

GDF 15 as a novel biomarker in patients with IgA nephropathy

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Introduction: Growth differentiation factor 15 (GDF 15) is a member of the transforming growth factor- β superfamily. GDF 15 was reported as a potentially useful prognostic marker in patients with chronic inflammatory disease and heart disease. However, no prognostic biomarkers have been identified for IgA nephropathy. We evaluated the possibility that GDF 15 could serve as a prognostic predictor of renal outcome in immunoglobulin A nephropathy (IgAN). **Methods:** The study included 212 patients in the Chungnam National Hospital glomerulonephritis cohort who were diagnosed with biopsy-proven IgAN from March 2010 to June 2014. Blood samples were stored at -80°C . GDF 15 was analyzed by an enzyme-linked immunosorbent assay. Correlations were evaluated among initial serum GDF 15, blood urea nitrogen levels, serum creatinine level, and estimated glomerular filtration rate (eGFR). **Results:** GDF 15 correlated well with initial eGFR ($R = -0.649$), and the mean serum GDF 15 level correlated with chronic kidney disease (CKD) stage. A GDF 15 level > 496.32 pg/mL showed 90% sensitivity and 72.9% specificity for predicting the need for hemodialysis within 2 years of diagnosis, and > 490.4 pg/mL showed 63.64% sensitivity and 65% specificity for predicting a decline in eGFR > 30 mL/min in 1 year. In addition, the initial serum GDF 15 level was associated with the development of interstitial fibrosis/tubular atrophy. **Conclusions:** The initial serum GDF 15 level was a useful disease severity and prognostic biomarker in patients with IgA nephropathy.

N=200	
Age (Mean \pm SD)	39.51 \pm 14.79
Male (n, %)	103, 49.3%
DM (Mean \pm SD)	23.818 \pm 4.66
Past medical history (n, %)	
HTN	32, 15.3%
DM	19, 9.1%
HIV carrier	4, 1.9%
Solid cancer	10, 4.8%
Initial laboratory data	
BUN (mg/dL)	17.84 \pm 10.02
Creatinine (mg/dL)	1.24 \pm 1.25
eGFR (MDRD)	86.09 \pm 36.46
UPCR (mg/dL)	1.7 \pm 2.58
GDF15 (pg/mL)	426.54 \pm 398.57

Table 1. Baseline characteristics

Pearson's coefficient	UPCR	UPCR ²	GDF15	GDF15 ²
Age	0.247***		0.484**	
BUN	0.069		0.037	
Albumin	-0.587***	-0.540	-0.000	-0.472**
BUN	0.220**	0.198	0.023	0.444**
C ₂	0.160**	0.141	0.002	0.214*
eGFR	-0.217***	-0.189	0.022	-0.449**
BUN at 1y	0.100	0.176	0.070	0.184*
C ₂ at 1y	0.153	0.109	0.245	0.153*
eGFR at 1y	-0.188*	-0.164	0.124	-0.109*
eGFR at 1y	-0.131	-0.108	0.260	-0.207*
BUN at 2y	0.174	0.142	0.120	0.184*
C ₂ at 2y	0.160	0.119	0.000	0.014*
eGFR at 2y	-0.079	-0.052	0.366	-0.333*
eGFR at 2y	-0.207***	-0.240	0.007	-0.335**

Table 2. GDF 15 showed higher correlation with laboratory results compared to UPCR (n-adjusted for age and DM)

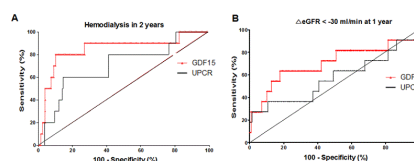


Figure 1. Receiver operating characteristic curve between GDF 15 and kidney prognosis. A: Serum growth differentiation factor 15 (GDF 15) level > 496.32 pg/mL showed 90% sensitivity and 72.9% specificity to predict the need for hemodialysis within 2 years. The area under curve (AUC) of GDF 15 was 0.8477 ± 0.075 . B: GDF 15 level > 490.4 pg/mL showed 63.64% sensitivity and 65% specificity to predict a decline in eGFR > 30 mL/min in 1 year.

GDF15	112.69 pg/mL	385.56 pg/mL	887.71 pg/mL	1637.33 pg/mL
eGFR	129.26 mL/min	74.48 mL/min	15.53 mL/min	5.57 mL/min
UPCR	3.817 g/g	2.371 g/g	4.762 g/g	3.115 g/g

Figure 2. Representative serum GDF 15 and interstitial fibrosis/tubular atrophy (IFTA) images. As the IFTA percentage increased, serum GDF 15 level increased.

Relationships between blood pressure and clinico-pathological findings in IgA nephropathy

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Objective: Several factors contribute to the development of hypertension in patients with IgA nephropathy (IgAN). This study was conducted to find the relationships between baseline blood pressure (BP) and clinico-pathological findings in patients with IgAN and normal renal function. **Design and Method:** Clinico-pathological findings were analyzed in a total of 163 patients with IgAN and serum creatinine ≤ 1.1 mg/dL from The Kyung-Hee Cohort of Glomerulonephritis. The glomerular surface area (GSA) was determined using imaging analysis software. The serum and urine angiotensinogen (AGT) concentrations were measured using human ELISA kits. **Results:** Mean serum creatinine concentration was 0.86 ($0.5 \sim 1.1$) mg/dL. Systolic BP was ≥ 130 mmHg in 72 patients (44%) and ≥ 140 mmHg in 42 (26%). Patients with systolic BP ≥ 130 mmHg as compared with those < 130 mmHg had higher GSA and tubulointerstitial fibrosis and showed worse follow-up clinical findings: higher concentrations of serum creatinine, larger amount of proteinuria and lower levels of GFR. Systolic BP was positively correlated with age, baseline and follow-up proteinuria, serum uric acid concentrations and IgM deposit and negatively with follow-up GFR and the slope of change in $1/\text{serum creatinine}$ for 2 years, while it has no significant relationships with serum and urine AGT and 24 hour urinary sodium excretion. **Conclusions:** This study showed that systolic BP was associated with renal progression and pathological findings, glomerulomegaly and tubulointerstitial fibrosis, in patients with IgAN.