Timing of the CKD Complications: A Longitudinal Analysis

Articoli originali

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ABSTRACT

Background. Complications of chronic kidney disease include endocrine and metabolic abnormalities, anaemia and a wide range of disorders of homeostasis. Our study aims to better determine the role of CKD stage on the timing of the various complications associated with renal dysfunction.

Methods. We performed an observational study on 71 (F:M = 39:32) patients with 486 repeated measurements, recording anemia, BUN, hyperparathyroidism, hyperphosphatemia, hyperkalemia, metabolic acidosis. Data were summarized as mean and standard deviation, median and interquartile range, or absolute number. Differences among groups were tested through the Mann-Whitney test or Pearson's Chi-Square. The associations between eGFR and each outcome was tested by Spearman's correlation test. All variables related to the outcomes (with p-value <0.1) were included in the multivariate models. Longitudinal analysis was performed using generalized estimated equations (GEE) for binary outcome and by Linear Mixed Models for continuous variables. The ROC Curve with the Youden J index was evaluated for all binary outcomes.

Results. Baseline analysis revealed hyperparathyroidism in 49 patients (69.1%), hyperphosphatemia in 11 patients (15.5%), hyperkalemia in 20 patients (28.6%), and mean serum urea was 78 mg/dl [IQR: 59-99]. CKD stage was related with all outcomes. Youden J index suggested an eGFR predictive value of 37 ml/min/m^2 for anemia, 34 ml/min/m^2 for hyperkalemia, 26 ml/min/m^2 for hyperphosphatemia, and 46 ml/min/m^2 for hyperparathyroidism.

Conclusion. Based on our findings, screening tests for endocrine and metabolic complications of CKD should be initiated at the beginning of the CKD stage III. We suggest screening for hyperphosphataemia at the CKD stage IV.

KEYWORDS: Acidosis, Anemia, CKD, Parathormone, Phosphate, Potassium

Introduction

Chronic kidney disease (CKD) is characterized by an alteration of adequate metabolic homeostasis, increasing the risk of acidosis, hyperkalemia, hyperuricemia, hyperparathyroidism, hyperphosphatemia, and anemia.

This condition leads to a reduced excretory function, resulting in the accumulation of toxins in the body [1]. Among these catabolism products, urea is not completely excreted by the kidney when renal function is impaired.

As well for urea, renal filtration of hydrogen cations is altered when the residual nephron mass is impaired, increasing the risk of acidosis. Indeed, the severiry of acidosis is higher in patients with severe CKD [2]. Potassium removal is also reduced due to impaired renal function. Moreover, potassium is reabsorbed by proximal tubular cells through the exchange between H^+ and K^+ to correct acidosis [3].

Furthermore, reduced phosphate removal leads to an increase in PTH from the early stages and to hyperphosphatemia starting from CKD stage III [4].

According to the Kidney Disease Outcomes Quality Initiative (KDOQI), these consequences should be monitored from stage III onwards. Early diagnosis of CKD and the management of its consequences make it possible to reduce cardiovascular events and mineral bone disease [5].

Our study aims to determine the influence of eGFR and CKD severity on the consequences of incidence and timing of the different complications associated with renal dysfunction.

Materials and Methods

Patients

71 volunteer outpatients were retrospectively admitted in our observational study and their follow-up has been recorded. The total number of visits was different for each patient. Personal information, biochemical data (serum creatinine, proteinuria, PTH, hemoglobin, serum bicarbonate, serum potassium, serum phosphate, serum urea), home treatment and medical history were collected.

Our outcomes were defined as follows:

- Anemia: hemoglobin level lower than 11 g/dl and/or ESA treatment
- HyperPTH: parathormone higher than 60 pg/ml and/or VitaminD/calcimemtic treatment
- Hyperphosphatemia: serum phosphate higher than 4.5 mg/dl and/or phosphorous-binder assumption
- Hyperkalemia: serum potassium higher than 5.1 mmol/L or potassium-binder assumption
- Metabolic acidosis: pH less than 22 mmol/L and/or bicarbonate assumption.

Statistical analysis

Data were summarized as median and interquartile range, or absolute number, as appropriate. No variables were reported as mean and standard deviation due to no Gaussian distribution was retrieved. The distribution of variables was examined using the Kolmogorov-Smirnov test followed by graphical evaluation. Baseline characteristics were summarized for the whole sample. Differences among groups were tested through the Mann-Whitney test or Pearson's Chi-Square, as appropriate.

The association between eGFR and each outcome was tested by Spearman's correlation test.

Longitudinal analysis was performed using GEE with the dichotomous value of each binary outcome as the dependent variable and by Linear Mixed Models (LMM) for repeated measurements of serum urea. In this analysis, all variables related to the outcomes (with p-value <0.1) were included in the multivariate models as potential predictors. Analysis of the residuals was also performed. The same models were run with the independent variable CKD stages and eGFR. Models including CKD stage are shown in Tables 2-6, whereas models including eGFR are shown available upon request in Supplementary Tables 2-5.

The ROC Curve with the Youden J index was evaluated for all binary outcomes.

Results

The study population included 71 (F:M = 39:32) patients, resulting in a total of 486 repeated measurements. At baseline, their median age was 63 years [IQR: 47-72] and the median eGFR was 39 ml/min/m^2 [IQR: 27-53]. Among them, 16 patients had diabetes and 57 patients had arterial hypertension. Analysis of our baseline data revealed hyperparathyroidism in 49 patients (69.1%), hyperphosphatemia in 11 patients (15.5%), hyperkalemia in 20 patients (28.6%), and median serum urea was 78 mg/dl [IQR: 59-99]. The other baseline characteristics are summarized in Table 1.

Baseline correlations are reported available upon request in Supplementary Table 1. Anemia was significantly related to eGFR, urea, and phosphate binders, and a trend was found with acidosis, hyperparathyroidism, and bicarbonate treatment. Acidosis was significantly associated with previous cardiovascular events and proteinuria whereas a trend was shown with anemia and serum urea. Hyperkalemia was related to serum urea, proteinuria, and serum bicarbonate. Serum urea was related to anemia and EPO treatment, whereas a trend was found with acidosis. These variables were added to the multivariate models, as predictors for the predictive analysis (available upon request in Supplementary Table 1).

Variable	Whole sample (N = 71)
Age (year)	63 [47-72]
eGFR (ml/min/m^2)	39 [27-53]
Proteinuria (g/die)	0,9 [0, 24-3,64]
iPTH (pg/ml)	74 [51-93]
Hb (g/dl)	11.7 [10.8-13.2]
Serum bicarbonate (mmol/L)	20.9 [13.6-24.5]
Serum potassium (mmol/L)	4.7 [4.4-5.1]
Serum phosphate (mg/dl)	4.3 [3.8-4.6]
Serum Urea, (mg/dl)	78 [59-99]
Sex F/M	39/32
Previous CV events n(%)	20 (28.6)
Diabetes n(%)	16 (22.5)
Arterial hypertension n(%)	57 (80.3)
Active vitamin D treatment n(%)	45 (84.9)
ESA n(%)	20 (29.4)
Bicarbonate absumption n(%)	12 (80)
Potassium binders n(%)	9 (18)
Low protein diet n(%)	8 (13.6)
Anemia n(%)	26 (38.2)
Hyperparathyroydism n(%)	49 (89.1)
Hyperphosphatemia n(%)	11 (15.5)
Hyperkalemia n(%)	20 (28.6)

Table 1. Baseline features. Variables are reported as Median [IQR] or absolute number (%).

Excluding the anemia, as reported in Tables 2-5, CKD stages was significantly related to all the outcomes [(anemia: adjOR 0.83, 95%CI 0.40/1.75), (hyperkalemia: adjOR 2.25, 95%CI 1.36/3.73), (hyperphosphatemia: adjOR 2.27, 95%CI 1.49/3.46), (Serum urea: adjβ 16.85, 95%CI 13.43/20.26)]. Similar results were found when eGFR was used as independent variables ([(anemia: adjOR 0.89, 95%CI 0.9/1.07), (hyperkalemia: adjOR 0.95, 95%CI 0.91/0.99), (hyperphosphatemia: adjOR 0.94, 95%CI 0.91/0.97), (Serum urea: adjβ -1.36, 95%CI -2.44/-0.823)]) (available upon request in Supplementary Tables 2-5). A trend was found for hyperparathyroidism in the CKD stage (adjOR 0.96, 95%CI 0.092/1.002). As shown in Figures 1-4 and computed using the Youden J index of the ROC curve, the predictive eGFR values for anemia, hyperkalemia, hyperphosphatemia, and hyperparathyroidism, were 37, 34, 26, and 46 ml/min/m^2, respectively.

Discussion

Our study longitudinally analyzed the effect of eGFR or CKD stages on major complications and determined the timing of their manifestation. Based on our analysis, the severity of CKD was independently related to all our endpoints, except for anemia, which was related to CKD only in the univariate regression, and that our endpoint appeared from stage IIIA of CKD (hyperparathyroidism) to stage IV (hyperphosphatemia). Hyperkalemia and anemia appeared since stage IIIB.

Anemia

Anemia in people with CKD is primarily a consequence of reduced secretion of the hormone erythropoietin. Patients with worsening of CKD or low Hb despite standard treatment are at higher risk of unfavourable outcomes. In fact, the presence of anemia in patients with renal impairment is associated with a higher risk of hospitalisation and death [6]. The use of erythropoiesis-stimulating agents and optimisation of iron therapy have contributed significantly to improve the quality of life of patients with CKD [7]. The nephrologist plays a critical role in selecting the best strategies to treat anemia, taking into account its severity, the hemoglobin level and the patient's symptoms. All treatments should be evaluated in terms of risks and benefits for the patient, and the lowest effective dose to manage anemia is generally recommended [8].

	Univariate model			Multivariate model		
	OR	95%CI	p	OR	95%CI	p
CKD stage	1.13	1.08/1.19	<0.001	0.83	0.4/1.75	0.630
Age, year	–	–	–	0.96	0.87/1.06	0.391
Sex, male	–	–	–	4.69	0.25/86.98	0.300
Diabetes, yes	–	–	–	0.27	0.01/5.85	0.408
Arterial hypertension, yes	–	–	–	1.40	0.11/17.47	0.793
Serum Urea, mg/dl	–	–	–	0.87	0.83/1.25	0.432
Acidosis, yes	–	–	–	1.09	0.11/11.12	0.942
Phosphate binders, yes	–	–	–	8.71	0.67/113	0.099

Table 2. GEE using anemia as dependent variable.

According to our analysis, the risk of anemia was increased when eGFR was below 37 ml/min/m^2, although multivariate analysis showed no significant association between renal function and anemia. Anemia had multiple pathogenetic pathways, and was typically normochromic and normocytic. Decline of renal function is associated with decreased EPO synthesis, which leads to a decrease in hemoglobin concentration [9]. However, in our study, EPO intake was included in the anemia definition. Therefore, we can suppose that the effects of uremia and phosphate binders [10, 11] might affect the association between CKD and anemia more than eGFR in our analysis, where EPO supplementation was included in the anemia definition. According to this, our analysis showed a significant association between anemia and serum urea, as well as between anemia and PTH levels. Both reduce erythrocyte membrane stability and EPO production, leading to erythrocyte

lysis and impairing hemoglobin concentration [12, 13]. Similarly to PTH, FGF23 is increased with the worsening of renal function, as well as phosphate concentration. Both worsen vascular stiffness, increase the production of phlogistic protein, and reduce iron availability impairing hepcidin pathway [14]. Furthermore, it is demonstrated that ferritin in CKD patients, mostly in dialysis patients, should be higher than healthy patients and for this iron supplement are often used in chronic kidney disease also in not clearly microcytic anemia [15]. While the effects of serum urea and PTH on anemia were unidirectional, the association between anemia and acidosis could be explained by two mechanisms: anemia could impair oxygen transport, leading to overproduction of lactic acid, and acidosis could cause erythrocyte lysis and a reduction in hemoglobin [16]. In addition, acidosis impairs the oxygen-hemoglobin link and cardiac function, worsening cellular survival and progression of acidosis.

Hyperkalemia

The association between serum potassium and CKD has been extensively studied and demonstrated [3] and its impact on clinical status in severe CKD is well known [17, 18]. In our sample, similar to a large cross-sectional study [19], the risk of hyperkalemia risk was increased since CKD stage IIIB and the independent influence of eGFR was confirmed. Stage IIIB represents a higher risk of hyperkalemia due to impaired potassium excretion in reduced renal function and enhanced tubular potassium reabsorption to eliminate hydrogen cations in acidosis, which is often associated with CKD. In our analysis, hyperkalemia was directly related to arterial hypertension and proteinuria. There have been controversial opinions on this aspect in literature. As reported in a large observational study of 5185 patients [20], low potassium levels reduced proteinuria compared to the same sodium level. Similarly, in an observational study by Santhanam P et al. a reduction in proteinuria in normotensive patients was associated with higher potassium intake [21], but these results were not confirmed in hypertensive patients.

	Univariate model			Multivariate model		
	OR	95%CI	p	OR	95%CI	p
CKD stage	1.14	1.09/1.20	<0.001	2.25	1.36/3.73	0.002
Age, year	–	–	–	0.98	0.95/1.01	0.302
Sex, male	–	–	–	0.60	0.17/2.06	0.415
Diabetes, yes	–	–	–	1.11	0.33/3.67	0.868
Arterial hypertension, yes	–	–	–	3.56	1.31/9.71	0.013
Serum Urea, mg/dl	–	–	–	1.02	0.99/1.05	0.222
Proteinuria, mg/die	–	–	–	1.14	0.90/1.44	0.277

Table 3. GEE using hyperkalemia as dependent variable.

However, in our analysis, more than 80% of patients who had arterial hypertension and proteinuria were treated with RAASIs known as hyperkalemic drugs [3]. In fact, proteinuria lost its influence in the multivariate analysis that included arterial hypertension which remained instead for arterial hypertension.

Hyperphosphatemia and hyperparathyroidism

Hyperphosphatemia was strongly related to renal function in our sample, assessed as eGFR and CKD. However, the cut-off value shown in our analysis was lower than in Moranne O et al. Conversely, Levin A et al. reported a significant difference in serum phosphate when CKD was higher than stage IV [22]. Compared to Moranne O, our analysis and that of Levin included older patients and fewer vitamin D treatments. These two variables affect phosphate directly, in terms of vitamin D assumption, or indirectly, in terms of lower meat consumption in the older patients.
Indeed, phosphate excretion was impaired since the lost of minimal renal function, but the increased PTH and FGF23 levels tried to compensate for the reduced renal function.

	Univariate model			Multivariate model		
	OR	95%CI	p	OR	95%CI	p
CKD stage	1.15	1.08/1.22	<0.001	2.27	1.49/3.46	0.000
Age, year	–	–	–	0.97	0.94/1.00	0.446
Sex, male	–	–	–	0.70	0.28/1.75	0.446
Diabetes, yes	–	–	–	0.82	0.25/2.62	0.733
Arterial hypertension, yes	–	–	–	0.47	0.14/1.62	0.231
Low protein diet, yes	–	–	–	1.20	0.45/3.25	0.714

Table 4. GEE using hyperphosphatemia as dependent variable.

Accordingly, hyperphosphatemia was detected earlier than hyperphosphatemia in our sample. Although hormone dysregulation usually starts from stage II as reported by Cernaro V et al. [4, 23], our analysis showed that the better value for hyperPTH risk was at stage IIIA, according to the studies by Moranne O and Levin A. However, it is needed to specify as some differences between conservative CKD and dialysis patients exist. Indeed, both phosphate and FGF23 seem to have different impacts on comorbidity in these two different populations, where these impacts seem to be stronger in conservative CKD than in dialysis patients. It can be explained both for rapid phosphate reduction during dialysis treatment and for highest FGF23 in dialysis patients [24].

	Univariate model			Multivariate model		
	OR	95%CI	p	OR	95%CI	p
CKD Stage	1.06	1.03/1.1	<0.001	0.96	0.92/1.00	0.06
Age, year	–	–	–	0.998	0.99/1.00	0.120
Sex, male	–	–	–	1.143	1.00/1.28	0.017
Diabetes, yes	–	–	–	1.218	1.01/1.4	0.004
Arterial hypertension, yes	–	–	–	1.006	0.97/1.17	0.162
Anemia, yes	–	–	–	0.985	0.92/1.05	0.666
Serum Urea, mg/dl	–	–	–	1.001	0.1/1.00	0.338
Acidosis, , yes	–	–	–	1.578	1.34/1.86	<0.001
Proteinuria, mg/24h	–	–	–	1.003	0.99/1.02	0.689
VitD therapy, yes	–	–	–	2.179	1.91/2.49	<0.001
HCO3 treatment, yes	–	–	–	0.665	0.57/0.78	<0.001
Low protein diet, yes	–	–	–	0.824	0.83/0.93	0.002

Table 5. GEE using hyperparathyroidism as dependent variable.

Serum Urea

Urea is the principal metabolite derived from protein catabolism. It has previously been considered a relatively inert molecule, but recent data show that it induces biochemical changes that can affect the body's homeostasis [25]. Blood urea nitrogen (BUN) indicates the nitrogen content of serum urea, it is strongly and directly related to renal function, but other factors, such as hypercatabolic state and diet [5] could also influence it.

	Univariate model			Multivariate model		
	β	95%CI	p	OR	95%CI	p
CKD Stage	20.36	17.48/23.24	<0.001	16.85	13.44 / 20.26	<0.001
Age, year	–	–	–	-0.36	-0.54 / -0.18	<0.001
Sex, male	–	–	–	3.23	-3.06 / 9.53	0.312
Diabetes, yes	–	–	–	-1.07	-8.29 / 6.15	0.771
Arterial hypertension, yes	–	–	–	-2.22	-11.69 / 7.25	0.644
Anemia, yes	–	–	–	3.06	-3.45 / 9.57	0.354
Hyperkalemia, yes	–	–	–	7.14	-0.02 / 14.32	0.051
Low protein diet, yes	–	–	–	5.23	-2.35 / 12.82	0.176

Table 6. Linear Mixed Model using Serum Urea as depedent variable.

Indeed, in our analysis, only CKD stage and age were significantly associated with serum urea, even after correction for a low-protein diet (LPD). About this, it is well studied that low-protein diet reduces CKD progression, even though it is not generalizable. Indeed, although high adherence to a LPD can reduce serum urea and phosphate levels, it is not recommended for patients who are unable

to follow the diet strictly, as often happens with elderly individuals. In these cases, the risk of malnutrition is higher, and they may benefit from a Mediterranean diet, which is often better tolerated.[26].

Furthermore, correlation analysis showed significant correlations or trends between serum urea and each of our outcomes. However, these associations were lost in the multivariate analysis, underlining that GFR is the most important factor influencing BUN.

Conclusion

These results show how endocrine and metabolic alterations related to CKD occur at different glomerular filtration rate thresholds; consequently, they do not support the use of a single eGFR threshold to initiate screening for all complications.

Based on our findings, screening tests for endocrine and metabolic complications of CKD should be initiated at the beginning of the CKD stage III. In addition, screening for the assessment of hyperphosphatemia should be performed at the beginning of the CKD stage IV.

On a clinical level, this knowledge allows us to adapt the patient's follow-up to their eGFR values, with the aim of detecting and treating the occurrence of complications at an early stage, thus preventing systemic complications and improving the patient's quality of life.

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