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.

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 (1,950.0 ± 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 subjects.
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 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 the results obtained in control subjects. It is important 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 the results obtained in control subjects. It is important 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 the results obtained in control subjects. It is important 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 the results obtained in control subjects. It is important 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.
FGF21 and renal function

Acknowledgments—This study was supported by a grant from the Deutsche Forschungsgemeinschaft (DFG), KFO 152: “Atherobesity” project FA476/4-1 (TP4) to M.F., project BL833/1-1 (TP3) to M.B., the IZKF Leipzig to M.F. (Project B25), and the Deutsche Diabetes-Stiftung to M.F.

No potential conflicts of interest relevant to this article were reported.

References

1. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, Sandusky GE, Hammond LJ, Moyers JS, Owens RA, Gromada J, Brozinick JT, Hawkins ED, Wroblewski VJ, Li DS, Mehrbod F, Jaskunas SR, Shanafelt AB: FGF-21 as a novel metabolic regulator. J Clin Invest 115:1627–1635, 2005

2. Kharitonenkov A, Wroblewski VJ, Koester A, Chen YF, Clutinger CK, Tigno XT, Hansen BC, Shanafelt AB, Etgen GJ: The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. Endocrinology 148:774–781, 2007

3. Wente W, Efanov AM, Brenner M, Khartitonenkov A, Koester A, Chen YF, Clutinger CK, Tigno XT, Hansen BC, Shanafelt AB, Etgen GJ: The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. Endocrinology 148:774–781, 2007

4. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E: Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab 5:426–437, 2007

5. Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, Wong RL, Chow WS, Tso AW, Lam KS, Xu A: Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. Diabetes 57:1246–1253, 2008

6. Seeger J, Ziegelmeier M, Bachmann A, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M: Serum levels of the adipokine vaspin in relation to metabolic and renal parameters. J Clin Endocrinol Metab 93:247–251, 2008

7. Sommer G, Ziegelmeier M, Bachmann A, Kralisch S, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M: Serum levels of adipocyte fatty acid binding protein are increased in chronic haemodialysis. Clin Endocrinol (Oxf), 2008 (Epub ahead of print)

8. Ziegelmeier M, Bachmann A, Seeger J, Lossner U, Kratzsch J, Bluher M, Stumvoll M, Fasshauer M: Serum levels of the adipokine RBP-4 in relation to renal function. Diabetes Care 30:2588–2592, 2007

9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation: Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–470, 1999

10. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y: Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 13:134–141, 2002

11. Filippidis G, Liakopoulos V, Mertens PR, Kiropoulos T, Stakias N, Verikouki C, Patsidis E, Kourkoulis G, Stefanidis I: Resistin serum levels are increased but not correlated with insulin resistance in chronic hemodialysis patients. Blood Purif 23:421–428, 2005

12. Huang JW, Yen CJ, Chiang HW, Hung KY, Tsai TJ, Wu KD: Adiponectin in peritoneal dialysis patients: a comparison with hemodialysis patients and subjects with normal renal function. Am J Kidney Dis 43:1047–1055, 2004

13. Zhang Y, Scarpace PJ: The role of leptin in leptin resistance and obesity. Physiol Behav 88:249–256, 2006

14. Lin HV, Kim JY, Pocai A, Rossetti L, Shapiro L, Scherer PE, Accili D: Adiponectin resistance exacerbates insulin resistance in insulin receptor transgenic/knockout mice. Diabetes 56:1969–1976, 2007

15. Larzer CZ, Yeh MM, Williams J, Bell-Anderson KS, Farrell GC: MCD-induced steatohepatitis is associated with hepatic adiponectin resistance and adiogenic transformation of hepatocytes. J Hepatol 49:407–416, 2008