THE REALITY OF HYPERPHOSPHATEMIA

COMPACT-RENAL 2012-2014:
TOP 10 ARTICLES
FACTORS INFLUENCING PATIENT'S OUTCOME:
DIALYSIS PATIENT

MEDICATION ↔ NUTRITION

EDUCATION
EPIDEMIOLOGY

COSMOS: use of phosphate-binding agents is associated with a lower risk of mortality

Optimal therapy for hyperphosphatemia: new insight on a clinical challenge

TREATMENT ADHERENCE – A CHALLENGE IN SERUM PHOSPHORUS MANAGEMENT

How significant an issue is non-adherence to hyperphosphatemia treatment regimens?

The challenge of non-adherence in hyperphosphatemia

HIGH PILL BURDEN – HIGH BURDEN OF DISEASE

What are the causes of patient non-adherence to hyperphosphatemia treatment?

Diets rich in phosphorus-based additives could be contributing to high pill burden in dialysis patients

PHOSPHATE AND NUTRITION – FREEDOM AND BOUNDARIES

Challenges of implementing renal diets that target both protein and phosphorus

The high prevalence of phosphorus additives in best-selling groceries

CKD-MBD IN LIGHT OF NOVEL RESEARCH AND STRATEGIES

The clinical significance of FGF-23 in CKD

Possible therapeutic strategies to lower FGF-23
**CompAct Renal** is a platform for nephrologists and specialists involved in the treatment of hyperphosphatemia and beyond. CompAct Renal provides scientific information with a personal view – for that purpose, international experts discuss current issues on hyperphosphatemia therapy and CKD-MBD in general, present new scientific data and review interesting publications and congresses.

This booklet presents CompAct's Top 10 most read articles of the past two years since the launch of CompAct Renal. These articles cover different topics and aspects in the treatment of CKD-MBD and hyperphosphatemia like: Epidemiology, Adherence, Pill Burden, Nutrition, novel research and strategies.

**CompAct Renal** is supported by an Editorial Board which includes leading international experts in the CKD-MBD area – for more information regarding the Editorial Board and CompAct Renal in general please visit us on compact-renal.com.
Treatment with phosphate-binding therapy was associated with a lower all-cause and cardiovascular mortality risk in the European COSMOS observational study of hemodialysis patients.

Cannata-Andía et al. studied almost 6,800 patients from 227 dialysis centers in 20 European countries over a three-year period. 85% of patients were prescribed phosphate binders, a similar proportion to the 88% reported in a recent DOPPS analysis. In multivariate analysis, patients prescribed binders had a 29% and 22% lower all-cause and cardiovascular mortality risk, respectively.

The findings from the COSMOS study provide further support for the results from two prior epidemiological studies:

- In 2009, Isakova et al. reported on a one-year study of 10,000 incident dialysis patients. In this group, the investigators found a 25% reduction in all-cause mortality risk from phosphate binder use. In both Isakova et al. and COSMOS, the survival benefit also remained statistically significant in propensity-score matched cohorts.

- In 2012, Lopes et al. reported a 25% reduction in mortality risk from phosphate binder prescription in the DOPPS cohort of maintenance dialysis patients with serum phosphorus concentrations ≥ 3.5 mg/dL. In a one-year analysis of a subgroup of incident dialysis patients (approximating the Isakova study), the authors observed an 18.7% lower mortality risk.

Two additional findings in the Lopes et al. study are also particularly relevant to COSMOS.

First, the survival impact of phosphate binder prescription at a facility level was similar between the two studies. With each 10% increase in the case-mix adjusted facility prescription of phosphate binders, Lopes et al. identified a 7% decrease in the relative all-cause mortality. COSMOS found an 8% reduction in all-cause mortality risk and a 7% reduction in cardiovascular mortality.

Second, Lopes et al. hypothesized that the survival advantage from phosphate binder use could partially be explained by better nutritional status in the treated cohort, as the inclusion of nutritional factors in the multivariate model attenuated the survival advantage. In COSMOS, as in the DOPPS study, patients prescribed phosphate binders were found to have better nutritional status than those not prescribed binders. However, in COSMOS the inclusion of BMI and albumin in the multivariate models did not modify the survival advantage. Cannata-Andía et al. suggest that a potential explanation for both of these findings is that phosphate binder prescription “may improve survival by allowing a more liberal diet and therefore improving nutritional status”.

One limitation of the COSMOS study, as with previous investigations, is the low percentage of patients not treated with phosphate binders in these studies. This limitation can be partially overcome by the large number of patients included in these epidemiological studies, as well as by analysis based on propensity-score matching, but it does restrict the robustness of the conclusions and provides an opportunity for further research to support the findings.

The COSMOS study also provided insight into the survival benefit associated with specific phosphate binders published in The Lancet.

References
Several recent studies and opinion articles have provided new insights on the "unsolved clinical problem" of what should be the optimal therapeutic regimen for CKD-related hyperphosphatemia.2,3,4,5

In the COSMOS study, dialysis patients who were prescribed phosphate binders had a 29% and 22% lower all-cause and cardiovascular mortality risk, respectively. However, in addition to these findings, the COSMOS investigators also analysed outcomes achieved with various phosphate binders or binder combinations used by the dialysis patients.

With the exception of aluminium salts, all prescribed phosphate binders – given either as monotherapy or in combinations – were associated with relative risk reduction in all-cause mortality. Similar trends were seen in cardiovascular mortality rates, but fewer of the treatment options reached statistical significance, potentially due to the reduction in overall events attributable to each of the disparate binder groups.

When the investigators focused on the nine therapy options that are most used in clinical practice, the relative risk of protection from all-cause mortality ranged from 27% to 72%. In these nine groups, the highest survival benefits tended to be associated with prescription of binders in combination, again excluding aluminium-based binders.

While the COSMOS investigators did not provide a comparison between calcium and non-calcium binders, a recent study by Jamal et al., published in The Lancet, did address this topic directly.

In their meta-analysis of 11 randomised trials, Jamal et al. reported that CKD patients assigned to non-calcium-based binders experienced a statistically significant 22% reduction in all-cause mortality compared with those assigned to calcium-based binders (risk ratio 0.78, 95% CI 0.61-0.98).

While an accompanying commentary article suggested that "physicians’ perceptions of the cost-effectiveness of phosphate-binder choices might change following this meta-analysis", the Jamal et al. study does suffer from several important limitations.

1. Over 75% of the 4,622 patients in the meta-analysis were sourced from two randomized control trials, one of which was the DCOR study.6,7 The results of these two trials were not statistically significant. As such, the overall meta-analysis model relies to a certain extent on multiple smaller trials that saw greater treatment effects from non-calcium binders.

2. The heterogeneity of the source data may have impacted the results of the meta-analysis, and in particular the weighting given to these smaller studies. Since trial weightings were based on both randomized and non-randomized studies, and since the analysis of randomized controlled trials had a higher heterogeneity than the non-randomized trials included, this may have caused the smaller studies to have been weighted slightly more than they would otherwise have been in a fixed effects analysis.

3. Calcium acetate and calcium carbonate were assumed to be equivalent in the meta-analysis. While studies have suggested such equivalence in terms of outcomes, regimens based on calcium carbonate contain more elemental calcium than those based on calcium acetate or calcium acetate/magnesium carbonate binders.8,9 Assuming equivalence between calcium-based binders may therefore not account for efficacy differences between calcium-based binders.

4. When trials were analyzed by follow-up period, survival benefit was only seen at 24 months follow-up. When measured at a follow-up of 36-42 months, therapy with non-calcium-based binders was not associated with a relative survival benefit, but Jamal et al. highlighted that this was "probably because there was insufficient power to assess the outcome" at this time interval.

5. Due to the design of the reviewed studies the authors could not establish whether "non-calcium-based phosphate binders are inherently beneficial, or if calcium-based binders are harmful, or a bit of both." A retrospective analysis presented at the ERA-EDTA Congress in May 2013 raised much the same question.11
While the limitations of the Jamal et al. study are important, it is also worth noting that the review period used in the meta-analysis was prior to the publication of a recent randomized, controlled trial by Di Iorio et al. which suggested that therapy with a specific non-calcium binder conferred a survival benefit over calcium carbonate, when measured over a mean of 28 months in 466 patients. While this study also has several limitations, its results appear to align with the overall conclusion in favour of non-calcium binders made by Jamal et al.

So where does this leave the debate? Undoubtedly it continues, although bolstered with an influx of recently-published opinion.

• “In view of the burden of cardiovascular disease in this population of patients, we suggest that the first-line therapy for phosphate lowering should be non-calcium-based binders…” Jamal et al.

• “The debate concerning use of calcium-containing versus non-calcium-containing phosphate binders is ongoing. However, additional well-powered studies of sufficient duration with hard end points are required to confirm these positive results [in favour of calcium-free phosphate binders].” Covic and Voroneanu, referencing Di Iorio et al.

References
Patient non-adherence is a significant, multi-dimensional challenge to securing the best long-term treatment outcomes in hyperphosphatemia of CKD. In a 2010 survey-based study, 76% of nephrologists and 63% of dialysis staff thought non-compliance with phosphate binders was the main reason for poor control of phosphate in patients.

In this article we question:

- How prevalent is non-adherence in CKD-related hyperphosphatemia?
- What is the impact of this non-adherence?

How prevalent is non-adherence?
Available data is scarce, but it appears reasonable to assume that non-adherence to phosphate binders is not lower than the 40% to 50% non-adherence rates seen across other chronic treatment regimens.

A systematic review of the prevalence of non-adherence was published in BMC Nephrology in 2008. The study identified the mean rate of non-adherence as 51%, although there was wide variation in the reported rates, ranging from 22% to 74% of patients. This variation was in part due to how the source studies defined and measured adherence. Mean rates of non-adherence were higher when patients were assessed through serum phosphorus levels rather than through self-report, at 58% versus 31%.

The review only identified one demographic predictor of non-adherence: young age. By contrast, psychosocial variables, such as patients’ beliefs about medication, social support, and their personality characteristics, were more likely to be associated with non-adherence.

Highlighting the fundamental lack of available evidence on the topic, the review only found 13 studies in a 40-year period between 1967 and 2006 that reported rates of non-adherence to phosphate binders.

A subsequent 2010 cross-sectional cohort study of 165 Spanish hemodialysis patients by Arenas et al. found 40% of patients non-adherent to their prescribed drugs, with 21% of patients admitting non-adherence to phosphate binders. Given the lack of specific data, a useful way to validate these findings is through comparison with non-adherence data from other diseases. As referenced in a WHO report, Adherence to Long-term Therapies: Evidence for Action, a number of reviews have found that, "in developed countries, adherence among patients suffering chronic diseases averages only 50%. This would appear to provide support for the 50% mean range observed in the hyperphosphatemia studies.

What are the impacts of this non-compliance?
There is also limited data available on the impact of non-compliance on treatment outcomes in hyperphosphatemia, as well as on the cost-effectiveness of treatment.

One recent study of 121 hemodialysis patients taking phosphate binders showed that serum phosphorus levels were significantly higher in patients that did not comply with their treatment regimen versus patients who did. Adherence was assessed in this instance via a patient survey, rather than by serum phosphorus levels.

In addition, this paper suggested that non-adherent patients were more likely to have phosphorus levels >5.5 mg/dL, a widely-used upper boundary of the target range in CKD stage 5 patients.

While the association between adherence and phosphorous control is not surprising, further research is needed to confirm the association. To illustrate this point, another recent study was unable to demonstrate any relationship between therapy adherence and serum phosphorus levels. The authors of this paper, which also shed light on the association between pill burden and adherence, suggested that physicians were responding to uncontrolled serum phosphorous by prescribing a larger number of phosphate binders to compensate for non-adherence.

In fact, this hints at another impact of non-adherence: escalating costs. Given that cost increases associated with implementing recent treatment guidelines can be significant, additional studies could also be performed to quantify the cost of non-adherence. Furthermore, estima-
tes for non-adherence rates could also be factored into the cost-effectiveness models of available treatments.

In summary: the available evidence, while scarce, points to a 40%-50% non-adherence rate and an association between non-adherence and poorer treatment outcomes.

References
Phosphate binders have been shown to be effective in regulating phosphorus levels\(^1\) and yet according to a recent large observational study, 50% of patients have serum phosphorus concentrations outside the target range. Clinical studies have demonstrated the efficacy of phosphate binders in controlling serum phosphorus and observational studies confirm their widespread use\(^1\), so to what extent is the difficulty of controlling phosphorus levels caused by non-adherence to binder regimens?\(^3\)

**Phosphate binders have shown to be effective at controlling phosphorus levels**

Phosphate binders are widely used in dialysis patients to control phosphate levels and observational studies have shown their use to be associated with improved survival outcomes.

- In a study of 6,797 dialysis patients Cannata-Andia et al. found that patients prescribed phosphate binders had 29% lower all-cause mortality risk and a 22% lower cardiovascular mortality risk\(^1\).
- Treatment with phosphate binders was independently associated with decreased mortality in an observational study of 10,044 incident dialysis patients.\(^2\)

Despite the widespread use of binders, phosphorus levels in general are poorly controlled, with 50% of patients in a recent study found to have poorly controlled phosphorus levels at baseline. One possible reason for this is the underestimation of the amount of highly absorbable, ‘hidden’ phosphorus in Western diets, which has been shown to be particularly high in processed foods.\(^4\) Alongside this, there is also a growing body of evidence highlighting that many dialysis patients are not adhering to their binder medication.

**Evidence suggests patient adherence to phosphate binders is poor**

Non-adherence is a problem in many chronic diseases, but can be especially challenging for dialysis patients due to a complex treatment regimen involving both dietary restrictions and multiple medications. Numerous studies have shown that the prevalence of patient non-adherence to phosphate binder treatments is high:

- A survey in 2010 found 76% of nephrologists and 63% of dialysis staff thought non-adherence was the main reason for poor control of phosphorus levels in patients.\(^3\)
- In a cross-sectional study, 502 haemodialysis patients responded to a questionnaire with approximately 70% stating they were non-adherent to phosphate binders.\(^6\)
- A recent study of Spanish dialysis patients found that 60% were non-adherent to their phosphate binder treatment regimens.\(^7\)
- In another study by the same author, results found that in 165 dialysis patients, 40% were non-adherent to their treatments and 21% admitted non-adherence to phosphate binders.\(^8\)
- A systemic review of 34 studies found non-adherence rates averaged at 51% and ranged from 22% to 74%. The result of this review highlighted the variability in measures of adherence.\(^9\)

These data suggest that non-adherence is an important issue in phosphate binder therapy and it is a logical step to suggest that improving these adherence rates could lead to better treatment outcomes for dialysis patients.

References

5. Toussaint ND, Pedagogos E, Beavis J, Becker GJ, Polkinghorne KR, Kerr PG. Improving CKD-MBD management in haemodialysis patients:


Rate of non-adherence to phosphate binders:

51%

In this article, we examine the effect that high pill burden has on patient adherence and specifically we ask:

- What is the pill burden associated with CKD and hyperphosphatemia treatment?
- What impact does pill burden have on adherence and clinical outcomes?

What is the pill burden associated with CKD and hyperphosphatemia treatment?

When assessing pill burden, it is important to view the issue from the patient’s perspective and consider the overall pill burden, including therapies associated with co-morbidities. From this standpoint, few diseases impose a larger average pill burden on patients than end-stage chronic kidney disease. In fact, it is not uncommon for patients to have to take upwards of 20 pills each day. This observation was supported by a study of 233 dialysis patients in the US that showed that:

- The median number of pills taken each day by patients was 19;
- One quarter of patients had to take more than 25 pills per day;
- Phosphate binders accounted for 49% the pill burden while the next largest component was antihypertensive drugs, constituting 18% of the total;
- Patients prescribed sevelamer and calcium-based agents took a median number of nine phosphate binder pills per day, compared to six with lanthanum carbonate.

There are two components of pill burden: number of tablets to be taken at a given time and the frequency of administration. The frequency of administration cannot be easily reduced with any of the currently available phosphate binders, as they generally need to be taken with food to be effective. However, the number of tablets taken each time is potentially modifiable. Further research in this area could help to devise more optimal treatment schedules, potentially tied to the patient preferences.

What impact does pill burden have on adherence and clinical outcomes?

One of the key issues still not fully explored is the link between higher pill burden, lower adherence and higher serum phosphate levels. However, data from the previously discussed study showed that over 60% of patients were non-adherent and that there was a significant inverse relationship between adherence to phosphate binders and pill burden.

Furthermore, the study also showed that there was a significant direct relationship between serum phosphorus levels and pill burden, and that higher pill burdens were independently associated with lower quality of life.

The relationship between adherence and pill burden appeared to be nonlinear, such that the greatest fall-off in adherence occurred in patients prescribed 12 or more phosphate binder pills per day. The study authors suggested that, given this data, doctors need to carefully consider the potential risk of non-adherence when prescribing more than 12 phosphate binder pills daily.

Also, when looking for parallels in other disease areas, the data from the study appears comparable and numerous studies have suggested that patient adherence is inversely associated with the complexity of the prescribed treatment regimen.

Many large studies have also looked at the impact of fixed-dose combinations on compliance, contrasting adherence rates to that of multiple single therapy regimens. In one example, a meta-analysis showed that there was a statistically significant 26% decrease in the risk of non-compliance compared when patients took fixed-dose combination therapies for conditions such as hypertension, HIV and tuberculosis, as opposed to multiple single therapies.

Another example was a longitudinal study in which 9,170 diabetes patients were assessed who were treated with either two separate medications or a fixed-dose combination product. Adherence to the drug regimen, as measured by the average treatment effect, was 12.8% higher in the group that took the combination product.
These results suggest that to achieve better adherence rates and improve disease outcomes, treatment strategies that enable a reduction in hyperphosphatemia pill burden should be the subject of continued research, both in terms of optimizing existing treatment regimens and the development of new options.

References
Diets rich in phosphorus-based food additives could be contributing considerably to high pill burden in dialysis patients, according to a recent analysis published in the Journal of Renal Nutrition. In their study, Carrigan et al. considered the contribution of food additives to the phosphorus content of a complete 4-day diet, and provided a clear contrast between low-additive and additive-rich meal plans.

While there has been considerable discussion in the nephrology community over the past few years regarding the clinical significance of phosphorus-based food additives, dietary analysis has tended to focus on additive content in individual food items. By contrast, Carrigan et al. examined the total phosphorus and sodium content of two 4-day menus to compare a low-additive diet and an additive-enhanced diet. The menus were designed to be identical in energy and nutrient content, but substituted fresh, minimally processed food for highly processed products, for example fresh pineapple vs. canned pineapple, or fresh chicken breast vs. deli chicken.

After blending up and analysing the two diets, the study produced the following results:

- The additive-enhanced diet contained an average of 606 +/- 125 mg more phosphorus per day than the low-additive diet.
- This was approximately a 60% increase from the low-additive diet.
- In a balanced 2,200-kcal/day diet, daily phosphorus intake is significantly greater when eating additive-rich foods.

The investigators estimated that a CKD patient would have to ingest up to 23 additional phosphate binding tablets a day, or require 12 extra hours of hemodialysis a week to remove just the additional phosphorus intake coming from the additive-rich foods. This would mean a dramatic increase of the pill burden and the time spent on hemodialysis sessions and would substantially affect the quality of life of patients.

The Carrigan et al. study was designed to emphasise the difference between a low-additive and additive-enhanced diet. However, the authors argue that the additive-rich foods in this study are commonly consumed items and part of an otherwise healthy diet. Given that a large proportion of the Western world consume diets less healthy than the one analysed here, the contribution of additives to phosphorus intake is possibly greater in the real world.

Research into the amount of phosphorus absorbed from different phosphorus sources has shown that 90-100% of inorganic phosphorus, such as contained in additives, is absorbed from the gut. Inorganic phosphorous is not bound to protein and is therefore hydrolysed more easily than organic phosphorus. In line with the evidence shown here, the impact that food additives have on phosphorus levels in CKD patients is extremely significant. By consuming a low-additive diet, CKD patients could significantly lower their daily phosphorus uptake.

A comparative study presented by Gutierrez and Beck at the ASN Kidney Week 2013 congress used similar diets to the ones presented here. One week on the high sodium and phosphorus additive-rich diet significantly increased FGF23 and osteopontin concentrations, and significantly decreased sclerostin concentrations in healthy volunteers.

Results such as these highlight that high levels of phosphorus-based food additives in common Western diets may be a significance cause for concern in dialysis patients.

References
Introduction
Although recent studies have suggested that a more nuanced approach to dietary phosphate restriction may be possible, significant challenges remain with the clinical implementation of these more complex dietary regimens. Determining the quantity of phosphorus that will be absorbed from a given food item or a drink is difficult for renal dietitians, and even more so for patients. In this article we will discuss challenges associated with:

- Determining the phosphorus content of food and drink, as well as the type of phosphorus that they contain
- Educating patients on the avoidance of phosphorus-containing foods
- The impact of socioeconomic factors on food choices

How easy is it to determine the phosphorus content of food and drink?
Determining the phosphorus content of food products can be difficult for patients and dietitians alike. Currently, food manufacturers in the US and Europe are not required to list phosphorus content on food labels and therefore CKD patients are deprived of a simple way to identify the phosphorus content in certain foods. In addition to this, complex names in the ingredients list may mask inorganic-phosphorus-based additives. These inorganic sources have high rates of intestinal absorption and impact serum phosphate levels considerably. Therefore improved labeling regarding the phosphate content of food and drink items would be extremely beneficial to both dialysis patients and clinicians alike. At the recent ASN 2012 congress, many clinicians suggested that this was one area where the ASN & FDA could collaborate more closely as part of their Kidney Health Initiative partnership.

A 2007 study provided a clear example of the challenges that poor labeling can pose for renal dietitians. The investigators purchased chicken products readily available in supermarkets in Cleveland, USA and analyzed their phosphorus content, including additives. They found that available nutrient databases did not accurately reflect phosphorus content derived from additives, and that the variation between similar products made it extremely difficult for patients and dietitians to accurately estimate the phosphorus content of these products. A recent study by Cupisti et al. also highlighted the impact that phosphorus-containing preservatives have on phosphorus levels in food products. The study assessed the phosphorus-to-protein ratio in 40 cooked hams purchased at random in an Italian supermarket using spectrophotometric methods. Cooked ham that contained preservatives had 66% more measurable inorganic phosphorus and a 64% higher phosphorus-to-protein ratio than ham without preservatives. It would have been difficult for a renal dietitian to identify the relative phosphorus levels in these ham products from nutritional databases and to advise patients adequately.

Interventions to improve patient education may reduce dietary intake of phosphorus
To complicate dietary advice further, studies have shown that adherence to restricted protein diets (0.6 to 0.8 g/kg/day) is low, and may vary between approximately 20% and 50%. There is limited data available on educational interventions that can improve adherence to low protein diets, particularly data based on randomized, controlled trials of interventions.

One randomized controlled trial in 2009 examined whether educating hemodialysis patients to avoid phosphorous-containing food additives could result in improvements in hyperphosphatemia. 279 patients were divided between the intervention and control arms, with the intervention group receiving education on how to avoid food products, including fast food, that contained phosphorous additives. The intervention group also received tools to assist in decision making on food purchases, such as a magnifier in a plastic case on which were printed the names of relevant additives. After three months the decline in serum phosphorous levels was 0.6mg/dL larger among intervention versus control participants. The investigators observed that such a reduction corresponded "to a 5% to 15% reduction in relative mortality risk in observational studies."
Data also suggests that dietitian-led interventions can help patients manage their dietary phosphorus levels better.9

For example:
- A dietitian-led education program was associated with a significant reduction in serum phosphate in patients with hyperphosphatemia.10
- Renal dietitians may be equally effective as nurses and/or nephrologists in bone metabolism algorithm management.11
- The implementation of nutrition management guidelines by renal dietitians was associated with an improvement in nutritional status and diet, without the need for increased resources or dietitian time.12

However, a recent survey of 600 dietitians (91% in US) noted that a significant majority of renal dietitians do not follow the KDOQI guidelines for diet assessment due to time constraints, highlighting one of the key ongoing pressures associated with helping renal patients to manage their dietary intake.13

Socioeconomic factors may also impact dietary phosphorus intake

Socioeconomic factors also play a role in the management of renal diets. A 2010 study14 by Gutierrez et al. suggests that low socioeconomic status can contribute to excess intake of relatively inexpensive processed and fast foods enriched with highly absorbable phosphorus additives.14 It has also been demonstrated that low socioeconomic status is associated with higher serum phosphate concentrations. The study authors conclude that:

“Novel nutritional assessment instruments specifically designed to more accurately capture true dietary phosphorus intake are urgently needed to support detailed physiologic and population-based studies that explore whether excess intake of phosphorus additives explains the link between poverty and hyperphosphatemia that we observed, and if so, whether nutritional interventions proven to reduce the consumption of additive-rich foods may improve CKD outcomes among minority populations and the very poor.”

References
In earlier articles of our series on nutrition, we highlighted the difficulties associated with determining the phosphorus content of food and drink products, as well as the challenges of avoiding inorganic phosphate additives that are readily absorbed in the gastrointestinal tract.

A recent paper by León et al., published in the Journal of Renal Nutrition, has further emphasized the importance of these issues. In this study, a team from Cleveland, Ohio analyzed the prevalence of phosphorus additives in branded grocery food items in the United States.

The investigators focused on the top 200 selling products in 15 of the top 20 food and drink categories by sales in northeast Ohio. The ingredients of approximately 2,400 of these 3,000 products were reviewed and 44% were found to contain phosphorus-based additives. Phosphorus additives were most common in the prepared frozen foods (72%), dry food mixes (70%), and packaged meat (65%) categories.

While these results alone illustrate the difficulty in avoiding phosphorus additives in a typical shopping basket, León et al. provided additional analyses that highlighted a potential opportunity for improved CKD-MBD management and also emphasized a potential economic challenge.

A further laboratory assessment of 56 of the top-selling items containing phosphorus additives found that they contained an average of 67 mg of phosphorus per 100 g more than close-comparator products that were free of such additives. Importantly, when scaled up to typical meals, phosphorus additive foods contributed an average excess phosphorus burden of 736 mg per day, much of which may be highly bioavailable.

Studies suggest that 90-100% of inorganic dietary phosphorus, such as that found in additives, is absorbed as it is not bound to protein and so is easier to hydrolyze. These findings suggest that a dietary regimen that successfully avoids phosphorus additives may significantly reduce a CKD patient’s overall phosphorus burden and improve the effectiveness of phosphate binding therapy, while potentially allowing protein intake levels to be maintained.

However, such a dietary regimen may present economic challenges to the patient. León et al. found that phosphorus additive-free meals cost an average of $2.00 (~€1.50) more per day than comparator meals that contained additives. The authors highlighted how this could lead to socioeconomic-based health disparities in terms of CKD-MBD outcomes.

In conclusion, León et al. proposed that an “emphasis on label reading to avoid phosphorus additives is an appropriate strategy to manage serum phosphorus in persons with kidney disease.” The authors also call for the clear labeling of phosphate content in food, an approach supported by other commentators.

In the absence of such labeling it would appear important for renal clinicians and investigators to continue with their profiling of the phosphorus and protein content of common foods. A table of phosphorus-to-protein ratios in typical Spanish foods, published earlier this year by Barril-Cuadrado et al., provides a good example of how such profiling could be developed over time.

References
A proliferation of studies linking excess levels of the endocrine hormone fibroblast growth factor 23 (FGF-23) to adverse renal and cardiovascular outcomes in patients with Chronic Kidney Disease (CKD) is setting the stage for new clinical trials, which could lead to FGF-23 becoming an important marker and/or therapeutic target in the management of CKD.

In this series on FGF-23, we will provide:
- a background to the relationship between FGF-23 and CKD,
- an analysis of FGF-23 as a predictor of outcomes in CKD,
- an exploration of FGF-23 as a clinically useful marker for diagnosing CKD mineral and bone disorder (CKD-MBD), and
- a future and current perspective on therapeutic strategies for lowering FGF-23 levels.

Background to the relationship between FGF-23 and CKD

In this article, we summarize a recent review paper published in Kidney International by one of the leading experts in FGF-23 – Myles Wolf. Wolf’s lab and others have shown that increased FGF-23 is strongly associated with CKD progression, cardiovascular disease (CVD), and death, even when serum phosphate is normal, suggesting that increased FGF-23 may represent an earlier and more sensitive biomarker of disordered phosphorus metabolism than concomitant serum phosphate levels.

FGF-23 has several endocrine effects on calcium-phosphate metabolism. Together with its cofactor Klotho, FGF-23 enhances renal phosphate excretion in order to maintain serum phosphate levels within the normal range. In healthy individuals, FGF-23 levels rise and fall in parallel with the amount of dietary phosphate. The Health Professionals Follow-up Study confirmed a correlation between phosphate levels and FGF-23, although so far, there is little evidence that higher levels of serum phosphate stimulate FGF-23 secretion directly.

FGF-23 levels also rise in parallel with declining renal function, long before a significant increase in serum phosphate concentration can be detected. Wolf accepts that we do not yet have a full picture of how this physiological balance is maintained. However, the roles that vitamin D, parathyroid hormone (PTH), calcium and iron, have on FGF-23 secretion are addressed in the paper.

Why are FGF-23 levels elevated in CKD?

Cross-sectional studies show that FGF-23 levels are elevated in individuals with CKD. However, the CKD stage when FGF-23 levels first become significantly elevated differs across these studies. Although it is difficult to define the exact underlying pathophysiological sequence, Wolf draws some conclusions from studies such as the Chronic Renal Insufficiency Cohort (CRIC) Study. FGF-23 levels were elevated in most stage 3-4 patients, and levels were more prevalent than either PTH or serum phosphate at all eFGFR levels. Although more serial studies are required, Wolf comments that this initial data suggests that FGF-23 could be superior to existing markers as a sensitive screening test in identifying which patients are developing disordered metabolism in early CKD.

In patients with end-stage renal disease (ESRD) undergoing dialysis, FGF-23 again increases over time and often reaches levels that are more than one thousand times above normal. Last year’s landmark paper by Isakova et al. confirmed the association of FGF-23 levels with systemic effects. FGF-23 concentrations were an independent predictor over a 5 year period of progression to ESRD in patients with baseline eGFR > 30 mL/min/1.73m².

But what drives FGF-23 levels up in early CKD? Current data suggests that early CKD may be a result of primary FGF-23 excess that reduces serum phosphate levels and klotho expression. Wolf provides a rational explanation for the observed primary FGF-23 excess in early CKD: it could be caused by a defect in the bone that somehow stimulates FGF-23 secretion directly. He suggests that the osteocyte could be a likely site for phosphate sensing, and that a progressive reduction of klotho expression could have a critical role in CKD.
References


POSSIBLE THERAPEUTIC STRATEGIES TO LOWER FGF-23

September 7, 2012 by CompAct Editorial Team

Twelve years after the discovery of the hormone FGF-23 (fibroblast growth factor 23), many therapeutic options for targeting FGF-23 levels are emerging.

Myles Wolf’s latest review paper addresses the pertinent question as to whether CKD treatment regimens should now be tailored to address FGF-23 levels in addition to those of calcium, phosphate, parathyroid hormone and vitamin D. He critically reviews the different therapeutic strategies currently in development, and how they might be leveraged in a future randomized trial improving outcomes for patients with CKD.

The phosphorus that we consume in our diets is one of the major stimulants of FGF-23. Simple dietary manipulation by reducing total phosphate consumption has been shown to lower FGF-23 levels in non-CKD patients. So far, the data in CKD patients is limited and somewhat contradictory in its findings. However last year, a small cross-over study that compared the effects on FGF-23 levels of a meat-based high-protein diet to a vegetarian-based diet, did show a vegetarian diet led to lower serum phosphorus levels and decreased FGF-23 levels. However, to support this intervention, larger studies are warranted that demonstrate the feasibility of such an approach (and compare phosphate bioavailability and absolute phosphate intake) over an extended time period.

Phosphate binders lower serum phosphorus and can also decrease FGF-23 levels by reducing reabsorption in the gut. Wolf highlights several studies showing that administration of phosphate binders lowered FGF-23 levels in healthy volunteers, hyperphosphatemic ESRD patients, and CKD patients with normal or elevated serum phosphate.

Two studies also have shown that particular binders lowered serum phosphate, significantly lowered FGF-23, and improved renal function in patients with Stage 3-4 CKD. Yilmaz (REF) study is important as it demonstrated that ‘a therapeutic intervention targeting phosphate homeostasis is capable of improving a meaningful intermediate measure of cardiovascular disease in CKD patients.’ The study also validated an earlier finding that non-calcium-based phosphate binders reduce FGF-23 more effectively than calcium-containing binders despite comparable effects in serum phosphate. A future possibility for investigation would be a placebo-controlled randomised trial examining specific phosphate binders with or without vitamin D therapy in CKD stages 3-4.

But what factors, other than phosphorus, affect FGF-23 levels? Some studies also suggest that calcimimetic therapies can lower FGF-23 levels in the setting of CKD. However, the exact mechanisms are still unknown, but it seems likely that the effect isn’t mediated by serum phosphate. On the other hand, vitamin D therapy raises FGF-23 levels without significant differences between specific preparations. One can speculate that no reduction in LVH was observed in the PRIMO study as patients were treated with active vitamin D. This paradoxical situation needs further investigating, in order to help clarify the interaction between FGF-23 and active vitamin D.

In the next five years, the clinical nephrologist may eventually see FGF-23 move into clinical practice as a target of therapy. If high FGF-23 levels over a long period of time contribute to heart disease, there might indeed be a fundamental requirement for reducing FGF-23 levels. Nevertheless, many questions remain unanswered. While Wolf’s review is inspiring for FGF-23 proponents it does highlight several important gaps in our clinical knowledge that need investigating further.

References


CompAct Renal is a platform for nephrologists and specialists involved in the treatment of hyperphosphatemia and beyond. CompAct Renal provides scientific information with a personal view – for that purpose, international experts discuss current issues on hyperphosphatemia therapy and CKD-MBD in general, present new scientific data and review interesting publications and congresses.

CompAct Renal is supported by an Editorial Board which includes leading international experts in the CKD-MBD area – for more information regarding the Editorial Board and CompAct Renal in general please visit us on compact-renal.com.