignancy. The prevalence of an abnormal kappa/lambda ratio is high in patients with proteinuria or reduced eGFR (or both), but this abnormality does not seem to be clinically relevant. A long-term follow-up of patients with an abnormal kappa/lambda ratio is needed to evaluate its true significance.

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Częstość występowania i znaczenie kliniczne nieprawidłowego stosunku łańcuchów lekkich kappa/lambda w surowicy pacjentów z przewlekłą chorobą nerek

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SŁOWA KLUCZOWE

białkomocz, przewlekła choroba nerek, szpiczak plazmocytowy, wolne łańcuchy lekkie, zespół nerczycowy

STRESZCZENIE

WPROWADZENIE W przebiegu wielu chorób nowotworowych (zarówno guzów litych, jak i nowotworów układu krwiotwórczego) może dochodzić do rozwoju białkomoczu / zespołu nerczycowego. Szpiczak plazmocytowy (*multiple myeloma* – MM) typowo przebiega z zajęciem nerek i białkomoczem; jego pierwszą manifestacją może być także przewlekła choroba nerek (PChN).

CELE Celem badania była ocena częstości występowania i znaczenia klinicznego nieprawidłowego stosunku wolnych łańcuchów lekkich kappa/lambda w surowicy u chorych kierowanych do ośrodka nefrologicznego w celu przeprowadzenia diagnostyki białkomoczu i/lub PChN o nieznanej przyczynie.

PACJENCI I METODY Stosunek łańcuchów kappa/lambda oceniono u 92 kolejnych pacjentów (średnia wieku 63 ±13,9 lat; 38% kobiet, 62% mężczyzn) za pomocą zestawów FreeLite. Ponadto dokonano pomiaru stężenia kreatyniny, wapnia i albuminy w surowicy oraz szacowanego wskaźnika przesączania kłębuszkowego (*estimated glomerular filtration rate* – eGFR), a także wykonano morfologię krwi oraz sprawdzono obecność białka w moczu. U 39 pacjentów wykonano także biopsję nerki. U 38% chorych stwierdzano zespół nerczycowy, u 39,1% – białkomocz subnerczycowy, natomiast u 22,9% chorych – izolowane obniżenie eGFR (bez białkomoczu).

WYNIKI U 5 pacjentów (5,43%) potwierdzono obecność MM (wszyscy pacjenci mieli wysoce nieprawidłowy stosunek kappa/lambda). Po wyłączeniu pacjentów z MM nieprawidłowy stosunek kappa/lambda był obecny u 37 (42,5%) badanych; u wszystkich pacjentów wykluczono chorobę po dokładnej ocenie hematologicznej, włączając biopsję szpiku kostnego w 12 przypadkach. Odsetek nieprawidłowych wartości stosunku kappa/lambda był wysoki niezależnie od poziomu białkomoczu, wartości eGFR oraz postaci glomerulopatii rozpoznawanych w oparciu o biopsję nerki. Stosunek kappa/lambda nie korelował z wiekiem, białkomoczem i eGFR.

WNIOSKI Uzyskane wyniki sugerują, że nieprawidłowy (w większości przypadków – powyżej normy) stosunek kappa/lambda jest częstym i zapewne niespecyficznym objawem u pacjentów z białkomoczem i/lub PChN o nieznanej przyczynie.

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