Racial differences in postprandial mineral ion handling in health and in chronic kidney disease

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Abstract

Background. Increased serum phosphate is associated with cardiovascular disease. Compared with whites, blacks have significantly higher serum phosphate and increased risk of hyperphosphataemia in health and chronic kidney disease (CKD). While population-based studies suggest that diminished urinary phosphorus excretion in blacks may explain these differences, few physiological studies explored the potential mechanisms. The aim of this study was to examine racial differences in postprandial urinary mineral ion excretion in health and in CKD.

Methods. Twenty-eight healthy (18 white and 10 black) and 19 CKD (9 white and 10 black) subjects consumed a standardized meal; after which, blood and urine samples were collected for 4 h for measurement of phosphate, calcium, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23).

Results. Although serum phosphate did not differ by race, blacks had ∼30% lower postprandial fractional excretion of phosphate than whites in health (P<0.001) and CKD (P=0.02). Similarly, blacks had ∼35% lower fractional excretion of calcium in health (P=0.02) and CKD (P=0.3). Moreover, the postprandial response in serum calcium among CKD subjects differed by race (P=0.03), with serum calcium significantly decreasing in whites but not blacks.

Conclusions. Blacks had lower fractional excretion of phosphate than whites despite similar levels of PTH and FGF23 in health and in CKD, suggesting racial variability in renal sensitivity to phosphaturic hormones. Furthermore, blacks defend postprandial serum calcium more effectively than whites in CKD. Further studies are needed to define the mechanisms underlying these observations and evaluate whether racial differences in mineral ion handling may contribute to disparities in CKD outcomes.

Keywords: calcium; ethnic differences; fibroblast growth factor 23; parathyroid hormone; phosphorus

Introduction

Chronic kidney disease (CKD) is a growing public health epidemic that disproportionately impacts racial and ethnic minorities [1]. Despite a similar prevalence of early-stage CKD, blacks in the USA are up to four times more likely to progress to end-stage renal disease as compared with whites [2–5]. In addition, blacks with early CKD have increased risk of cardiovascular disease and mortality than whites with early CKD [6,7]. Although these differences have traditionally been attributed to greater socioeconomic disadvantages among blacks, increasing evidence suggests that biological factors, such as disorders of mineral metabolism, may also contribute to racial disparities in CKD outcomes [8–10].

Increased serum phosphate concentrations are linked to cardiovascular disease, CKD progression and death [11–14]. We previously reported that the prevalence and severity of hyperphosphataemia are greater among blacks compared with whites with pre-dialysis CKD [15]. These findings were independent of key confounding variables, including renal function, such that blacks had 80% greater risk of hyperphosphataemia than whites in multivariable-adjusted analyses. In addition, similar differences have been reported in blacks compared with whites without kidney disease [16,17]. Given that relatively higher serum phosphate concentrations within the normal range are associated with accelerated kidney and cardiovascular disease progression [12–14], understanding the mechanisms that underlie these differences may help elucidate novel risk factors for well-known but poorly understood racial disparities in CKD outcomes.

Serum phosphate concentrations reflect a dynamic balance between dietary phosphorus absorption, urinary phosphorus excretion, and exchanges with bone, soft tissue and intracellular stores [18]. Accordingly, higher serum phosphate concentrations among blacks could relate to differences in bone turnover, dietary phosphorus intake or absorption, renal phosphorus handling, or a combina-
tion of these factors. Indeed, compared with whites, blacks demonstrate reduced bone turnover and relative resistance to the bone-resorptive actions of parathyroid hormone (PTH) [19,20]. However, lower bone mineral resorption would more likely lead to decreased rather than increased release of phosphate into the circulation. Similarly, several studies have suggested that blacks consume less or equivalent amounts of dietary phosphorus per day as whites, but not more [21]. Data concerning racial differences in urinary phosphorus excretion are more consistent with the observed differences in serum phosphate concentrations, with virtually all studies showing that blacks excrete less urinary phosphorus per day than whites, even when dietary intake is standardized [22–25]. While these data suggest important racial differences in renal phosphorus handling, they were largely extracted from studies examining risk factors for nephrolithiasis or low bone mass. Few physiological studies have examined potential racial differences in urinary phosphorus excretion in health or in CKD.

In a previous feeding study, we observed important alterations in postprandial phosphorus and calcium handling in subjects with mild-to-moderate kidney disease as compared with healthy volunteers [26]. Since few of those subjects were black, however, we were unable to study potential racial differences in postprandial phosphorus and calcium handling. The purpose of the current study was to focus on postprandial urinary mineral ion excretion in blacks compared with whites, both in health and in CKD.

Materials and methods

Study population

Twenty-eight healthy volunteers (10 black and 18 white) and 19 subjects with CKD (10 black and 9 white) participated in the study. Race was ascertained by self-report. Eighteen of the healthy volunteers (all white) and 12 of the CKD subjects (3 black and 9 white) participated in the prior study that compared postprandial mineral ion metabolism in CKD versus non-CKD subjects, but did not specifically assess the effects of race [26]. To be eligible, all subjects had to be at least 18 years old; in addition, healthy volunteers had to have a glomerular filtration rate (eGFR) >60 mL/min/1.73 m², and CKD subjects had to have an eGFR of 15–60 mL/min/1.73 m² for ≥3 months. eGFR was determined using the simplified Modification of Diet in Renal Disease formula [27] calculated from the screening visit creatinine concentration. Exclusion criteria for both healthy volunteers and CKD subjects included hypo- or hyperphosphataemia (<2.5 or >4.6 mg/dL, respectively); hypo- or hypercalcaemia (<8.5 or >10 mg/dL, respectively); current use of phosphorus supplements, phosphorus binders or activated vitamin D analogs; pregnancy; or a history or laboratory evidence of severe anaemia, primary parathyroid disease, gut absorption defects or severe liver disease. In addition, healthy subjects were excluded if they had an abnormal urinalysis.

Since low serum 25-hydroxyvitamin D (25(OH)D) concentrations may limit dietary phosphorus and calcium absorption, all subjects with 25(OH)D concentrations <20 ng/mL on screening blood tests were treated with 50 000 IU of ergocalciferol every other day for four doses, and subsequently had 25(OH)D concentrations re-checked in order to ensure that they were ≥20 ng/mL prior to eating the study meal. In total, 8 of the 28 healthy subjects required ergocalciferol supplementation (1 white and 7 black), and 2 of the 19 subjects with CKD required supplementation (both black). On average, there was a 2-week interval between the last ergocalciferol dose and the meal visit in treated subjects. This study was approved by the Institutional Review Board of the Massachusetts General Hospital (MGH), and all subjects provided written, informed consent.

Study protocol

All study participants provided a 24-h urine collection while consuming an ad lib diet for measurement of creatinine clearance, and urinary excretion of phosphorus and calcium. Thereafter, study participants consumed a standardized breakfast meal containing 500 mg of phosphorus, 389 mg of calcium, 65% carbohydrates and 12% protein on the MGH Mallinckrodt Center breakfast menu. The contents of the meal, which have been published previously [26], were validated by performing a detailed nutrient analysis (Covance Laboratories, Madison, WI, USA). Subjects were instructed to consume the meal within 15 min. Blood and urine samples were collected immediately before the meal (time zero) and then every half-hour for 4 hours after the meal was consumed. Subjects were encouraged to drink at least 100 mL of water every hour to maintain urine flow.

Phosphorus, calcium and creatinine concentrations were measured in blood and urine samples collected at each time point using standard assays. Since serum albumin values were normal for all participants, total serum calcium values did not need to be corrected for albumin levels. PTH was measured using a bio-intact PTH assay that detects the intact 1–84 PTH peptide (Immutopics, San Clemente, CA, USA, CV <6%); fibroblast growth factor 23 (FGF23) was measured using an assay that exclusively detects the intact FGF23 peptide (Immutopics, CV <6%). 1,25-Dihydroxyvitamin D (1,25(OH)₂D) concentrations were measured in baseline blood samples using extraction/liquid chromatography–tandem mass spectrometry (Mayo Medical Laboratories, Rochester, MN, USA).

Fractional excretion of phosphorus (FEₚ) and calcium (FE₉Ca) were calculated as (urine mineral × serum creatinine) / (serum mineral × urine creatinine).

Statistical analysis

Baseline characteristics were compared between blacks and whites using two-sample t-tests or Wilcoxon rank-sum tests as appropriate. The postprandial area under the curve (AUC) for each analyte was calculated using the linear trapezoidal rule [28]. Linear mixed-effects models were used to examine postprandial changes in serum phosphate, calcium, PTH, FGF23, FEₚ and FE₉Ca comparing healthy blacks with healthy whites, and blacks with CKD to whites with CKD. This technique was utilized in part because of its versatility in handling unbalanced datasets. In these models, time represented the repeated-measures factor, individuals were treated as random-effects terms, and race was treated as a fixed-effect term. In order to determine whether the rate of change of the outcome variable differed by race, we first included interaction terms (race × time) into each model. When interaction was detected (P<0.05), we analysed separate models by race. When no interaction was detected, we examined the main effects of race and time. When there was a significant effect of time, we localized individually significant changes in postprandial time points by comparing them with the baseline fasting level using linear regression. In addition, we adjusted the linear mixed-effects models for differences in age and gender distribution across the race groups and for use versus non-use of ergocalciferol supplementation prior to the study meal. Furthermore, since anthropomorphic differences by race may impact phosphate and calcium handling, we also adjusted these analyses for body mass index, body surface area and serum creatinine (as a surrogate measure of muscle mass). FEₚ was not normally distributed, so log-transformed values were analysed. Two-sided P-values <0.05 were considered statistically significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Subject characteristics

Table 1 depicts baseline characteristics of study participants by race and presence or absence of CKD. The aetiology of kidney disease among CKD participants included diabetic nephropathy (11%), glomerulonephritis (16%), hypertension (32%), renovascular disease (16%) and others (26%). There were no significant differences in the aetiology of kidney disease by race. Twenty-four-hour urinary excretion of...
both phosphorus and calcium was lower in blacks than whites consuming ad lib diets, though only the difference in urinary phosphorus excretion among CKD subjects was statistically significant.

Table 2 depicts fasting laboratory results by race and presence or absence of CKD. Of note, serum 1,25(OH)2D concentrations were significantly higher in blacks than whites in both health and CKD. These differences remained significant even when accounting for prior treatment with ergocalciferol (P=0.008 comparing healthy blacks with whites; and P<0.001 comparing blacks with CKD with whites with CKD). Interestingly, there was a trend towards higher fasting FGF23 levels among the eight healthy subjects who received ergocalciferol supplementation prior to the study meal compared with the 20 who did not (80±52 vs. 46±36 pg/mL, P=0.06).

Postprandial phosphorus metabolism by race

Figure 1A depicts the postprandial response in serum phosphate comparing healthy blacks with healthy whites. There was no significant difference in the change in serum phosphate over time between the groups (P for interaction between race and time=0.5). In addition, there was no overall difference by race (P for main effect of race = 0.7). However, there were significant within-group differences over time, with serum phosphate concentrations transiently decreasing among white subjects at 90 min, and significantly increasing above baseline after 180 min among black subjects. Similarly, there was no significant difference in the change in serum phosphate over time between black and white subjects with CKD (Figure 2A), nor was there an overall difference by race. However, serum phosphate concentrations transiently decreased in both groups, with the decrease being statistically significant in blacks but not in whites (P for main effect of time <0.001 for blacks and 0.57 for whites).

Figures 1B and 2B depict the postprandial response in FE\textsubscript{Pi} among healthy subjects and CKD subjects, respectively. FE\textsubscript{Pi} was significantly higher in CKD subjects compared with healthy subjects overall and also when stratified by race. Among healthy subjects, there was no significant difference in the change in FE\textsubscript{Pi} over time between blacks and whites (P=0.4), with FE\textsubscript{Pi} peaking in both groups at 60 min. However, the overall difference by race was significant (P<0.001), with the area under the FE\textsubscript{Pi} curve being ∼30% lower in blacks as compared with whites. Similarly, while there was no significant difference in the change in FE\textsubscript{Pi} over time between blacks and whites with CKD (P=0.4), the area under the FE\textsubscript{Pi} curve was ∼30% lower in blacks than whites with kidney disease (P=0.02). These results were unchanged after accounting for differences in age, gender distribution, use versus non-use of ergocalciferol prior to the study meal, body mass index, body surface area and serum creatinine between the groups. Fasting and postprandial FGF23 concentrations did not significantly differ over time or by race in health or CKD.

Postprandial calcium metabolism by race

There was no significant difference in the change in serum calcium over time between healthy blacks and whites (Figure 1C), nor an overall difference by race. Compared with baseline, serum calcium concentrations significantly decreased at 60 min among whites, but significantly increased from baseline at 90 and 210 min among blacks. In contrast, the postprandial response in serum calcium among CKD subjects differed by race (P for interaction between race and time=0.03). As depicted in Figure 2C, postprandial serum calcium concentrations did not significantly change over time among black CKD subjects, whereas serum calcium significantly decreased below baseline at 60 min and remained below baseline for the remainder of the observation period among white CKD subjects.

Concurrent postprandial changes in FE\textsubscript{Ca} are depicted in Figures 1D and 2D. Although FE\textsubscript{Ca} increased in parallel in both groups among the healthy subjects, the area under the FE\textsubscript{Ca} curve was ∼35% lower in blacks compared with whites, with the overall difference by race being significant, even after accounting for racial differences in age, gender distribution, use of ergocalciferol and anthropomorphic characteristics (P=0.02, Figure 1D). Similarly, while postprandial FE\textsubscript{Ca} significantly increased in both groups among the CKD subjects, FE\textsubscript{Ca} was lower in blacks than whites at all time points, though the overall difference by race did not reach statistical significance (P = 0.3, Figure 2D).

Table 1. Baseline characteristics of study participants by race and presence or absence of chronic kidney disease

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Chronic kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black n = 10</td>
<td>White n = 18</td>
</tr>
<tr>
<td>Age</td>
<td>38 ± 14</td>
<td>46 ± 13</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>60%</td>
<td>66%</td>
</tr>
<tr>
<td>Body surface area (m\textsuperscript{2})</td>
<td>1.94 ± 0.2</td>
<td>1.78 ± 0.2</td>
</tr>
<tr>
<td>Body mass index (kg/m\textsuperscript{2})</td>
<td>27 ± 5</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.89 ± 0.1</td>
<td>0.92 ± 0.1</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>111 ± 16</td>
<td>86 ± 17</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.4 ± 0.4</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>24-h urine phosphate (mg/day)</td>
<td>629 (462, 729)</td>
<td>801 (542, 985)</td>
</tr>
<tr>
<td>24-h urine calcium (mg/day)</td>
<td>168 (101, 236)</td>
<td>208 (138, 280)</td>
</tr>
</tbody>
</table>

Results are depicted as frequencies, means ± standard deviation or median (interquartile range).

*P-value for comparison of healthy blacks with healthy whites.

*P-value for comparison of blacks with whites with chronic kidney disease.
There was no significant difference in the change in PTH over time when comparing healthy blacks with healthy whites ($P = 0.3$, Figure 3A), and no overall difference by race; however, serum PTH significantly decreased in blacks before returning to baseline ($P = 0.008$), whereas PTH concentrations did not significantly change over time among whites ($P = 0.67$). In contrast, serum PTH concentrations were higher in whites than blacks with CKD overall ($P = 0.04$, Figure 3B). Furthermore, PTH increased above baseline in both black and white subjects with CKD, with the increase being statistically significant in whites ($P = 0.03$) but not blacks ($P = 0.1$).

**Discussion**

Although previous studies have demonstrated significant racial differences in serum phosphate concentrations, few explored potential mechanisms underlying these observations. In this study, we found significant racial differences in postprandial urinary phosphate excretion in health and in kidney disease. Importantly, these differences were observed even though PTH and FGF23 concentrations did not consistently differ in blacks compared with whites, suggesting that renal sensitivity to phosphaturic hormones may vary by race. In addition, in contrast to whites with CKD, blacks with CKD maintained normal serum calcium concentrations in the postprandial period, suggesting that blacks may defend serum calcium more effectively than whites in kidney disease. Further studies are needed to define the mechanisms underlying these findings, particularly with respect to the potential role of differences in gut absorption or bone mineralization by race.

In steady-state conditions of mineral ion balance, urinary excretion of phosphorus and calcium corresponds to net absorption from dietary sources [18]. Accordingly, previous investigators have speculated that the most likely explanation for decreased urinary phosphate excretion among blacks is decreased dietary phosphorus absorption [22,23]. While possible, a similar mechanism was also initially proposed to explain analogous racial differences in urinary calcium excretion, in large part because, when compared with whites, blacks consume less dietary calcium and have lower levels of 25(OH)D [29]. However, detailed metabolic studies have shown that racial differences in urinary calcium persist even when calcium intake is standardized [22,23,30]. Moreover, several studies have demonstrated that lower urinary calcium excretion in blacks is primarily owing to more avid renal calcium conservation rather than lower gut calcium absorption [23,31]. Indeed, a greater renal calcium retention is thought to represent an adaptive mechanism for maintaining bone mass in the face of low dietary calcium intake and low 25(OH)D levels among blacks [32].

Whether similar findings apply to phosphorus handling is unclear. Several studies have shown that standardizing dietary intake does not abrogate racial differences in urinary phosphorus excretion [23,31]. While less efficient dietary phosphorus absorption in blacks may account for these findings, gut phosphorus absorption primarily occurs via passive paracellular diffusion [18], which would seem unlikely to markedly differ by race. Resistance to active transcellular transport in blacks is possible [23], and might explain why urinary phosphorus was lower in blacks than whites in this study despite their significantly higher 1,25(OH)$_2$D concentrations. Since we were unable to quantify gut phosphorus absorption directly, we could not address this possibility, and dedicated studies of dietary phosphorus absorption in blacks compared with whites are needed to resolve this critical issue. Nevertheless, it is possible that, like calcium, the primary difference may be that blacks conserve urinary phosphorus more avidly than whites as a physiological adaptation for preserving bone mass.

Racial differences in urinary phosphorus excretion could also result from differences in renal sensitivity to the primary phosphaturic hormones, PTH and FGF23. Both enhance phosphaturia by stimulating endocytosis of sodium–phosphate co-transporters from the brush border membrane of renal proximal tubule cells [33], thereby decreasing the fraction of filtered phosphorus that is reabsorbed from the proximal tubule lumen. Thus, it is noteworthy that blacks had lower fasting FE$_{Pi}$ than whites in health and CKD despite having similar circulating concentrations of PTH and FGF23. This finding suggests that blacks may demonstrate less renal sensitivity to phosphaturic hormones than whites. For example, just
as skeletal resistance to the action of PTH has been reported in blacks [19], relative resistance to the phosphaturic stimuli of PTH, FGF23 or both may explain why blacks had lower urinary phosphorus excretion than whites in this study and previous studies. Indeed, it is intriguing to speculate whether this may represent an adaptive mechanism for preserving bone mineralization in health by impairing compensatory mechanisms for augmenting urinary phosphorus excretion. Detailed studies of renal phosphorus handling in response to varying concentrations of PTH and FGF23 are needed to test these potential mechanisms.

Relative deficiency of FGF23 in blacks may also play a role. We previously observed that blacks had significantly lower FGF23 concentrations than whites among patients initiating haemodialysis [8]. Similarly, although not statistically significant, blacks with CKD had lower median FGF23 concentrations than whites in this study. Given the critical role of FGF23 in stimulating phosphaturia and inhibiting the synthesis of 1,25(OH)\(_2\)D, it is interesting to speculate whether lower FGF23 concentrations may account for lower FE\(_{\text{Pi}}\) and higher 1,25(OH)\(_2\)D in blacks than whites. Though the higher median FGF23 levels in healthy blacks than whites in this study would be inconsistent with this hypothesis, it is important to note that 7 of the 10 healthy black subjects, as opposed to 1 of 18 white subjects, received high-dose ergocalciferol supplementation prior to the study meal, and that fasting FGF23 concentrations were higher in subjects who received supplementation than those who did not. Thus, just as 1,25(OH)\(_2\)D stimulates FGF23 secretion [8], it is possible that ergocalciferol may have similarly stimulated FGF23 secretion among healthy blacks—either directly or indirectly via increased 1,25(OH)\(_2\)D—potentially accounting for this discrepancy.

We previously reported that, compared with healthy volunteers, CKD subjects appear to be at risk of developing relative hypocalcaemia after eating a meal [26]. The findings of this study suggest that this effect was primarily driven by whites since blacks with CKD appeared to be ‘protected’ from developing relative postprandial hypocalcaemia. This observation is not necessarily surprising given known racial differences in calcium economy. For example, studies have shown that blacks conserve urinary calcium more efficiently than whites in the setting of hypocalcaemia [34]. Indeed, compared with whites with CKD, blacks with CKD had lower urinary calcium excretion at baseline and throughout the postprandial period despite lower serum PTH concentrations in this study. In addition, higher 1,25(OH)\(_2\)D concentrations may have allowed for a greater dietary calcium absorption in blacks, off-setting the increase in urinary FE\(_{\text{Ca}}\) in the immediate postprandial period. This possibility is indirectly supported by the decrease in postprandial PTH concentrations in

**Fig. 1.** Fasting and postprandial measurements of serum phosphorus (A), fractional excretion of phosphorus (B), serum calcium (C) and fractional excretion of calcium (D) in black (filled squares) and white (open squares) healthy volunteers. Results are reported as means±standard error. *P<0.05 (significant differences at individual time points compared with the within-group’s fasting level based on linear regression models).
healthy blacks but not healthy whites that coincides with the timing of maximal dietary calcium absorption.

Our study has limitations. First, the relatively small sample size may have limited our ability to detect more robust associations between race and differences in postprandial phosphate and calcium handling. However, this is also a potential strength of this study in that we were able to show statistically significant racial differences in these parameters despite this potential limitation. Second, we did not have information concerning dietary sodium intake, sodium excretion, glucose metabolism, ionized calcium, blood pH, bone turnover markers or menstrual cycles among female participants, all of which may have impacted these results. Third, the lack of racial differences in serum

Race and mineral ion handling

Fig. 2. Fasting and postprandial measurements of serum phosphorus (A), fractional excretion of phosphorus (B), serum calcium (C) and fractional excretion of calcium (D) in black (filled squares) and white (open squares) patients with chronic kidney disease. Results are reported as means ± standard error. *P<0.05 (significant differences at individual time points compared with the within-group’s fasting level based on linear regression models).

Fig. 3. Fasting and postprandial measurements of serum parathyroid hormone in healthy black and white volunteers (A), and in black and white patients with chronic kidney disease (B). Blacks are indicated by filled squares and whites by open squares. Results are reported as means ± standard error. *P<0.05 (significant differences at individual time points compared with the within-group’s fasting level based on linear regression models).
phosphate concentrations in this study is in contrast to signifi-
cant differences that have been demonstrated in popula-
tion-based studies [15–17]. This may be owing to the small
case size of this study, or because observable differences
were minimized by the collection of all blood sam-

cles in the early morning, when serum phosphate levels
are at their diurnal nadir [35]. Fourth, it is possible that
the rapid ergocalciferol supplementation protocol used in
this study was not sufficient to correct underlying 25 (
OH)\textsubscript{2}D deficiency in the seven healthy and two CKD
black subjects who required therapy prior to consuming
the study meal. Nevertheless, there were no baseline dif-
fferences in 25(OH)\textsubscript{2}D concentrations between blacks and
whites at the time the meal was consumed, and 1,25(OH)
\textsubscript{2}D concentrations were higher in blacks, which would be
expected to promote increased, not decreased, calcium and
phosphorus absorption. Furthermore, it is possible that
ergocalciferol-treated subjects may not have fully
re-established steady-state conditions at the time of the
meal visit. However, this would be expected to increase
random variability in the main outcome measurements in
these subjects, limiting our ability to detect between-
group differences. That we were still able to detect these
differences despite the small overall sample size and even
when accounting for differences in gender distribution
and anthropomorphic characterisitcs suggests that a lack
of steady-state conditions did not dramatically impact
these results. Imbalances in the number of black and
white participants were also a potential limitation, though
it is important to note that linear mixed-effects models
help to mitigate the impact of unbalanced datasets.

Finally, we did not measure the total amount of phos-
phorus excreted in urine and stool during the postpran-
dial period, and so, we were unable to determine whether
there were significant racial differences with respect to
phosphorus ‘retention’ following the consumption of the
study meal. Nevertheless, this is the first study to our
knowledge that has demonstrated significantly lower
urinary phosphate excretion in blacks than whites with
CKD. These observations suggest that diminished capac-

ity for excreting phosphorus in blacks may be a novel
mechanism contributing to higher serum phosphate in
blacks than whites. Given that increased serum phos-
phosphate concentrations are associated with kidney and
cardiovascular disease progression, both of which dis-
proportionately impact racial and ethnic minorities, further
studies are needed to confirm these findings, and deter-
mine whether earlier or more aggressive interventions to
reduce dietary phosphorus absorption in blacks with
CKD could ameliorate marked racial disparities in CKD
outcomes.

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The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease

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Abstract

Background. Inhibition of the renin–angiotensin–aldosterone system (RAAS) has shown to slow chronic kidney disease (CKD) progression. This is most notable at the earlier stages of diabetics and proteinuric nephropathies.

Objective. Here, we observed the impact of discontinuation of angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptors blockers (ARB) in patients with advanced kidney disease.

Methods. 52 patients (21 females and 31 males) with advanced CKD (stages 4 and 5), who attended our low clearance clinic (LCC) in preparation for renal replacement therapy (RRT). Mean age was 73.3 ± 1.8 years with an estimated glomerular filtration rate (eGFR) of 16.38 ± 1 ml/min/1.73 m². Baseline urine protein:creatinine ratio (PCR) was 77 ± 20 mg/mmol. 46% suffered from diabetes mellitus. Patients were followed for at least 12 months before and after ACEi/ARB were stopped.

Results. 12 months after discontinuation of ACEi/ARB eGFR increased significantly to 26.6 ± 2.2 ml/min/1.73 m² (p = 0.0001). 61.5% of patients had more than a 25% increase in eGFR, whilst 36.5% had an increase exceeding 50%. There was a significant decline in the eGFR slope −0.39 ± 0.07 in the 12 months preceding discontinuation. The negative slope was reversed +0.48 ± 0.1 (p = 0.0001). Mean arterial blood pressure (MAP) increased from 90 ± 1.8 mmHg to 94 ± 1.3 mmHg (p = 0.02), however ≥50% of patients remained within target. Overall proteinuria was not affected (PCR before = 77 ± 20 and after = 121.6 ± 33.6 mg/mmol).

Conclusion. Discontinuation of ACEi/ARB has undoubtedly delayed the onset of RRT in the majority of those studied. This observation may justify a rethink of our approach to the inhibition of the RAAS in patients with advanced CKD who are nearing the start of RRT.

Keywords: advanced CKD, angiotensin II receptor blockade; angiotensin-converting enzyme inhibition; low clearance clinic

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