Serum Levels of the Adipokine FGF21 Depend on Renal Function

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OBJECTIVE — To investigate renal elimination of the adipokine fibroblast growth factor 21 (FGF21) by determining circulating FGF21 levels in patients on chronic hemodialysis (CD) as compared with control subjects with a glomerular filtration rate (GFR) >50 ml/min.

RESEARCH DESIGN AND METHODS — FGF21 was determined by enzyme-linked immunosorbent assay in control ($n = 60$) and CD ($n = 60$) patients and correlated to clinical and biochemical measures of renal function, glucose and lipid metabolism, and inflammation in both groups.

RESULTS — Median serum FGF21 levels were >15-fold higher in CD patients (3,710.6 ng/l) than in subjects with a GFR >50 ml/min (201.9 ng/l) ($P < 0.001$). Furthermore, serum creatinine positively and GFR negatively predicted FGF21 concentrations in multiple regression analyses in control subjects ($P < 0.05$).

CONCLUSIONS — FGF21 serum levels increase in CD patients and are related to markers of renal function in control subjects.

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Recently, fibroblast growth factor 21 (FGF21) was introduced as a novel adipokine with potent antidiabetic properties (1–4). In contrast to extensive experiments in animals, only one study to date has determined regulation and function of FGF21 in humans in vivo (5), and no data have been published about the relation of this adipokine to renal function.

RESEARCH DESIGN AND METHODS

— The design of the study has been described in detail recently (6–8). Briefly, 120 Caucasian men ($n = 62$) and women ($n = 58$) were recruited with 60 patients having a glomerular filtration rate (GFR) >50 ml/min (control subjects) as assessed by the original Modification of Diet in Renal Disease formula (9) and 60 patients being on chronic hemodialysis (CD). A total of 30 control subjects and 32 CD patients had type 2 diabetes. The study was approved by the local ethics committee, and all subjects gave written informed consent before taking part in the study.

Assays

Blood samples were taken after an overnight fast. In CD patients, blood was drawn just before hemodialysis started. FGF21 (Biovendor, Modrice, Czech Republic), adiponectin (Mediagnost, Reutlingen, Germany), and leptin (Mediagnost) were determined with enzyme-linked immunosorbent assays according to the manufacturer's instructions.

Statistical analysis

Statistical analyses are specified in RESULTS and in the Table 1 legend.

RESULTS

FGF21 serum levels are increased in CD patients

Table 1 summarizes clinical characteristics of the subgroups studied (control, CD) further divided into nondiabetic and diabetic subjects. Median circulating FGF21 was >15-fold higher in CD patients (3,710.6 ± 5,541.3 ng/l) compared with control subjects (201.9 ± 275.5 ng/l) ($P < 0.001$) (Table 1). Furthermore, FGF21 serum levels were significantly higher in men (1,959.0 ± 4,505.5 ng/l) compared with women (446.9 ± 1,609.0 ng/l) ($P < 0.05$) but did not depend on type 2 diabetes.

Univariate correlations

Using the Spearman's rank correlation method, serum FGF21 concentrations positively correlated with BMI ($r = 0.33$, 95% CI 0.08–0.54, $P = 0.011$) and creatinine ($r = 0.32$, 0.07–0.53, $P = 0.014$) in control subjects. In addition, FGF21 negatively correlated with LDL cholesterol ($r = -0.33$, -0.08 to -0.54, $P = 0.010$) and GFR ($r = -0.26$, -0.01 to -0.49, $P = 0.041$) in control patients. In CD patients, circulating FGF21 levels were positively associated with waist-to-hip ratio ($r = 0.29$, 0.03–0.50, $P = 0.027$) and fasting glucose ($r = 0.33$, 0.09–0.54, $P = 0.009$).

Multivariate regression analyses

Multiple linear regression analysis revealed that creatinine (β coefficient 0.361, 95% CI 0.088–0.634, $P = 0.011$) and LDL cholesterol (β coefficient -0.413, -0.660 to -0.166, $P = 0.001$) remained independently associated with circulating FGF21 levels in control subjects after adjustment for sex, BMI, and type 2 diabetes. When GFR instead of creatinine was included in this multivariate analysis, GFR remained independently associated with serum FGF21 concentrations (β coefficient -0.296, -0.529 to -0.063, $P = 0.014$). Furthermore, creatinine and GFR remained significant independent predictors of circulating FGF21 in diabetic control subjects ($P < 0.05$), and a trend toward an independent association of creatinine and GFR with FGF21 levels was also observed in nondiabetic

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Table 1—*Baseline characteristics of the study population*

	Control/T2DM$^-$	Control/T2DM$^+$	CD/T2DM$^-$	CD/T2DM$^+$
n	30	30	28	32
FGF21 (ng/l)	195.1 ± 239.9	207.6 ± 384.1	3,825.1 ± 5,593.9	3,593.8 ± 6,562.2
Age (years)	63 ± 19	63 ± 16	59 ± 23	68 ± 12
Sex (M/F)	11/19	16/14	15/13	20/12
BMI (kg/m^2)	28.2 ± 5.6	29.1 ± 5.2	25.2 ± 6.5*†	27.9 ± 6.6
Waist-to-hip ratio	0.88 ± 0.12	0.94 ± 0.10*	0.96 ± 0.18	1.00 ± 0.14*
Systolic blood pressure (mmHg)	125 ± 21	126 ± 20	125 ± 38	120 ± 25
Diastolic blood pressure (mmHg)	77 ± 10	73 ± 15	77 ± 20	70 ± 18
Creatinine (μmol/l)	76 ± 17	72 ± 22	829 ± 431*†	717 ± 221*†
Albumin (g/l)	46.2 ± 3.7	46.5 ± 3.4	41.6 ± 4.9*†	41.3 ± 4.9*†
Urea (mmol/l)	5.1 ± 1.5	5.3 ± 2.1	17.1 ± 7.4*†	18.7 ± 7.9*†
GFR (ml/min)	82.5 ± 23.9	89.3 ± 35.5	7.0 ± 4.0*†	7.6 ± 3.2*†
Fasting glucose (mmol/l)	5.1 ± 1.3	7.6 ± 3.2*	4.6 ± 1.2†	5.2 ± 3.3†‡
Fasting insulin (pmol/l)	45.1 ± 33.3	47.9 ± 62.6	28.2 ± 47.6	50.1 ± 91.6
HOMA-IR	1.4 ± 1.2	2.8 ± 3.0	0.8 ± 1.4†	1.4 ± 3.3
Free fatty acid (mmol/l)	0.5 ± 0.2	0.6 ± 0.4	0.6 ± 0.5	0.7 ± 0.5
Cholesterol (mmol/l)	5.3 ± 0.9	4.9 ± 1.5	4.4 ± 1.1*	4.2 ± 1.3*
HDL cholesterol (mmol/l)	1.4 ± 0.4	1.2 ± 0.5	1.0 ± 0.5*†	1.0 ± 0.3*†
LDL cholesterol (mmol/l)	3.5 ± 1.1	2.9 ± 0.9[1]	2.7 ± 0.9*	2.1 ± 1.4*†
Triglycerides (mmol/l)	1.1 ± 0.8	1.4 ± 0.9	1.6 ± 0.9*	1.8 ± 1.4*
Adiponectin (mg/l)	6.8 ± 3.8	4.6 ± 4.8	14.3 ± 15.7*†	11.4 ± 12.6*†
Leptin (μg/l)	17.8 ± 25.4	16.8 ± 22.3	11.4 ± 35.1	28.0 ± 54.4†‡
C-reactive peptide (mg/l)	2.5 ± 4.4	2.8 ± 3.8	3.5 ± 11.9	6.9 ± 24.7*†

Data are median ± interquartile range. The groups are divided into control subjects without diabetes (control/T2DM$^-$) or with diabetes (control/T2DM$^+$) and CD patients without diabetes (CD/T2DM$^-$) or with diabetes (CD/T2DM$^+$). HOMA-IR, homeostasis model assessment of insulin resistance. Parameters were analyzed by the Kruskal-Wallis test followed by Bonferroni's post hoc analysis. *$P < 0.05$ vs. Control/T2DM$^-$, †$P < 0.05$ vs. Control/T2DM$^+$, ‡$P < 0.05$ vs. CD/T2DM$^-$.

control subjects ($P < 0.07$) (data not shown). In CD patients, fasting glucose (β coefficient 0.354, 0.090–0.618, $P = 0.009$) predicted circulating FGF21 independent of sex, waist-to-hip ratio, GFR, and type 2 diabetes. However, an association between creatinine and GFR on one hand and FGF21 on the other hand could not be shown in CD patients in univariate and multivariate analyses.

CONCLUSIONS — In the current study, the hypothesis that renal elimination is a major route by which physiological FGF21 serum levels are maintained is supported by two novel findings. First, we demonstrate that both creatinine and GFR are significantly associated with circulating FGF21 in control subjects with a GFR >50 ml/min independent of sex, BMI, LDL cholesterol, and type 2 diabetes in multivariate analysis. Furthermore, we show that FGF21 is increased 15-fold in CD patients, i.e., in patients with severely impaired renal function. Based on the results of our study, serum creatinine or other markers of renal function should always be included in future studies concerning FGF21 physiology.

Adiponectin serum levels are significantly increased in CD patients compared with control subjects in the current study. These results support previous findings (10–12) that renal elimination contributes to circulating concentrations of this adipokine.

Circulating FGF21 and adiponectin are slightly but significantly higher after as compared with before hemodialysis in a subset of the CD patients ($n = 29$) recruited again ~2 years after blood was obtained for this study (data not shown). These results support the notion that both adipokines are not dialyzable.

The physiological significance of increased FGF21 serum concentrations in renal failure remains to be elucidated. It is interesting to note that circulating FGF21 is also significantly higher in another population with increased cardiovascular risk, i.e., patients exhibiting components of the metabolic syndrome (5). Because FGF21 is an adipokine with glucose-lowering effects (1–4), it is tempting to speculate that paradoxical increase of this protein in cardiovascular risk populations is a compensatory mechanism to counteract metabolic stress. Alternatively, FGF21 resistance might be found in obesity and renal failure, leading to compensatory up-regulation of this adipokine. This mechanism would be reminiscent of hyperinsulinemia and hyperleptinemia, which are a consequence of increased production in compensation for obesity-associated resistance to insulin and leptin (13). Here, further studies are needed to investigate whether subjects and animal models with obesity and renal failure exhibit decreased FGF21 sensitivity and impaired receptor or postreceptor signaling in its target tissues. In addition, adiponectin resistance has been described in different animal models (14,15) and might play a role in upregulation of adiponectin in CD patients.

Some limitations of the study have to be pointed out. First, there is a risk of overfitting the multivariate models since our study is limited by a relatively small sample size. Furthermore, it remains unclear at present why creatinine and GFR are not independently correlated to FGF21 levels in CD patients in contrast to the results obtained in control subjects. It is tempting to speculate that mechanisms besides renal elimination contribute to FGF21 regulation in CD, since renal function is severely impaired in these patients.

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