Natural History and Metabolic Implications of the new Hormone Fibroblast Growth Factor 21 in Uremic Patients on Peritoneal Dialysis

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Introduction

Human fibroblast growth factor 21 (FGF21) is a new liver hormone that stimulate adipocyte glucose uptake and is involved in regulation of body fat.

Patients and Methods

We studied 48 uremic patients undergoing peritoneal dialysis (PD). Patients were evaluated at baseline, and 1, 2 and 3 years after starting PD. At each evaluation, clinical status, biochemical parameters (including FGF21, glucose, insulin, homeostatic model assessment of insulin resistance index [HOMA-IR] and non-esterified fatty acids concentration [NEFA]), and peritoneal function parameters were assessed.

Table 1. Clinical, biochemical, renal and dialysis parameters in 37 non-diabetic patients on PD at baseline and during the 3 years of the study

	Baseline	First year	Second year	Third year
BMI (kg/m^2)	26.5±3.3	26.8±3.7	27.0 ±3.9	27.8.3±3.9
RRF (ml/min)	7.4±2.8	5.7±3.4**	4.3±3.4**	3.6±3.6**
Glucose (mg/dl)	88.1±14.8	94.6±20.7	89.1±11.3	91±14.8
Albumin (g/dl)	3.4±0.4	3.3±0.4	3.3±0.4	3.6±0.5
NEFAs (mg/dl)	146 (88-177.5)	127 (75-144)	130 (114-175.5)	114 (79-190)
Insulin (µUI/ml)	11 (6.5-17)	10 (5.5-17.5)	9 (4-13)	8 (4-12)
HOMA-IR	1.96(1.23-4.15)	2.32 (1.25-4.39)	1.65 (0.79-2.86)**	1.45 (0.81-3.4)
FGF-21 (pg/ml)	253 (59-685)	582 (60.5-949)	447 (200-1307)**	647 (120.5-1117)**
PPL, g/24h	5.8±1.7	5.9±1.9	6±2.3	5.5±2.4
Urea MTC (ml/min)	23.9±4.9	24.4±7.1	24.2±6	22±6
Creat. MTC (ml/min)	8.6±2.1	8.7±3.8	9±2.5	9.6±5.8

Data are the mean±SD for normally distributed data and median (interquartile range) for nonparametric data.
Abbreviations: PD, peritoneal dialysis; BMI, body mass index; NEFAs, non-esterified fatty acid; RRF, residual renal function; PPL, peritoneal protein losses; MTC, mass transport area coefficient.
*p<0.05 and **p<0.01 vs baseline (Wilcoxon signed-rank test)

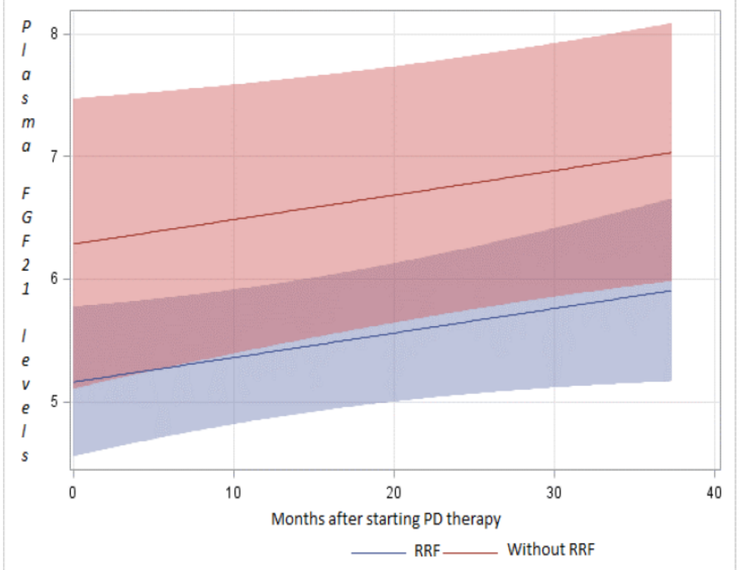

Figure 2. Contour plot representing the evolution of plasma FGF-21 levels (y-axis, log scale) over time according to residual renal function (RRF).
The quantitative color scheme was chosen in a log scale (blue, the lowest; red, the highest) to achieve optimal range in the display; the annotated color quantitation scale shows the 95% confidence interval for the values

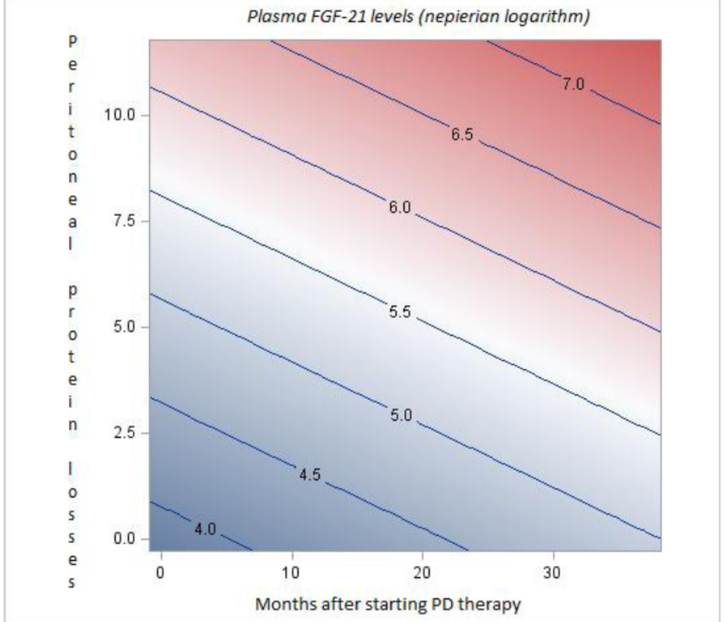

Figure 3. Contour plot representing the independent association between plasma FGF-21 levels (represented by the blue lines), peritoneal protein losses (y-axis) and time on PD (x-axis).
This contour plot indicates the FGF-21 level expected according to time on PD and PPL.

Table 2. Correlation between clinical and analytical parameters with FGF-21 at baseline and at first year. Correlation of increment during the first year in clinical and analytical parameters with FGF-21 increment in non diabetic patients

Data are expressed as correlation coefficient for nonparametric data (Spearman Rho). In the last column, we showed the correlation between the change in FGF-21 levels within the first year with the change in the values in these parameters, in the same time, in non-diabetic patients.
Abbreviations: BMI, body mass index; NEFA, non-esterified fatty acid; RRF, residual renal function; PPL, peritoneal protein losses; MTC, mass transport area coefficient.
*p<0.05 and **p<0.01.

Objective

Our aim has been to define the natural history of FGF21 in PD patients and analyze its relationship with glucose metabolism, peritoneal function, and residual renal function (RRF).

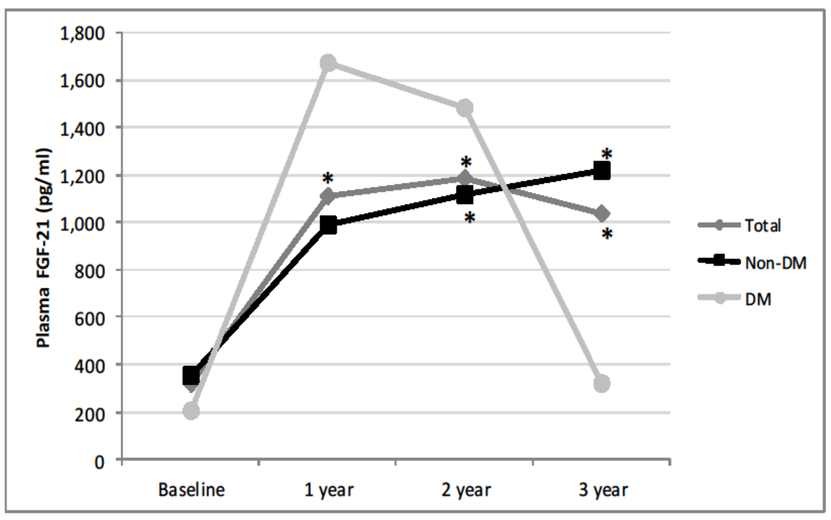

Figure 1. FGF-21 plasma levels variation over time in the studied 48 patients, according to the presence or absence of diabetes (DM).

Results

- Plasma FGF21 concentrations significantly increased over the first year and maintained at high levels during the rest of the study period, especially among non-diabetic patients (n=37; figure 1).
- In non-diabetic patients glucose levels did not modify, whereas HOMA-IR showed a significant reduction at second year (1.96[1.23-4.15] *vs.* 1.65[0.79-2.86], p<0.01; table 1).
- Baseline FGF21 concentrations correlated with RRF (rho=-0.484, p<0.05) and peritoneal protein losses (PPL, rho=0.410, p<0.05; table 2).
- Using a mixed model analysis, we found a positive correlation between time on dialysis and FGF21 levels (p<0.001). There was no association between FGF21 levels and age, body mass index, HOMA-IR, NEFA, glucose, glucose load from PD solutions, and peritoneal mass transfer coefficients of urea and creatinine (table 2).
- Patients with RRF had significantly (p<0.05) lower levels of FGF21 than those without it (figure 2), and there was a significant positive association between FGF21 and PPL (p<0.05), independently of the time on dialysis (table 2, figure 3).

	Baseline parameters with baseline FGF-21	1st year parameters with 1ST year FGF-21	Δ FGF-21 with change in parameters
BMI (kg/m^2)	-0.200	-0.091	-0.253
RRF (ml/min)	-0.484*	-0.272	-0.311
Glucose (mg/dl)	0.038	-0.302	-0.053
Albumin (g/dl)	0.064	-0.299	-0.055
NEFAs (mg/dl)	-0.058	-0.006	-0.076
Insulin (µUI/ml)	0.280	-0.332	-0.214
HOMA-IR	0.203	-0.396*	-0.154
PPL (g/24h)	0.410*	0.566**	0.233
Urea MTC (ml/min)	-0.042	-0.235	-0.016
Cre. MTC (ml/min)	0.006	0.113	0.065

Conclusion

Our data suggest that FGF21 plasma levels importantly increase during PD therapy. This increment is associated with RRF and PPL. The absence of increment in insulin resistance in spite of maintained peritoneal glucose load suggests that FGF-21 might behave as a protective factor against insulin resistance.