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NEPHROLOGY - ORIGINAL PAPER

Implication of serum growth differentiation factor-15 level in patients with renal diseases

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Abstract

Background The synthesis of growth differentiation factor-15 (GDF-15) is induced by inflammation, hypoxia, and oxidative stress and is receiving great interest as a predictive biomarker for cardiovascular disease. However, its detailed impact on patients with renal disease remains uncertain.

Methods Patients who underwent renal biopsy for evaluation of renal disease between 2012 and 2017 in our institute were prospectively included. Serum GDF-15 levels were measured and its association with baseline characteristics and its impact on the 3-year composites of renal prognosis (composites of > 1.5 folds of serum creatinine and renal replacement therapy) were investigated.

Results A total of 110 patients (64 [42, 73] years old, 61 men) were included. The median serum GDF-15 level at baseline was 1885 (998, 3496) pg/mL. A higher serum GDF-15 level was associated with comorbidities including diabetes mellitus, anemia, renal impairment, and pathologic features including crescent formation, hyaline degeneration, and interstitial fibrosis ($p < 0.05$ for all). Serum GDF-15 level was a significant predictor of 3-year composite renal outcomes with an odds ratio per 100 pg/mL of 1.072 (95% confidence interval 1.001–1.103, $p = 0.036$) after adjustment for potential confounders.

Conclusions Serum GDF-15 levels were associated with several renal pathological features and renal prognosis in patients with renal diseases.

Keywords GDF-15 · Renal disease · Renal biopsy · Renal prognosis

Introduction

The number of patients with chronic kidney diseases due to a variety of renal diseases is increasing, and novel biomarkers are desired to risk stratify the patient cohort for a tailored therapeutic strategy to improve patient mortality and morbidity [1]

Growth differentiation factor-15 (GDF-15) is a member of the proteins assigned to the transforming growth factor-β family. GDF-15 is secreted by various organs, including kidney and heart in the clinical situation of hypoxia, inflammation, and oxidative stress [2]. A synthesis of GDF-15 seems to be a compensatory response to these tissue injuries and GDF-15 seems to have a protective effect upon multiple organs, including heart and kidney [3, 4]. GDF-15 is receiving great concern thus far as a key biomarker to assess the stages of cardiovascular and renal diseases and predict clinical outcomes in patients with these diseases [5–7].

Serum GDF-15 levels are associated with the progression of renal impairment in patients with various etiologies, including chronic kidney disease [6], IgA nephropathy [8], and diabetes mellitus [9]. GDF-15 predicts mortality in hemodialysis patients [10]. In contrast, a decrease in serum GDF-15 levels was observed after kidney transplantation [11].

However, the serum GDF-15 level in each pathological renal disease and its prognostic impact in patients receiving renal biopsy remains uncertain. Such a knowledge would help to design a tailored therapeutic strategy for them. In this study, we investigated the association between serum GDF-15 level and clinical parameters, including pathological features and the impact of serum GDF-15 level on renal

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outcomes in those who underwent renal biopsy for suspected renal disease.

Methods

Patient selection

Consecutive patients with suspected renal disease who underwent renal biopsy at our institute between July 2012 and December 2017 were considered for inclusion in this prospective study. Serum samples for the measurement of GDF-15 levels were obtained from them on the same day of renal biopsy as described below.

Those with proteinuria, hematuria, or renal dysfunction of unknown etiology were considered to undergo renal biopsy. Those with unilateral kidney, multiple polycystic kidney disease, hydronephrosis, uncontrolled systemic disease, urinary tract infection, extensive renal atrophy, and hemostasis abnormality did not receive renal biopsy and were excluded from this study. The final indication for renal biopsy was determined by the multidisciplinary team conference according to its risks and benefits.

The study was approved by the local institutional ethical review board beforehand (ethical review number: R2019121). All patients received informed consent prior to enrollment.

GDF-15 analyses

Blood samples were drawn via intravenous access from all participants and serum samples were stored at −80 °C following centrifugation. Serum GDF-15 concentration was measured by commercially available enzyme-linked immune sorbent assay (Quantikine Human GDF-15, R&D Systems, Minneapolis) in one batch according to the manufacturer's instruction.

Other baseline characteristics

Baseline characteristics including demographics, comorbidity, standard laboratory data, urinary data, and medication data were retrieved. All urine data were collected from spot urine analyses. Retrieved data were adjudicated by the two independent researchers (SK and TK).

Histopathological analyses

All procedures were performed using needle biopsy and the obtained specimen were pathologically assessed. We required at least 10 glomeruli for the diagnosis.

The optical microscopic analyses were performed using hematoxylin and eosin, periodic acid-schiff, periodic acid-silver methenamine, Azan, and Elastica van Gieson stainings, as appropriate. The immunological analyses were performed by fluorescent antibody method using IgG, IgA, IgM, C3, C4, C1q, fibrinogen, and kappa and lambda light chains. The electronic microscopic analyses were also performed if necessary.

The pathological features and their severity were assessed as follows. In the obtained tissue, at least one finding of mesangial cell proliferation, endocapillary proliferation, crescent formation, segmental sclerosis, and hyaline degeneration were assumed to be positive according to the Oxford classification. For example, a patient could have several findings if applicable. Interstitial fibrosis/tubular atrophy was semi-quantitatively assigned to none ($<25\%$), mild ($<50\%$), and severe ($\geq 50\%$). Presence of interstitial cell infiltration, fibrous intimal thickening of interlobular artery were also assessed.

Clinical outcomes

Following the renal biopsy, all patients were followed with guideline-directed medical therapy in a standard manner. Of all, patients who were followed for over 3 years were included in the outcome analyses. A primary outcome was defined as composites of (1) > 1.5-fold increase in serum creatinine levels at the end of observational period and (2) initiation of renal replacement therapy during the observational period.

Statistical analysis

Continuous variables were presented as median and interquartile and compared between the two groups using Mann–Whitney *U* test. Given small sample size, we assumed all continuous variables as non-parametric. Categorical variables were expressed as numbers and percentages and compared between the two groups using Fisher's exact test.

Multivariable linear regression analyses with a stepwise method were performed to investigate the baseline characteristics and pathological findings that were associated with the serum GDF-15 level, respectively. Variables that were significant in the two-group comparison were included as potential confounders in each model, respectively.

Logistic regression analyses were performed to investigate the prognostic impact of serum GDF-15 level on renal outcomes. Potential confounders including age, estimated glomerular filtration rate, and urinary protein were used for the adjustment. Receiver operating characteristics analyses with Youden method were performed to calculate cutoffs of GDF-15 level to predict renal outcomes.

In all analyses, two-tailed $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS Statistics 23 (SPSS Inc, Armonk, IL, USA).

Results

Baseline characteristics

A total of 110 patients were included (Table 1). Median age was 64 (42, 73) years old and 61 (56%) were men. Median estimated glomerular filtration rate was 57.7 (34.9, 77.6) mL/min/1.73 m^2 and 48 patients (44%) were assigned to chronic kidney disease grade 3–5. Median urinary protein was 2.2 (0.7, 5.3) g/g of creatinine.

Pathological findings and diagnosis

All patients received renal biopsy without any complications. Pathological findings and diagnoses are summarized in Table 2.

A major pathological finding was mesangial cell proliferation (48%), followed by hyaline degeneration (41%), segmental sclerosis (32%), and crescent formation (31%). A dominant diagnosis was IgA nephropathy (35%), followed by membranous nephropathy (18%), diabetic nephropathy (15%), and necrotizing glomerulonephritis (10%).

Table 1 Baseline characteristics

	N = 110
Demographics	
Age, years	64 (42, 73)
Men	61 (56%)
Body mass index, kg/m^2	23.6 (20.9, 25.3)
Systolic blood pressure, mmHg	131 (118, 149)
Comorbidity	
Hypertension	59 (54%)
Diabetes mellitus	25 (23%)
Heart disease	15 (14%)
Malignancy	5 (5%)
Medications	
Renin–angiotensin system inhibitors	46 (42%)
Prednisolone	15 (14%)
Laboratory data	
Hemoglobin, g/dL	12.2 (11.0, 13.6)
Serum albumin, g/dL	3.3 (2.6, 4.0)
eGFR, mL/min/1.73 m^2	57.7 (34.9, 77.6)
Serum GDF-15, pg/mL	1885 (998, 3496)
Urinary data	
Protein, g/g of creatinine	2.2 (0.7, 5.3)
N-acetyl-β-D-glucosaminidase, IU/L	12.0 (7.2, 27.3)
β2-microglobulin, IU/L	503 (120, 4197)
Occult blood ≥ 2 +	54 (50%)

eGFR estimated glomerular filtration rate

Continuous variables are stated as median and interquartile. Categorical variables are stated as numbers and percentage

Table 2 Pathological features

	N = 110
Pathological findings	
Mesangial cell proliferation	51 (48%)
Endocapillary proliferation	18 (17%)
Crescent formation	34 (31%)
Segmental sclerosis	35 (32%)
Hyaline degeneration	45 (41%)
Interstitial fibrosis mild or greater	27 (25%)
Pathological diagnosis	
Diabetic nephropathy	15 (14%)
Focal segmental glomerulosclerosis	4 (4%)
Hypertrophic glomeruli	6 (5%)
IgA nephropathy	38 (35%)
Lupus nephritis	7 (6%)
Minor glomerular abnormalities	6 (5%)
Membranous glomerulonephritis	20 (18%)
Necrotizing glomerulonephritis	11 (10%)
Nephrosclerosis	3 (3%)

Categorical variables are stated as numbers and percentage

Serum GDF-15 level and other baseline characteristics

Serum GDF-15 levels distributed widely with median level of 1885 (998, 3496) pg/mL. Among baseline characteristics listed in Table 1, several variables were significantly associated with GDF-15 in the univariable analyses, including age, sex, diabetes mellitus, hypertension, history of cardiac disease, systolic blood pressure, albumin, hemoglobin, proteinuria, and *N*-acetyl-β-D-glucosaminidase. Of these, a higher serum GDF-15 level was independently associated with the existence of diabetes mellitus, lower hemoglobin, and lower estimated glomerular filtration rate in the multivariabe analysis ($p < 0.05$ for all; Table 3).

Table 3 Association between serum GDF-15 levels and baseline variables

	Beta value (95% CI)	*p* value	VIF
Diabetes mellitus	909 (155–1662)	0.019	1.10
Hemoglobin, g/dL	− 328 (− 484 to − 171)	< 0.001	1.28
eGFR, mL/min/1.73 m^2	− 38 (− 51 to − 26)	< 0.001	1.38

eGFR estimated glomerular filtration rate; *CI* confidence interval; *VIF* variable inflation factor

Multivariable linear regression analysis with stepwise method was performed

Serum GDF-15 levels and pathological features

Among pathologic findings that were significant in the univariable analyses, including crescent formation, hyaline degeneration, mild or greater interstitial fibrosis/tubular atrophy, mesangial cell proliferation, glomerular sclerosis, interstitial cell infiltration, fibrous intimal thickening of interlobular artery, the first three variables were positively and independently associated with incremental serum GDF-15 level in the multivariable analyses ($p < 0.05$ for all; Table 4).

Median serum GDF-15 levels in each pathological diagnosis are displayed in Fig. 1. Serum GDF-15 level was higher in patients with necrotizing glomerulonephritis, nephrosclerosis, and diabetic nephropathy, whereas it was lower in patients with IgA nephropathy, lupus nephritis, and minor glomerular abnormalities. These trends remained following the adjustment for estimated glomerular filtration rate (Supplementary Fig. 1).

Table 4 Association between serum GDF-15 levels and pathological findings

	Beta value (95% CI)	*p* value	VIF
Crescent formation	980 (176–1785)	0.017	1.00
Hyaline degeneration	840 (37–1643)	0.041	1.14
Interstitial fibrosis mild or greater	2243 (1359–3128)	< 0.001	1.15

CI confidence interval; *VIF* variable inflation factor

Multivariable linear regression analysis with stepwise method was performed

Prognostic impact of GDF-15

A total of 69 patients completed a 3-year follow-up after the index renal biopsy. There were 18 events of a 1.5-fold increase in serum creatinine and 14 initiations of renal replacement therapy. As a result, 18 patients experienced one of the renal outcomes.

Serum GDF-15 was significantly associated with the renal outcomes with an unadjusted odds ratio per 100 pg/mL of 1.072 (95% confidence interval 1.033–1.114; $p < 0.001$) and an adjusted odds ratio per 100 pg/mL of 1.052 (95% confidence interval 1.001–1.130; $p = 0.036$), adjusting for potential clinical confounders including age, estimated glomerular filtration rate, and urine protein.

A cutoff of serum GDF-15 level to predict the renal outcome was calculated as 1823 pg/mL with an area under the curve of 0.896 (95% confidence interval 0.823–0.969), sensitivity of 1.000, and specificity of 0.706 (Fig. 2). A total of 33 patients had serum GDF-15 levels above 1823 pg/mL and 18 (55%) met the endpoints ($p < 0.001$). An additional 36 patients had GDF-15 levels below the cutoff and all of them (100%) were endpoint free.

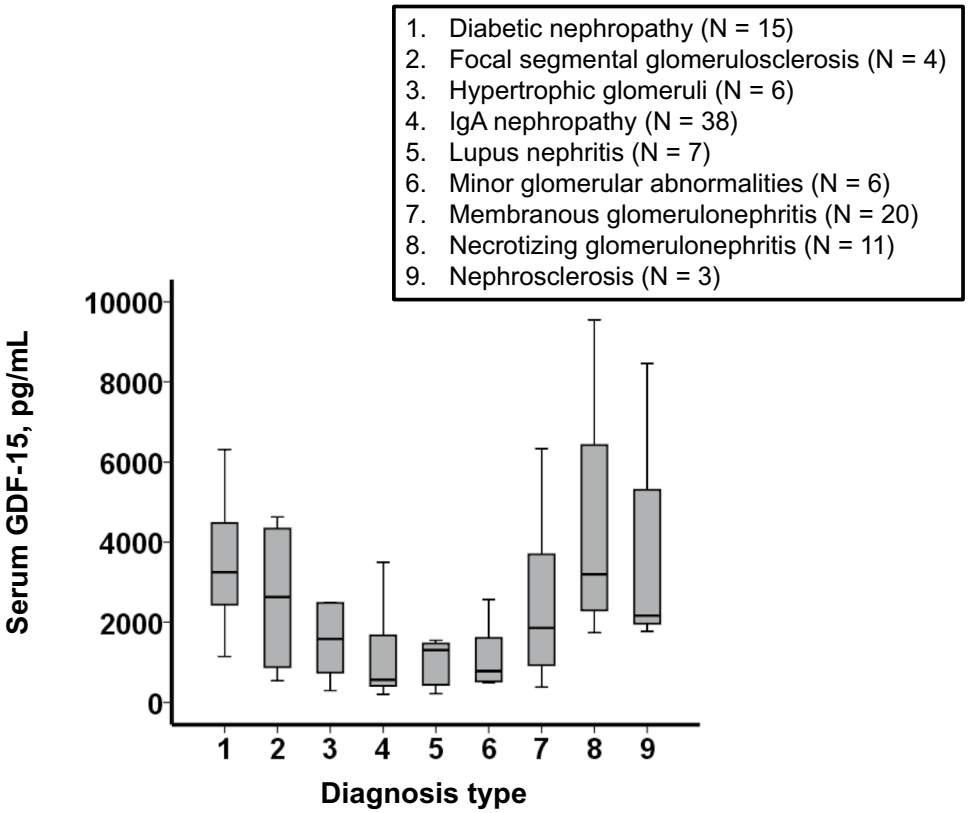

Fig. 1 Serum GDF-15 levels in each disease

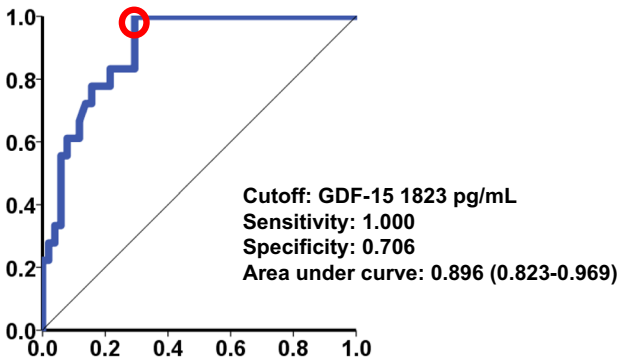

Fig. 2 Receiver operating characteristics analysis for serum GDF-15 level to predict composite renal outcomes. A red circle represents a cutoff of serum GDF-15 level

Discussion

In this study, we investigated the association between the serum GDF-15 levels and clinical parameters, including pathologic features, in patients with various renal diseases who underwent renal biopsy. We also evaluated the prognostic impact of serum GDF-15 levels on renal outcomes.

Serum GDF-15 levels were highly variable. Serum GDF-15 levels were associated with the presence of diabetes mellitus, anemia, and renal impairment. In particular, serum GDF-15 was higher in several renal pathologic features. In addition, serum GDF-15 levels had a prognostic impact on the 3-year renal outcomes.

Serum GDF-15 level in a variety of renal diseases

GDF-15 is secreted by endothelial cells, which is triggered by transforming growth factor-β activation such as inflammation, tissue injury, hypoxia, ischemia, and atherosclerosis. The presence of diabetes mellitus, anemia, chronic kidney disease, and hemodialysis are associated with these situations. It would be reasonable that serum GDF-15 levels would be associated with these comorbidities.

It is well known that transforming growth factor-β is associated with several pathologic findings, including crescent formation, glomerular sclerosis, and interstitial fibrosis. Bowman's capsule epithelial cells and crescent cells express receptors of transforming growth factor-β [12]. These cells transform into myofibroblasts upon stimulation by transforming growth factor-β [13]. Serum GDF-15 levels would ultimately be a surrogate marker of these systemic/renal inflammation-related tissue deterioration.

It is reasonable that serum GDF-15 level was relatively lower in patients with IgA nephropathy, lupus nephritis, and minimal change, having less crescent formation, interstitial fibrosis, and tubular atrophy. In the previous literature, the absolute value of serum GDF-15 in patients with these diseases was relatively lower than the other renal diseases as our cohort [8, 14]. GDF-15 would be secreted in a compensatory manner and have reno-protective and antifibrotic effects in transforming growth factor-β-related diseases. Perez-Gomez and colleagues also showed consistent findings between serum/urine GDF-15 levels and several pathologic findings, although the variety of pathologic findings was limited in their study [15].

Prognostic implication of serum GDF-15 level

It is well known that pathological findings including crescent formation, interstitial fibrosis and tubular atrophy, and glomerular sclerosis are associated with poor renal outcomes. It is not surprising that the surrogate of these systemic/renal inflammation-related tissue deterioration, GDF-15, was an independent predictor of renal outcomes.

Patient risk stratification and prediction of patient prognosis are often challenging in patients with renal disease, given a complexed comorbidities and a variety of background clinical scenario. Thus, serum GDF-15 level may become one of the useful clinical tool to guide clinical management, decision making, and informed consent. If patients with renal sclerosis had elevated serum GDF-15 levels, the renal impairment would be irreversible and aggressive intervention for hypertension and anemia might delay the deterioration of renal diseases. Aggressive remission-induction therapy should be considered for the patients with necrotizing glomerulonephritis accompanying crescent formation having elevated serum GDF-15 levels and those with the rapidly progressive nephritic syndrome who do not indicate renal biopsy.

In an experimental study using the mouse with unilateral ureteral ligation, administration of GDF-15 prevented the progression of renal fibrosis via inhibiting fibroblast growth and activation [16]. Recombinant GDF-15 might delay progression and renal impairment in the future.

Limitations

The sample size is moderate. The number of events is also small. Thus, further larger-scale studies are warranted to validate our findings. Our cohort consists of those with suspected renal disease who received renal biopsy. Patients who did not indicate renal biopsy were not included. Our cohort might not be representative of the standard renal disease cohort. We attempted to adjust for potential confounders to investigate the prognostic impact of serum GDF-15 level considering their prognostic impact according to the previous literature, but any other uninvestigated variables might exist. For example, we could not consider C-reactive protein and B-type natriuretic peptide, both of which might have a

deep association with GDF-15. Other systemic/infectious condition might affect GDF-15 levels. For example, circulating GDF-15 level is elevated in patients with chronic kidney disease suffering from COVID-19 probably due to systemic inflammation and multi-organ injury, and the elevated GDF-15 level is associated with mortality in this cohort [17]. We did not include any patients with COVID-19. We did not include the patients with renal amyloidosis, in which serum GDF-15 level is also elevated and associated with poor clinical outcome [18].

We did not directly measure tissue expression of GDF-15. We utilized serum GDF-15 level as alternative, given the previous study that demonstrated a significant correlation between the circulating GDF-15 levels in blood and kidney tissue expression of GDF-15 mRNA [6].

We measured serum GDF-15 level just one time for each patient, and their trends during the longitudinal observational period remain unknown. Also, given long-term observational period, many patients were returned to the affiliated institutes and accurate date to reach endpoints were unclear. Thus, we did not perform time-to-event analyses. Given the nature of clinical observational study, a detailed mechanism that explains our findings remains uncertain. Therapeutic strategy for those with elevated serum GDF-15 levels remains a future concern.

Conclusions

Serum GDF-15 level was associated with several renal pathological features and renal outcomes in patients with renal diseases who received renal biopsy. Detailed mechanism that explains our findings and therapeutic strategy for those with elevated serum GDF-15 levels remain a future concern.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-023-03580-7.

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Declarations

Conflicts of interest None.

Disclosure None.

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