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FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment

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Abstract

Background. High levels of the phosphaturic hormone fibroblast growth factor 23 (FGF-23) predict mortality in haemodialysis patients. The prognostic relevance of increased plasma FGF-23 levels in patients with less advanced chronic kidney disease (CKD) who are not on dialysis therapy is presently unknown.

Methods. We measured plasma c-terminal FGF-23 levels in 149 CKD patients not undergoing dialysis treatment. Patients were stratified by their baseline FGF-23 levels (>104 vs ≤104 rU/mL) and followed for a period of 4.8± 0.9 years. During the follow-up, the pre-specified combined clinical endpoint was the first occurrence of a cardiovascular event, e.g. myocardial infarction, coronary artery angioplasty/stenting/bypass surgery, stroke, carotid endarterectomy/stenting, non-traumatic lower extremity amputation, lower limb artery surgery/angioplasty/stenting or death.

Results. At baseline, elevated FGF-23 levels >104 rU/mL were associated with more advanced CKD. Traditional cardiovascular risk factors and prevalent cardiovascular disease did not differ between CKD patients with high vs low FGF-23 levels. Fifty patients experienced a cardiovascular event during follow-up. Compared with CKD patients with FGF-23 ≤104 rU/mL, CKD patients with FGF-23 levels above the cut-off had worse event-free survival at univariate (log-rank test P=0.012) and multivariate analysis [hazard ratio 2.49 (95% CI 1.40–4.39); P=0.002].

Conclusions. Elevated FGF-23 plasma levels predict cardiovascular events in CKD patients not on dialysis therapy. This finding complements two recent cohort studies in which incident and prevalent haemodialysis patients with highest FGF-23 levels had worst survival. Lowering FGF-23 levels (e.g. by oral phosphate binder medication) could emerge as a promising new therapeutic option to reduce cardiovascular morbidity in CKD patients.

Keywords: cardiovascular mortality; CKD; FGF-23; klotho; phosphate

Introduction

Patients suffering from chronic kidney disease (CKD) are at increased risk for fatal and non-fatal cardiovascular events. Compared with the general population, age-standardized cardiovascular mortality is increased by a factor of 8.8 in incident dialysis patients [1]. This increased cardiovascular mortality results from the interplay of traditional (e.g. hypertension, dyslipidaemia, diabetes) and non-traditional cardiovascular risk factors, comprising primarily microinflammation, oxidative stress and notably deranged calcium phosphate metabolism. With respect to the latter, large prospective cohort studies revealed that hyperphosphataemia, hyperparathyroidism [2–4] and hypovitaminosis D [5] are each independently associated with cardiovascular morbidity and mortality in CKD. In addition, preliminary results of recent intervention studies indicate that substitution of vitamin D [6], pharmacological lowering of parathyroid hormone [7] and intake of phosphate binders [8] might improve cardiovascular outcome, even though data from adequately powered randomized trials are still pending.

Fibroblast growth factor 23 (FGF-23), a 251-amino-acid protein synthesized and secreted by osteoblasts and osteocytes, is a recently discovered potent regulator of serum phosphate levels. Together with its co-receptor Klotho, FGF-23 induces renal phosphate excretion by suppression of renal Na/Pi co-transporter activity in the proximal tubule. Additionally, it reduces intestinal phosphate absorption by inhibiting the 25-hydroxyvitamin D3 1-α-hydroxylase, which catalyses the rate-determining step of calcitriol synthesis [9]. In CKD stage 5 patients, decreased renal phosphate elimination and/or impaired FGF-23 clearance result in a >100-fold elevation of serum FGF-23 levels [10]. In these patients, elevated FGF-23 not only fails to protect from hyperphosphataemia—as renal excretion capacity extinguishes in dialysis patients—but also predicts adverse outcome. Among incident dialysis patients participating in the ArMORR study, an association between elevated FGF-23 levels and 1-year mortality was reported.

Most surprisingly, the prognostic impact of high FGF-23 levels remained significant after adjustment for other established parameters of calcium phosphate metabolism [11]. Finally, FGF-23 levels were better outcome predictors than serum phosphate levels [12]. The findings from the ArMORR study were recently confirmed in prevalent dialysis patients [13].

While these epidemiological studies primarily focused on dialysis patients, FGF-23 levels rise much earlier in CKD [14] in order to keep serum phosphate levels within normal ranges. Thus, in these patients FGF-23 seemingly exerts physiological functions and might protect from harmful effects of hyperphosphataemia. Counterintuitively, in the Mild to Moderate Kidney Disease (MMKD) study, non-dialysis CKD patients with high FGF-23 levels were at increased risk for loss of renal function. More specifically, we found a cut-off value of 104 rU/mL for c-terminal FGF-23 that predicted renal endpoints—defined as doubling of serum creatinine and/or terminal renal failure—independently of baseline glomerular filtration rate [15]. Investigating relatively young, non-diabetic patients with mostly mild to moderate impairment of renal function, the MMKD study was not designed to evaluate cardiovascular outcome in CKD patients. We therefore analysed an independent cohort of CKD patients with more severe comorbidity and more advanced CKD, testing the hypothesis that FGF-23 levels predict cardiovascular outcome in non-dialysis CKD patients.

Materials and methods

We recruited 149 patients suffering from CKD between March 2004 and October 2004. All patients regularly visited our out-patient department and gave informed consent to their study participation. Patients who were undergoing renal replacement therapy were excluded. Underlying causes for CKD were glomerulonephritis [GN; n=43 (GN diagnosed by renal biopsy: n=25; GN diagnosed clinically: n=18)], diabetic nephropathy (n=27), interstitial nephropathy (n=19), hypertensive nephropathy (n=16), autosomal-dominant polycystic kidney disease (n=8), other primary renal disease (n=24) and unknown conditions (n=12). The study was approved by the local ethics committee.

A standardized questionnaire was used to record a history of smoking, diabetes, current drug intake and cardiovascular comorbidity. Additionally, comorbidity was assessed by chart review. Prevalent cardiovascular disease was defined as a history of myocardial infarction, coronary artery angioplasty/stenting/bypass surgery, major stroke, carotid endarterectomy/stenting, non-traumatic lower extremity amputation or lower limb artery bypass surgery/angioplasty/stenting. Patients were categorized as active smokers if they were current smokers or had stopped smoking <1 month before entry into the study. Patients with self-reported or physician-reported diabetes mellitus, with a non-fasting blood glucose level of >200 mg/dL, with a fasting blood glucose level of >126 mg/dL or with current use of hypoglycaemic medication, were categorized as diabetic. Body mass index was calculated as weight (kg)/height (m)^2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 min of rest. Pulse pressure was calculated as SBP−DBP. All clinical data were obtained by a single investigator (B.R.).

Blood samples were taken under standardized conditions at the baseline visit. The samples were immediately centrifuged at 4000 r.p.m. for 5 min at room temperature. Supernatants were stored in aliquots at −80°C until further use. FGF-23 levels were measured from plasma samples using the human c-terminal ELISA (Immutopics, San Clemente, CA, USA; low cut-off value 3 rU/mL, high cut-off value 2000 rU/mL) as described in detail before [15]. Glucose, creatinine, total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using standard techniques. Glomerular filtration rate was estimated (eGFR) using the Modification of Diet in Renal Disease study equation 4, and proteinuria was quantified as protein-to-creatinine ratio. Additionally, in a subgroup of 115 patients, calcitriol levels were determined.

All participants were followed from the baseline examination until death or until 31 July 2009. We deliberately chose not to censor patients at onset of renal replacement therapy (n=51). The pre-specified combined clinical endpoint was the first occurrence of a cardiovascular event defined as myocardial infarction, coronary artery angioplasty/stenting/bypass surgery, stroke with symptoms lasting >24 h, carotid endarterectomy/stenting, non-traumatic lower extremity amputation, lower limb artery surgery/angioplasty/stenting or death. Patients were invited for follow-up visits at least once yearly, and follow-up data were obtained by interviews and chart review by two investigators who were blinded for FGF-23 measurements (S.S. and D.R.).

Statistics

Data management and statistical analysis were performed with SPSS 13.0.1. The level of significance was set at P<0.05. Categorical variables are presented as percentage of patients and compared using Fisher's exact test. Continuous data are expressed as means±standard deviation and compared using the Mann–Whitney test [FGF-23 levels are presented

Table 1. Baseline characteristics of the study participants

	Overall (N=149)	FGF-23 ≤104 rU/mL (N=88)	FGF-23 >104 rU/mL (N=61)	P
Age (years)	61±14	61±13	60±16	0.917
Women (%)	69 (46%)	39 (44%)	30 (49%)	0.618
Smokers (%)	15 (10%)	9 (10%)	6 (10%)	1.000
Diabetes mellitus (%)	46 (31%)	25 (28%)	21 (34%)	0.474
History of CVD (%)	45 (30%)	24 (27%)	21 (34%)	0.369
eGFR (mL/min/1.73 m^2)	36±23	46±21	22±18	<0.001
Total cholesterol (mg/dL)	206±48	206±47	205±49	0.853
HDL cholesterol (mg/dL)	53±17	55±17	50±17	0.098
Body mass index (kg/m^2)	29±6	30±5	29±6	0.090
Plasma calcium (mmol/L)	2.3±0.2	2.4±0.1	2.3±0.2	0.010
Plasma phosphate (mg/dL)	3.8±1.2	3.4±0.8	4.4±1.4	<0.001
Proteinuria (g/g creatinine)	1.5±2.4	0.8±1.7	2.6±2.9	<0.001
Intake of phosphate binders	16 (11%)	2 (2%)	14 (23%)	<0.001
Intake of active vitamin D	37 (25%)	13 (15%)	24 (39%)	0.001
Systolic blood pressure (mmHg)	169±29	168±29	170±28	0.564
Diastolic blood pressure (mmHg)	98±18	98±19	97±16	0.969
Pulse pressure (mmHg)	71±21	70±21	73±21	0.429

Variables are presented as percentage, or as mean±SD, as appropriate.

Table 2. Baseline characteristics of patients with and without an incident cardiovascular event during follow-up

	No event (N=99)	Event (N=50)	P
Age (years)	58±15	67±11	<0.001
Women (%)	49 (49%)	20 (40%)	0.30
Smokers (%)	13 (13%)	2 (4%)	0.09
Diabetes mellitus (%)	20 (20%)	26 (52%)	<0.001
History of CVD (%)	22 (22%)	23 (46%)	0.004
eGFR (mL/min/1.73 m^2)	41±24	28±20	0.001
Total cholesterol (mg/dL)	206±45	207±54	0.781
HDL cholesterol (mg/dL)	55±18	50±14	0.089
Body mass index (kg/m^2)	29±6	30±6	0.319
Plasma calcium (mmol/L)	2.3±0.2	2.3±0.2	0.964
Plasma phosphate (mg/dL)	3.6±1.1	4.1±1.3	0.025
FGF-23 (rU/mL)[a]	67 (16–153)	151 (33–759)	<0.001
Proteinuria (g/g creatinine)	0.9±1.6	2.6±3.2	0.001
Intake of phosphate binders	10 (10%)	6 (12%)	0.782
Intake of active vitamin D	19 (19%)	18 (36%)	0.029
Systolic blood pressure (mmHg)	164±26	178±30	0.010
Diastolic blood pressure (mmHg)	96±13	101±25	0.616
Pulse pressure (mmHg)	67±20	77±21	0.004

[a]FGF-23 levels are presented as median (interquartile range) because of skewed distribution.

as median (interquartile range) because of skewed distribution]. For measuring the relationship between continuous data, Spearman's correlation coefficients were calculated, and partial correlation analyses adjusting for eGFR were performed. To assess the prognostic impact of elevated FGF-23 levels (>104 rU/mL, as defined by Fliser *et al.* [15]) on future cardiovascular events, Kaplan–Meier survival curves were calculated and compared by the log-rank test. Cox proportional hazards models were calculated to examine relationships of elevated FGF-23 levels with event-free survival in univariate analysis (Step 1), after adjustment for age and gender (Step 2), and after further adjustment for diabetes mellitus, prevalent cardiovascular disease plasma phosphate, eGFR, prevalent cardiovascular disease and intake of phosphate binders/active vitamin D (step 3; method: forward stepwise). In these proportional hazards models, FGF-23 levels were analysed both as a continuous log-transferred variable and as a categorical variable after stratifying patients (≤104 vs >104 rU/mL).

Results

The baseline characteristics of all 149 study participants are shown in Table 1. As expected, FGF-23 levels >104 rU/mL were associated with more advanced CKD, reflected by lower eGFR, higher proteinuria and higher phosphate levels. Traditional cardiovascular risk factors and prevalence of cardiovascular disease did not differ between CKD patients with elevated vs normal FGF-23 levels (Table 1).

An incident cardiovascular event had occurred in 50 patients (34%) before 31 July 2009. The remaining 99 patients have been followed for 4.8±0.9 years, including four patients who were lost during the follow-up period. Patients who experienced a cardiovascular event were older, had a higher prevalence of cardiovascular disease and diabetes mellitus at baseline, higher systolic blood pressure and pulse pressure measurements, and more advanced CKD with lower eGFR, higher proteinuria and higher plasma phosphate levels (Table 2). Compared with CKD patients with FGF-23 ≤104 rU/mL, CKD patients with higher FGF-23 levels had worse event-free survival (Figure 1). When stratifying the patients by glomerular filtration rate at baseline, FGF-23 levels >104 rU/mL predicted adverse outcome among patients with less severe CKD (eGFR >30 mL/min/1.73 m^2), but not among patients with more severe impairment of kidney function. Similarly, the prognostic impact of elevated FGF-23 tended to be more pronounced in patients with baseline phosphate levels below the median, even though these analyses did not reach the level of statistical significance given the small sample size after stratification into subgroups (Figure 2).

A significant impact of elevated FGF-23 levels on cardiovascular outcome remained when adjusting for age, gender, baseline eGFR, prevalent cardiovascular disease, diabetes mellitus, serum phosphate, intake of active vita-

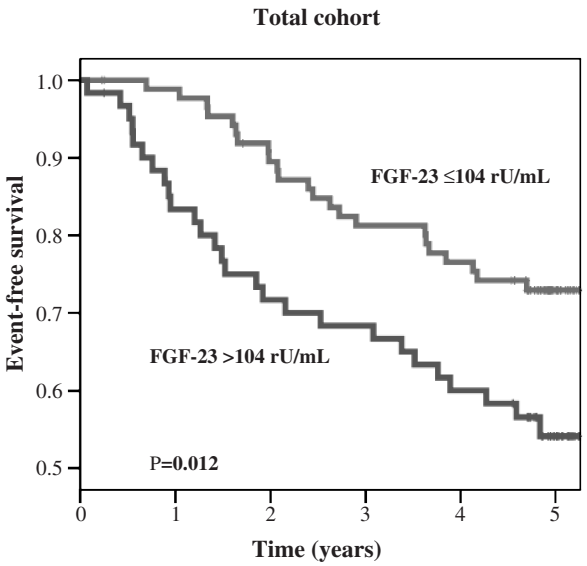

Fig. 1. FGF-23 levels and event-free survival. Patients were stratified by their plasma FGF-23 levels (FGF-23 ≤104 vs FGF-23 >104 rU/mL). Kaplan–Meier analysis with log-rank test revealed a significant difference between groups.

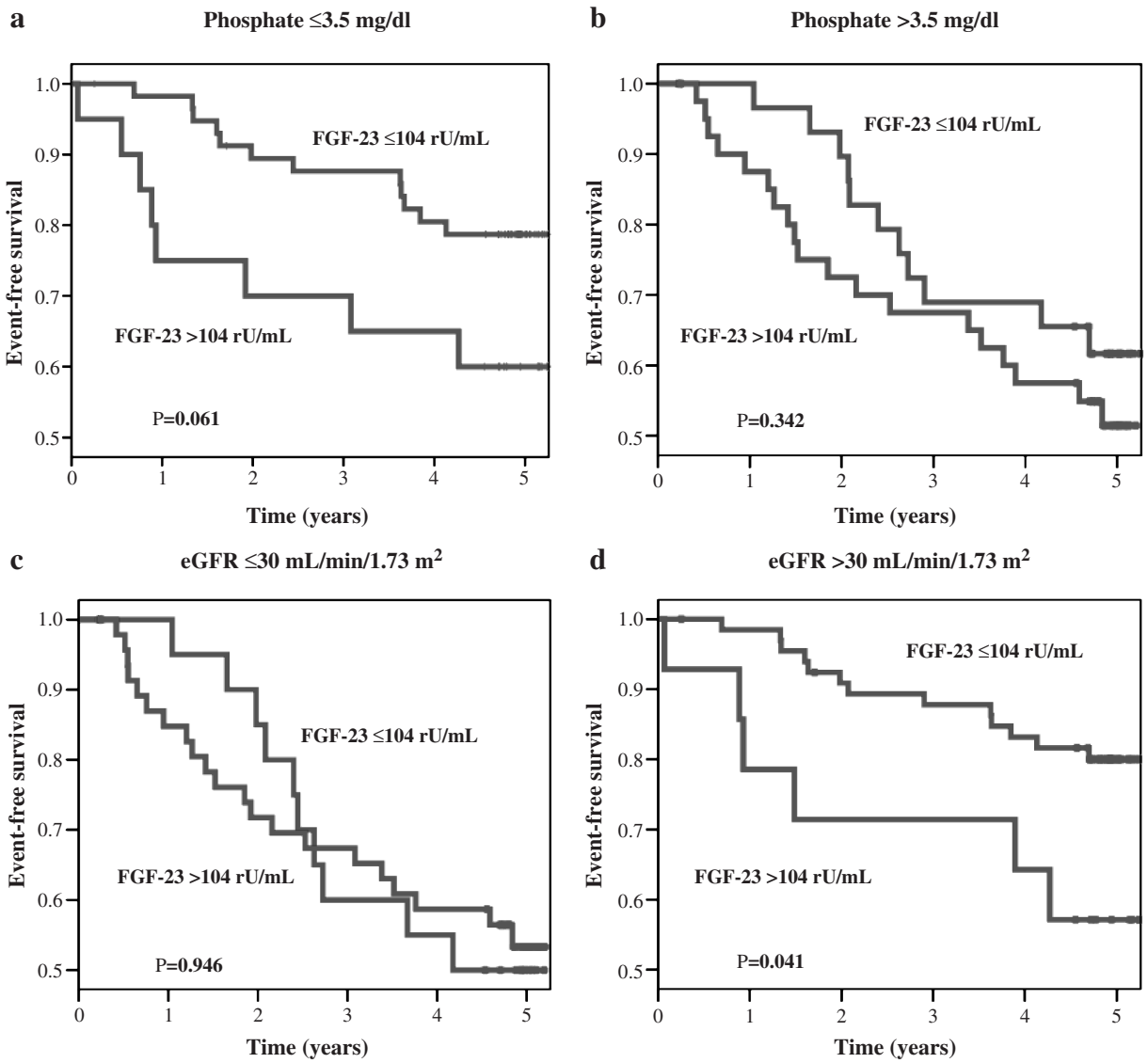

Fig. 2. FGF-23 levels and event-free survival in subgroups defined by phosphate levels [≤3.5 mg/dL (a) vs >3.5 mg/dL (b)] or by eGFR [≤30 mL/min/1.73 m^2 (c) vs >30 mL/min/1.73 m^2 (d)], respectively. Patients were stratified by their plasma FGF-23 levels (FGF-23 ≤104 vs FGF-23 >104 rU/mL; Kaplan–Meier analysis with log-rank test).

min D and phosphate binder medication in a Cox regression analysis (Table 3). When considering log-transferred FGF-23 as a continuous instead of a categorical variable, again elevated FGF-23 levels significantly predict future cardiovascular events in univariate and multivariate analysis (Table 3).

In the present study, calcitriol levels were measured in a subgroup of 115 patients. Log-transferred FGF-23 and cal-

Table 3. Cox regression analysis for cardiovascular events/death (method: forward stepwise)

	Step 1	P	Step 2	P	Step 3	P
Model 1						
FGF-23 >104 rU/mL	2.01 (1.15–3.51)	0.014	2.49 (1.41–4.40)	0.002	2.49 (1.40–4.39)	0.002
Model 2						
Log-transferred FGF-23	1.60 (1.15–2.24)	0.006	1.63 (1.16–2.29)	0.005	1.60 (1.13–2.26)	0.009

Indicated are hazard ratios, their 95% confidence interval and the level of significance. Step 1 includes FGF-23 levels [either as categorical variable (≤104 vs >104 rU/mL; model 1) or as a continuous, log-transferred variable (model 2)], Step 2 includes age and gender, and Step 3 further includes diabetes mellitus, prevalent cardiovascular disease at baseline, eGFR, plasma phosphate levels, intake of active vitamin D and intake of phosphate binder medication.

In the final step, FGF-23, age, diabetes mellitus and male gender remained independent predictors of the combined endpoint, while the other variables were excluded from analysis.

citriol were significantly correlated before ($r=-0.457$; $P<0.001$) and after exclusion of subjects who received oral calcitriol medication (remaining $n=89$; $r=-0.436$; $P<0.001$). These associations remained significant in a partial correlation analysis adjusting for eGFR (all 115 patients: $r=-0.233$; $P=0.013$; patients without calcitriol substitution: $r=-0.255$; $P=0.016$). In these latter 89 patients, adjustment for calcitriol levels did not eliminate the prognostic impact of log-transferred FGF-23 levels on cardiovascular outcome [hazard ratio 1.565 ($P=0.053$) before, 1.828 ($P=0.015$) after adjustment for calcitriol levels].

Discussion

We report for the first time an increased risk for future cardiovascular events in CKD patients with elevated FGF-23 levels not receiving renal replacement therapy. These findings complement two recent cohort studies in CKD stage 5, in which incident [11] and prevalent [13] haemodialysis patients with highest FGF-23 serum levels had the highest mortality during follow-up even after adjustment for serum phosphate levels. Our cohort differs from these earlier studies in that we included patients at earlier stages of CKD. While in CKD stage 5 patients with extinguished renal excretion capacity FGF-23 is unable to exert its physiological functions, i.e. regulation of phosphate levels by adapting renal phosphate elimination, elevated FGF-23 in earlier stages of CKD might be considered an advantageous compensatory mechanism to protect from harmful hyperphosphataemia. However, the results of the present study do not support the notion that increased FGF-23 levels are beneficial in CKD patients off dialysis.

We deliberately chose to define a cut-off value of 104 rU/mL, as this threshold best predicted CKD progression in our earlier MMKD study [15]. As the latter study was not designed to evaluate cardiovascular events in CKD patients, we decided to investigate this issue in an independent cohort of CKD patients at higher cardiovascular risk compared with MMKD study participants. More precisely, follow-up data were collected among non-diabetic CKD patients with a mean age of 46 years, a mean GFR of 63 mL/min/1.73 m^2 and proteinuria <3.5 g/day in the MMKD study, while the present study recruited older patients with worse renal function, higher proteinuria and a substantial prevalence of diabetes mellitus.

As a limitation, we were only able to determine c-terminal FGF-23, which is more stable in frozen samples [16] than the intact protein. In most cohort studies, a very strong correlation was found between c-terminal FGF-23 and intact FGF-23 [11,15], and both measurements similarly predicted outcome. Additionally, Shimada *et al.* demonstrated that both c-terminal and intact FGF-23 were accurate predictors of circulating biologically active FGF-23 [17]. Thus, detecting either the c-terminal or the intact form of the protein is considered suitable in epidemiological studies focusing on the prognostic impact of FGF-23 levels [17].

As a further limitation, FGF-23 and phosphate levels were determined at baseline, and we cannot provide data on repeated measurements. Future trials should investigate time-dependent changes in FGF-23 levels and test whether rising FGF-23 levels are more harmful than stable or declining levels.

Finally, fractional phosphate excretion was not assessed, data which would have allowed a better pathophysiological understanding of the association between elevated FGF-23 and adverse outcome.

At present time, the exact mechanisms underlying the grim prognosis in CKD patients with elevated FGF-23 levels remain uncertain. Firstly, elevated FGF-23 levels, which are closely associated with plasma phosphate levels, have been suggested to reflect a higher time-averaged phosphate burden in CKD patients. As hyperphosphataemia predicts all-cause and cardiovascular mortality in CKD patients [2], FGF-23 elevation might be considered an 'innocent bystander' of hyperphosphataemia. Against this assumption, both in the present study as well as in the two former CKD stage 5 studies [11,13], FGF-23 levels remained an independent prognostic marker after adjustment for serum phosphate. Interestingly, in the present study we found a stronger impact of FGF-23 in individuals with the lower phosphate levels, although this analysis did not reach statistical significance due to the small sample size after stratifying patients by the median for plasma phosphate levels. Secondly, FGF-23 levels are strongly correlated with residual renal function. Advanced CKD is considered a major risk factor for cardiovascular morbidity and all-cause mortality [18], and FGF-23 elevation may simply reflect CKD progression. Again, we found that adjustment for eGFR does not erase the prognostic impact of elevated FGF-23. Of note, after stratifying patients by their glomerular filtration rate, FGF-23 levels >104 rU/mL predicted adverse outcome among individuals with eGFR values >30 mL/min/1.73 m^2, not among individuals with severely impaired renal function (eGFR ≤30 mL/min/1.73 m^2).

Thirdly, elevated FGF-23 levels lower calcitriol levels via inhibition of 25-hydroxyvitamin D3 1-α-hydroxylase. Given the strong evidence for vitamin D deficiency as a non-traditional cardiovascular risk factor in CKD patients [5], increased FGF-23 levels may thus indirectly exert harm by inducing hypovitaminosis D. In the present study, calcitriol levels were measured only in a subgroup of 115 patients, of whom 89 patients received no substitution with active vitamin D. Even though the prognostic impact of elevated FGF-23 levels remains significant after adjustment for calcitriol levels in this subgroup, larger prospective trials are needed to prove how far inhibition of 25-hydroxyvitamin D3 1-α-hydroxylase mediates the harmful cardiovascular effects of FGF-23. Fourthly, FGF-23 may directly exert an unfavourable effect on the renocardiovascular system: in a cell culture model, in which vitamin D induced tubular cell apoptosis, FGF-23 and Klotho antagonized vitamin D effects by inducing cell proliferation [19]. Furthermore, while FGF-23 at physiological levels in non-CKD subjects needs Klotho for receptor binding, which renders FGF-23 effects tissue specific (given the selective renal and parathyroid Klotho expression), it has been hypothesized that highly elevated FGF-23 levels in CKD may exert certain non-specific and presumably adverse effects through low-affinity, Klotho-independent binding to FGF receptor in the cardiovascular system [20]. In line with this assumption, in

recent trials FGF-23 was found to be associated with left ventricular hypertrophy [21,22] and endothelial dysfunction [23], supporting the assumption that FGF-23 is a relevant pathophysiological factor in the adverse prognosis of CKD patients.

Preliminary data suggest that oral phosphate binders might reduce FGF-23 levels [24,25]. While treatment of traditional cardiovascular risk factors by e.g. cholesterol-lowering drugs [26,27] or ACE inhibitor therapy [28] yielded disappointing results in CKD patients, non-randomized clinical trials suggest a highly relevant benefit of treating deranged calcium phosphate metabolism. In particular, phosphate lowering with oral phosphate binders resulted in longer survival among incident dialysis patients in the large ArMORR study [8]. Surprisingly, this effect of phosphate lowering was largely independent of baseline and on-therapy phosphate levels, which suggests benefits of phosphate binders beyond lowering of serum phosphate. Given the strong association between high FGF-23 levels and adverse outcome among the same ArMORR cohort participants, it is highly suggestive that phosphate binders mediate their favourable effects by lowering FGF-23 levels, even though data on a direct association between phosphate binder medication, FGF-23 levels and mortality remain to be presented. Two randomized interventional studies are currently investigating the effect of phosphate binder medication vs placebo on FGF-23 levels and other markers of calcium phosphate metabolism in normophosphataemic CKD stage 3–5 patients (ClinicalTrials.gov Identifier: NCT00843349; NCT00438932). As a next important step, prospective trials assessing the long-term effects of these interventions on cardiovascular survival and all-cause mortality in normophosphataemic CKD patients are necessary.

In summary, we present first data on an association between elevated FGF-23 levels and future cardiovascular events in CKD patients not on renal replacement therapy. This finding complements recent cohort studies in dialysis patients and points to new therapeutic strategies for lowering cardiovascular burden in individuals suffering from CKD.

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