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**The Potential of Serum Growth Differentiation Factor-15 as a Screening
Marker in Hemodialysis Patients with Cognitive Impairment.**

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Objectives : Cognitive dysfunction is more frequent in end-stage renal disease (ESRD) patients undergoing hemodialysis compared with the healthy population, emphasizing the need for early detection. Elevated serum growth differentiation factor 15 (GDF-15) levels are known to be associated with an increased risk of decreased renal function and cognitive dysfunction. This study investigated the relationship between GDF-15 and cognitive dysfunction in hemodialysis patients.

Methods : This retrospective study analyzed data from 92 hemodialysis patients treated at Chungnam National University Hospital, Daejeon, Republic of Korea, from January 2017 to June 2020. Cognitive function was assessed using the Korean version of the Mini-Mental Status Examination (K-MMSE), categorizing patients into normal (≥ 24 points) and cognitive dysfunction (< 24 points). To evaluate whether exposure to uremic toxins, observed in hemodialysis patients with an inclination towards elevated GDF-15 levels and cognitive dysfunction, would result in comparable outcomes in terms of GDF-15 expression in brain cells and tissues, as well as the survival of brain cells.

Results : Serum GDF-15 concentrations were at significantly higher levels in the cognitive dysfunction group (7500.42 pg/mL, $p = 0.001$). Serum GDF-15 concentrations were at significantly higher levels in the cognitive dysfunction group (7500.42 pg/mL, $p = 0.001$). Logistic regression indicated an increased risk of K-MMSE scores < 24 points when serum GDF-15 exceeded 5408.33 pg/mL. Hierarchical regression suggests that GDF-15 has improved predictive capacity in relation to the MMSE score. After indoxyl sulfate exposure in brain cells, brain cells survival was decreased and GDF-15 expression in brain cells was increased. Similarly, exposure to indoxyl sulfate in mouse brain tissue resulted in an increased expression of GDF-15.

Conclusions : This study highlights the potential of serum GDF-15 as a marker for cognitive dysfunction in hemodialysis patients, offering a valuable screening tool.

Table 1.png

Table 1. Incremental contributions of the K-MMSE score (hierarchical regression).

	Model 1		Model 2			Model 3			
	B	SE	β	B	SE	β	B	SE	β
(Constant)	15.93	4.24		29.74	5.55		31.75	5.39	
Albumin	0.80	1.12	0.08	1.05	1.05	0.11	0.94	1.01	0.10
Cr	0.13	0.20	0.08	-0.07	0.19	-0.04	-0.08	0.19	-0.05
Phosphorus	0.64	0.43	0.20	0.17	0.42	0.05	0.11	0.41	0.03
Potassium	0.50	0.62	0.09	0.79	0.59	0.14	0.86	0.57	0.15
CRP	-0.15	0.12	-0.15	-0.15	0.11	-0.14	-0.11	0.11	-0.10
Age				-0.19	0.05	-0.40	-0.18	0.05	-0.38
GDF15							0.00	0.00	-0.25
R ²	0.17			0.28			0.34		
R ² change	0.172 *			0.108 **			0.61 **		

GDF-15, growth and differentiation factor-15; Cr, serum creatinine; CRP, C-reactive protein. * $p < 0.05$, ** $p < 0.01$.

Model 1: adjusted for serum creatinine, albumin, potassium, and phosphorus.

Model 2: adjusted for Model 1 + age.

Model 3: adjusted for Model 2 + GDF-15.

Table 1.png

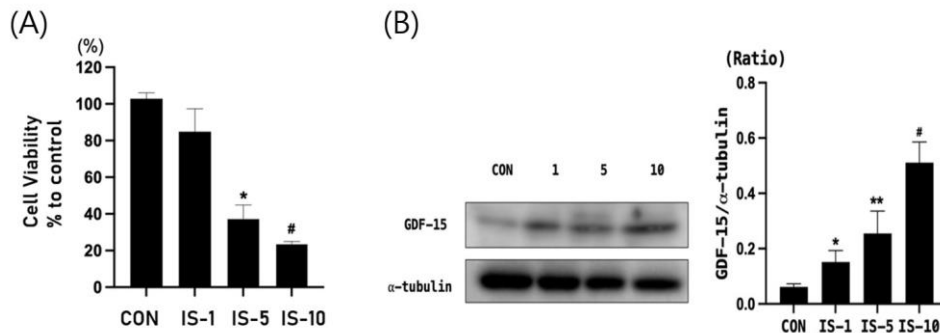


Figure 1. (A) Survival of mouse brain cell following indoxyl sulfate treatment at concentrations of 1, 5, and 10 mM. IS = indoxyl sulfate. * $p < 0.05$, control vs. indoxyl sulfate (IS) 5 mM, # $p < 0.05$, control vs. IS 10 mM. (B) GDF-15 level in mouse hippocampal neuronal cell line HT22 following indoxyl sulfate treatment. GDF-15 expression increased in a concentration-dependent manner. α -tubulin was used as the control. Con, control, GDF-15 = growth and differentiation factor-15, IS = indoxyl sulfate. * $p < 0.05$, control vs. IS 5 mM, ** $p < 0.05$, control vs. IS 5 mM, # $p < 0.05$, control vs. IS 10 mM.