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Serum fibroblast growth factor–21 concentration is associated with residual renal function and insulin resistance in end-stage renal disease patients receiving long-term peritoneal dialysis

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Abstract

Fibroblast growth factor–21 (FGF-21) is a new metabolic regulator, which is related to antiobesity and insulin sensitivity in vivo. However, the clinical implication of FGF-21 is poorly understood. To investigate whether FGF-21 may play a role as a metabolic regulator in patients with end-stage renal disease, we measured serum concentrations of FGF-21, inflammatory markers, and metabolic parameters in healthy people (n = 63) and nondiabetic patients receiving peritoneal dialysis (PD, n = 72). The patients were treated with angiotensin receptor blocker for 6 months, and the changes in FGF-21 concentration and metabolic parameters were assessed. Compared with controls, serum FGF-21 concentration was 8 times higher in patients undergoing PD (754.2 ± 463.5 vs 86.9 ± 60.2 pg/mL, $P < .001$). In controls, only lipid parameters correlated positively with FGF-21 concentration. In contrast, inflammatory markers (interleukin-6, fibrinogen, high-sensitivity C-reactive protein) and homeostasis model assessment of insulin resistance (HOMA-IR) correlated positively and residual renal function correlated inversely with serum FGF-21 concentration in PD patients. In a multivariate analysis adjusting these factors, residual renal function, HOMA-IR, and fibrinogen concentration were independent determinants of serum FGF-21 concentration. After 6-month angiotensin receptor blocker treatment, serum FGF-21 concentration declined significantly by 13% and HOMA-IR and inflammatory markers improved in PD patients. These findings suggest that FGF-21 may play a role in insulin resistance in patients with end-stage renal disease.

1. Introduction

Patients with end-stage renal disease (ESRD) show insulin resistance [1]. Insulin resistance is significantly associated with the progression of atherosclerosis and may predict cardiovascular mortality in this population [2]. High glucose exposure exerts detrimental effects on the peritoneal membrane in patients treated with peritoneal dialysis (PD), and a substantial amount of glucose is absorbed via the peritoneal capillary vessels. This may further aggravate insulin resistance in PD patients, although they are not classified as having diabetes [3].

Fibroblast growth factors (FGFs) are classified into 7 families and are involved in a variety of cellular functions including cell survival, differentiation, mitosis, and angiogenesis. The FGF-19 families (FGF-19, FGF-21, and FGF-23) function as metabolic regulators of glucose metabolism and mineral homeostasis. Fibroblast growth factor–21 is

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produced in the liver but acts mainly on white adipose tissue because of its receptor specificity for FGF receptors [4]. However, several studies suggest that FGF-21 could be expressed in pancreas, skeletal muscle, and various cells [5,6]. Recent studies show that FGF-21 increases glucose uptake in adipose tissue, ameliorates diet-induced obesity, and regulates hepatic lipid metabolism in ketotic states by activating peroxisome proliferator-activated receptor–α [7-11]. Human studies [12-14] show a potential relationship between FGF-21 level and obesity. However, more studies are needed to clarify the clinical role of FGF-21 in humans.

It is not understood clearly whether serum FGF-21 contributes to the detrimental metabolic status in patients with chronic kidney disease. Only one report has shown that serum FGF-21 concentration correlates with renal function and is elevated markedly in patients receiving hemodialysis, suggesting a possible link between FGF-21 concentration and its renal excretion [15]. Given the potential effects of FGF-21 as an endocrine factor involved in the regulation of glucose homeostasis [8-10,13], we hypothesized that this circulating protein plays a role in insulin resistance in nondiabetic, ESRD patients receiving PD. However, the relationship between serum FGF-21 concentration and insulin resistance has not been explored in patients receiving PD. We performed this study to identify which factors are associated with FGF-21 concentration and to elucidate whether FGF-21 plays a role in insulin resistance in nondiabetic ESRD patients undergoing PD.

2. Patients and methods

2.1. Study subjects and data collection

The study included 156 regular PD patients at the dialysis clinic of Yonsei University Medical Center, Seoul, Korea, between 2006 and 2007. Because we aimed to investigate the metabolic effects of FGF-21 in ESRD patients who exhibited insulin resistance induced by uremia per se, 55 patients with diabetes were excluded from our study. Patients younger than 18 years or who had been maintained on PD for less than 3 months were also excluded. Patients were considered eligible for this study if they had no overt infection for the 3 months before entering the study and had no history of malignancy or other chronic inflammatory diseases. Therefore, a total of 72 PD patients were included in this study. We included healthy controls (n = 63) who underwent a routine health examination at Seoul National University Bundang Hospital, had no history of medical disease, and were not taking regular medication.

Demographic and clinical data were recorded at the study entry and included sex, age, body mass index (BMI) calculated as weight/(height)^2, primary renal disease, previous history of cardiovascular disease (CVD), and duration of dialysis. *Cardiovascular disease* was defined as a history of coronary, cerebrovascular, or peripheral vascular disease. *Coronary disease* was defined as a history of angioplasty, coronary artery bypass graft, myocardial infarction, or angina. *Cerebrovascular disease* was defined as a previous transient ischemic attack, stroke, or carotid endarterectomy; and *peripheral vascular disease* was defined as a history of claudication, ischemic limb loss and/or ulceration, or peripheral revascularization procedure.

After an overnight fast, venous samples were drawn for assessment of the lipid and glucose profiles. The fasting concentrations of glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured using a Toshiba 200FR Neo Chemistry autoanalyzer (Toshiba Medical Systems, Tokyo, Japan). Hemoglobin A_{1c} was measured using high-performance liquid chromatography on a Bio-Rad VARIANT II instrument (Bio-Rad Laboratories, Munich, Germany). Residual glomerular filtration rate (GFR) was calculated as the average of urea and creatinine clearance from a 24-hour urine collection. Kt/V urea was calculated as the total loss of urea nitrogen in the spent dialysate using the Watson equation [16]. All patients provided informed consent before entry into the study.

2.2. Measurement of homeostasis model assessment of insulin resistance

Plasma insulin concentration was measured by sandwich enzyme-linked immunosorbent assay (ELISA) using anti-rat insulin antibodies (Linco Research, St Charles, MO). Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) described originally by Matthews et al [17], in which HOMA-IR (millimoles per liter × micro–international units per milliliter) = fasting glucose (millimoles per liter) × fasting insulin (micro–international units per milliliter)/22.5.

2.3. Measurement of serum FGF-21 concentrations

Plasma FGF-21 concentration was measured by a sandwich ELISA using biotin-labeled antibody and an RD191108200R human FGF-21 ELISA kit (BioVendor Laboratory Medicine, Modrice, Czech Republic). The ELISA system had an intraassay coefficient of variation (CV) of 3.6% and an interassay CV of 3.8%. All determinations were performed in triplicate.

2.4. Measurement of serum inflammatory biomarkers, adiponectin, and fibrinogen concentrations

High-sensitivity C-reactive protein (hs-CRP) concentration was measured using a latex-enhanced immunonephelometric method on a BN II analyzer (Dade Behring, Newark, DE). The concentrations of interleukin-6 (IL-6; R&D Systems Europe, Abingdon, Oxon, United Kingdom) and adiponectin (R&D Systems Europe) were measured using ELISA kits. The ELISA system had an intraassay CV of 3.48% and an interassay CV of 4.36%. Fibrinogen concentration was measured in citrated plasma by a modified

clot-rate assay using a Pacific Hemostasis Assay Set (Huntersville, NC).

2.5. Change in serum FGF-21 concentrations after angiotensin receptor blocker treatment

We conducted a pilot study to investigate the effect of angiotensin receptor blocker (ARB) on serum FGF-21 concentration. Of 72 patients, 56 (71.8%) patients who had already been on ARBs or angiotensin-converting enzyme inhibitors discontinued these medications and entered a 4-week washout period. During this period, other antihypertensive medications were prescribed to maintain blood pressure (BP) at stable levels. After the washout period, all patients (n = 72) started to be treated with ARB (valsartan 80 mg) for 6 months; and the concentrations of FGF-21, hs-CRP, and IL-6, lipid parameters, and HOMA-IR were measured as described above. We also investigated the relationship between the change in serum FGF-21 concentration and other parameters during the follow-up period.

2.6. Statistical analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS, Chicago, IL). All data are expressed as mean ± SD except for variables with a skewed distribution, which are expressed as the median and range. Kolmogorov-Smirnov test was used to analyze the normality of the distribution of the parameters measured. Variables were compared between the 2 groups using Student *t* test and the χ^2 test for normally distributed data. In addition, the relationship between parameters was assessed by Pearson correlation analysis. For skewed data, Mann-Whitney *U* test was conducted to compare variables between the 2 groups; and Spearman correlation coefficient was determined to identify the relationship between covariates. The independent association between serum FGF-21 concentration and other parameters was analyzed further by multiple linear regression analysis. Significance was defined as $P < .05$.

3. Results

3.1. Comparison of demographic and clinical parameters between healthy subjects and nondiabetic patients undergoing PD

Baseline characteristics of the 72 PD patients and 63 healthy controls with normal renal function were presented in Table 1. Age and sex were well matched between the 2 groups. Among the patients treated with PD, chronic glomerulonephritis was the most common cause of ESRD (48.6%), followed by hypertension (26.4%); and only 5 patients (6.9%) had previous CVD. The PD patients had higher mean systolic BP (132.8 ± 19.8 vs 114.1 ± 12.9 mm Hg, $P < .001$) and diastolic BP (80.5 ± 9.7 vs 70.0 ± 10.8 mm Hg, $P < .001$). Dyslipidemia was more evident in PD patients; PD patients had higher concentrations of triglyceride (106.5 [35.0-742.0] vs 93.0 [29.0-377.0] mg/dL, $P < .05$) and LDL cholesterol (115.1 ± 32.4 vs 105.2 ± 25.4 mg/dL, $P < .05$) and lower HDL cholesterol concentration (52.4 ± 15.5 vs 56.4 ± 15.7 mg/dL, $P < .05$). Fasting serum glucose and insulin concentrations were significantly higher in PD patients, resulting in a higher HOMA-IR (2.2 ± 1.0 vs 1.8 ± 1.8, $P < .05$). Fibroblast growth factor–21 levels were 8 times higher in PD patients (729.6 ± 461.5 vs 86.9 ± 60.2 pg/mL, $P < .001$). The concentrations of hs-CRP, IL-6, and fibrinogen were significantly higher in PD patients.

Table 1
Baseline characteristics of healthy subjects and nondiabetic patients undergoing PD

	Control	PD patients	*P* value
No. of patients	63	72	
Age (y)	49.7 ± 7.0	49.5 ± 10.8	NS
Sex (male-female)	30:33	37:35	NS
BMI (kg/m^2)	23.7 ± 2.4	22.9 ± 3.0	<.05
PD duration (mo)	–	76.0 ± 50.7	
Primary disease (n, %)	–		
Chronic GN	–	35 (48.6%)	
Hypertension	–	19 (26.4%)	
Others	–	6 (8.4%)	
Unknown	–	12 (16.7%)	
Previous history of CVD (n, %)	–	5 (6.9%)	
Medication use			
ARBs	–	53 (73.6%)	
Calcium channel blockers	–	47 (65.3%)	
β-Blockers	–	40 (55.6%)	
HMG-CoA reductase inhibitor	–	9 (12.5%)	
SBP (mm Hg)	114.1 ± 12.9	132.8 ± 19.8	<.05
DBP (mm Hg)	70.0 ± 10.8	80.5 ± 9.7	<.05
Hemoglobin (g/dL)	12.4 ± 1.5	10.9 ± 1.8	<.05
Calcium (mg/dL)	9.5 ± 1.3	8.8 ± 0.6	<.05
Phosphorus (mg/dL)	3.2 ± 1.2	4.9 ± 1.3	<.05
Uric acid (mg/dL)	5.8 ± 1.4	6.6 ± 1.2	<.05
Total cholesterol (mg/dL)	199.0 ± 33.3	185.7 ± 36.0	<.05
Triglyceride (mg/dL)*	93.0 (29.0-377.0)	106.5 (35.0-742.0)	<.05
LDL cholesterol (mg/dL)	105.2 ± 25.4	115.1 ± 32.4	<.05
HDL cholesterol (mg/dL)	56.4 ± 15.7	52.4 ± 15.5	<.05
HbA_{1c} (%)	5.2 ± 0.3	5.0 ± 0.7	NS
Fasting glucose (mg/dL)	86.2 ± 7.8	93.3 ± 19.4	<.05
Insulin (μU/mL)	6.2 ± 3.0	9.6 ± 4.6	<.05
HOMA-IR	1.8 ± 1.1	2.2 ± 1.0	<.05
FGF-21 (pg/mL)	86.8 ± 60.2	729.6 ± 461.5	<.001
hs-CRP (mg/L)	0.19 ± 0.10	1.5 ± 1.2	<.05
IL-6 (pg/mL)	3.9 ± 3.1	7.4 ± 2.8	<.05
Adiponectin (μ/mL)	15.6 ± 6.3	18.7 ± 8.2	NS
Fibrinogen (mg/dL)	253.4 ± 70.7	492.2 ± 92.6	<.05
Serum creatinine (mg/dL)	0.72 ± 0.18	11.6 ± 3.11	<.01
Kt/V urea	–	2.11 ± 0.44	
Residual GFR (mL/[min/1.73 m^2])*	–	1.40 (0-10.2)	

All data were expressed as mean ± SD. GN indicates glomerulonephritis; HMG-CoA, hydroxymethylglutaryl–coenzyme A; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}.

* Median with range for skewed data.

3.2. Factors correlated with FGF-21 in controls and in patients on PD

In the controls, only lipid parameters including the concentrations of total cholesterol, triglyceride, and LDL cholesterol correlated positively with serum FGF-21 concentration, wherein triglyceride concentration had the strongest correlation. High-density lipoprotein cholesterol correlated inversely with serum FGF-21 concentration. Age, BMI, fasting serum glucose and insulin concentrations, and HOMA-IR did not correlate significantly with serum FGF-21 concentration (Table 2). Bivariate correlation analysis revealed no significant correlation between FGF-21 concentration and age, BMI, and lipid parameters in PD patients. However, FGF-21 levels correlated inversely with residual glomerular GFR (Spearman $r = -0.456$, $P < .001$) and Kt/V ($r = -0.459$, $P < .001$) and positively with PD duration ($r = 0.336$, $P = .004$). Fibroblast growth factor–21 concentration correlated significantly with fasting insulin concentration ($r = 0.377$, $P = .001$) and HOMA-IR ($r = 0.394$, $P = .001$), whereas fasting glucose concentration did not ($r = 0.032$, $P = .787$). Fibroblast growth factor–21 concentration also correlated positively with serum concentrations of fibrinogen ($r = 0.495$, $P < .001$) and inflammatory biomarkers such as hs-CRP ($r = 0.296$, $P = .012$) and IL-6 ($r = 0.318$, $P = .006$). Fibroblast growth factor–21 concentration did not correlate significantly with adiponectin concentration (Table 2). In a multivariate linear regression analysis adjusted for age, PD duration, residual GFR, Kt/V urea, HOMA-IR, hs-CRP, IL-6, and fibrinogen concentrations, residual GFR ($\beta = -0.320$, $P = .033$), HOMA-IR ($\beta = 0.268$, $P = .016$), and fibrinogen ($\beta = 0.399$, $P = .007$) were significantly associated with FGF-21 concentrations (Table 3).

Table 3
Multivariate linear regression for FGF-21[a] in patients undergoing PD

	β	P value
Age	−0.050	.641
PD duration	0.070	.531
Residual GFR	−0.320	.033
Kt/V urea	−0.033	.817
HOMA-IR	0.268	.016
hs-CRP	−0.093	.463
IL-6	0.020	.865
Fibrinogen	0.399	.007

[a] Adjusted for age, PD duration, residual GFR, Kt/V urea, HOMA-IR, hs-CRP, IL-6, and fibrinogen.

3.3. Serum FGF-21 levels after 6-month treatment with ARB in patients on PD

As BP was maintained stable from the washout period, no significant changes in BP were observed during 6-month treatment period with ARB (133.3 ± 19.6 to 133.4 ± 20.4, P = not significant [NS]). In contrast, FGF-21 concentration decreased significantly from 729.6 ± 461.5 to 638.6 ± 405.2 pg/mL ($P < .01$, Fig. 1). This 13% decrease in FGF-21 levels was similar to those for hs-CRP (1.49 ± 1.45 to 0.96 ± 0.98 mg/L, $P < .01$), fibrinogen (492.2 ± 92.6 to 420.5 ± 68.0 mg/dL, $P < .01$), and HOMA-IR (2.2 ± 1.0 to 1.8 ± 1.1, $P < .05$, Fig. 1). However, the degree of change in FGF-21 concentration from before to after the 6 months of ARB treatment did not correlate with the changes in hs-CRP concentration and HOMA-IR; and it correlated significantly only with the change in fibrinogen concentration (data not shown).

Table 2
Factors correlated with FGF-21 in controls and patients undergoing PD

	Control		PD patients	
	Correlation coefficient	P value	Correlation coefficient	P value
Age	0.271	.091	0.292	.089
PD duration	–		0.336	.004
Residual GFR[a]	–		−0.456	<.001
Kt/V urea	–		−0.459	<.001
BMI	0.097	.188	0.055	.649
Total cholesterol	0.222	.002	−0.073	.540
TG[a]	0.394	.000	0.076	.525
HDL cholesterol	−0.150	.039	0.014	.904
LDL cholesterol	0.223	.002	−0.204	.086
Serum albumin	–		−0.148	.214
Fasting glucose	0.051	.493	0.032	.787
Fasting insulin	0.194	.207	0.377	.001
HOMA-IR	0.032	.837	0.394	.001
hs-CRP	0.079	.297	0.296	.012
IL-6	–		0.318	.006
Adiponectin	0.053	.687	−0.008	.946
Fibrinogen	–		0.495	<.001

TG indicates triglyceride.
[a] Spearman correlation analysis was used.

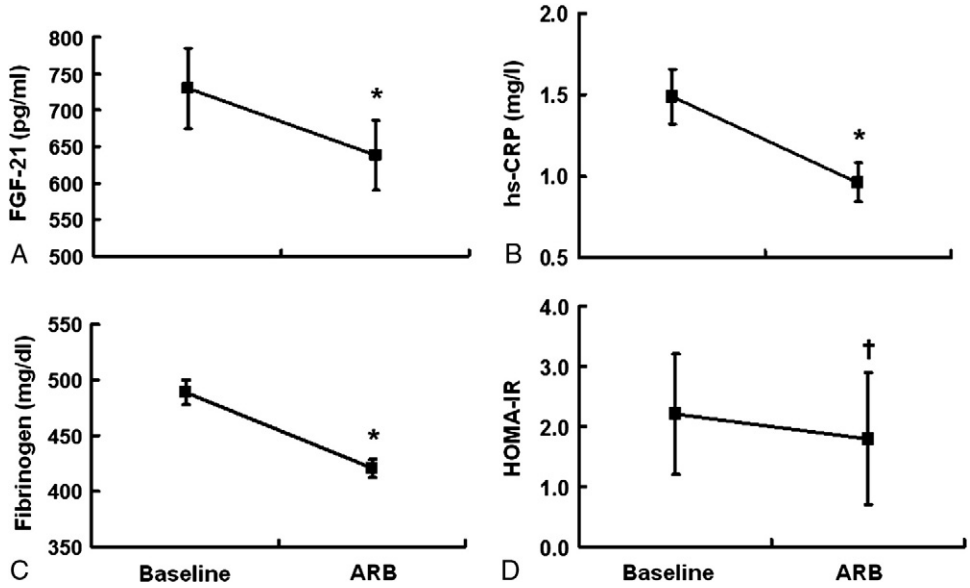

Fig. 1. The changes of serum FGF-21 (A), hs-CRP (B), fibrinogen (C) levels, and HOMA-IR (D) after 6-month ARB treatment in patients on PD. Serum FGF-21 concentration declined significantly by 13%, whereas HOMA-IR and inflammatory markers improved after 6-month ARB treatment. *$P < .01$ vs baseline, †$P < .05$ vs baseline.

4. Discussion

Although several human studies have investigated the clinical significance of FGF-21 [13-15], the clinical role of FGF-21 is understood incompletely; and it would be of great value to elucidate the function of this new metabolic regulator in humans. In the present study, we investigated (1) the relationship between metabolic parameters and serum FGF-21 concentrations in people with normal and impaired renal function, (2) whether FGF-21 concentration is related to residual renal function (RRF), and (3) the effect of long-term ARB treatment on FGF-21 concentration in patients receiving PD. Serum FGF-21 concentration was 8 times higher in patients undergoing PD than in healthy controls, and FGF-21 concentration correlated negatively with RRF and positively with parameters of insulin resistance in the patients. The 6-month ARB treatment significantly reduced FGF-21, hs-CRP, and fibrinogen concentrations and improved HOMA-IR in patients receiving PD.

Interestingly, serum FGF-21 concentration was much higher in patients on long-term PD than in the healthy controls with normal renal function. Relevant to this finding is a recent study by Stein et al [15] of a 15-fold higher serum FGF-21 concentration in long-term hemodialysis patients, suggesting that serum FGF-21 may be related to renal excretion in humans. In support of this finding, our data show an independent association between RRF and serum FGF-21 concentration. We note that serum FGF-21 concentration is influenced more by RRF than by the PD duration and dialysis adequacy. Although such parameters were significantly associated with serum FGF-21 concentration in the univariate analysis, only RRF remained as a significant determinant after adjusting for PD duration and Kt/V urea. Residual renal function declines a few years after the start of dialysis, and it plays a role in both small-solute clearance and removal of middle–molecular weight toxins [18]. These may explain the marked elevation of serum FGF-21 concentration in patients with impaired renal function and why RRF was an independent determinant of the elevated FGF-21 concentration. Serum FGF-21 concentration was significantly lower in patients with residual GFR greater than 1 mL/(min 1.73 m^2) than in those with residual GFR less than 1 mL/(min 1.73 m^2) (411.7 ± 332.8 vs 813.6 ± 441.4 pg/mL, $P < .01$). In addition, patients with higher residual GFR also had lower levels of hs-CRP (1.1 ± 0.9 vs 1.7 ± 1.5 mg/L, $P < .05$) and HOMA-IR (1.9 ± 0.9 vs 2.3 ± 1.1, $P = .07$). These findings suggest another rationale for the preservation of RRF from a viewpoint of improving insulin resistance.

Paradoxically, FGF-21 concentration can be high in people with type 2 diabetes mellitus [12] or hypertriglyceridemia [13] and in obese people with metabolic syndrome [14]. The mechanisms responsible for this paradoxical elevation of FGF-21 concentration are not fully understood, although it might be explained partly by a compensatory overexpression of FGF-21 in the liver or FGF-21 resistance in peripheral tissues with insulin resistance. It is likely that impaired renal excretion combined with compensatory mechanisms may explain the marked elevation of serum FGF-21 concentration in patients receiving long-term PD.

In the healthy subjects, only the lipid variables of total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol concentrations correlated significantly with higher serum FGF-21 concentration. This finding is consistent with previous data indicating that hypertriglyceridemia and peroxisome proliferator-activated receptor–α activation are associated with high FGF-21 levels in males [13]. In

contrast, obesity parameters or serum glucose concentration was not significantly associated with FGF-21 concentration in our subjects. This discrepancy may be attributable to the different characteristics of the study populations. Our study subjects were older and had a lower average BMI than in previous studies, and none had diabetes.

In contrast, although our patients on long-term PD were lean and did not have diabetes, their serum FGF-21 concentration was positively correlated with fasting serum concentrations of insulin, hs-CRP, IL-6, and fibrinogen and with HOMA-IR. Patients with ESRD have chronic low-grade inflammation, and this plays a key role in the development of cardiovascular lesions [19]; these patients also show signs of insulin resistance [1,20]. Patients receiving PD are at high risk of insulin resistance because a substantial amount of glucose is absorbed via the peritoneal capillary vessels, which elevates serum insulin levels [3]. In line with these findings, our patients receiving PD showed signs of chronic inflammation and insulin resistance as evidenced by higher levels of hs-CRP, IL-6, and HOMA-IR compared with the healthy controls. We also found significant correlations between serum FGF-21 concentration and inflammatory markers and insulin resistance in these patients. Furthermore, a recent study involving rhesus monkey also showed that several inflammatory markers were reduced along with lipid parameters after 8-week treatment of FGF-21 injection, suggesting its therapeutic potential in CVD [21]. Taken together, these findings suggest that FGF-21, a potential metabolic regulator, may play a role in insulin resistance in PD patients.

Fibrinogen is an independent predictor of cardiovascular mortality in ESRD patients [22], and its concentration is often elevated in patients on PD [23]. There are several possible mechanisms responsible for the elevated fibrinogen concentration in this population: (1) compensatory hepatic synthesis of fibrinogen as a result of its loss via PD fluid; (2) a chronic inflammatory state, which can stimulate fibrinogen synthesis; and (3) a direct effect of insulin on fibrinogen synthesis. Hyperinsulinemia may promote increased fibrinogen synthesis in PD patients. Given the potential role of FGF-21 in insulin resistance, a link between FGF-21 and hyperfibrinogenemia is feasible. Interestingly, our study showed that hyperfibrinogenemia was a strong determinant of elevated FGF-21 concentration. However, we did not explore the mechanism responsible for any interaction between FGF-21 and fibrinogen; and we do not know whether this is a causal relationship.

One of our key findings is that serum FGF-21 concentration decreased after ARB treatment. Angiotensin receptor blocker exerts anti-inflammatory effects and improves insulin resistance in patients with chronic kidney disease [24]. We found that ARB treatment significantly decreased hs-CRP concentration and attenuated insulin resistance. It is possible that ARB treatment decreased FGF-21 concentration by dampening the inflammatory state and insulin resistance. However, the change in FGF-21 concentration during the 6-month ARB treatment did not correlate with the changes in hs-CRP concentration and HOMA-IR. It is possible that hs-CRP concentration and HOMA-IR did not change much after the 6 months and that the magnitude of their changes was insufficient to show a significant correlation with the change in FGF-21 concentration. In addition, decreased FGF-21 concentration may be an incidental finding irrespective of the changes in inflammation or insulin resistance. This unresolved issue needs to be investigated further in a well-designed prospective study in this population.

Our study has several limitations. As a cross-sectional study design, this study does not provide clear evidence of causality; and the results need further confirmation. The relatively small sample size is another drawback that could have led to selection bias. In addition, the study population was limited to nondiabetic PD patients. However, because these patients have low-grade inflammation and insulin resistance similar to that observed in patients with the metabolic syndrome, our study subjects are good models to investigate whether FGF-21 has potential as a new indicator of metabolic regulation. Lastly, the intervention with ARB was a pilot study and did not include a control group; and studying the effect of ARB on serum FGF-21 concentration needs to also include healthy subjects.

In conclusion, this study showed that serum FGF-21 concentration was much higher in patients receiving PD. Fibroblast growth factor–21 concentration was significantly correlated with RRF, inflammatory markers, and HOMA-IR. These findings suggest that FGF-21 play a role in insulin resistance in ESRD patients. A well-designed, controlled prospective study is warranted to identify the clinical significance of FGF-21.

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