

# PHOSPHATEMIA

MANAGEMENT IN THE TREATMENT  
OF CHRONIC KIDNEY DISEASE

A ROUNDTABLE DISCUSSION



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## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE



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**Dr. Jonathan Elliott:** Today we will discuss an old-fashioned kidney problem: disorders of mineral balance and phosphate. One of our goals is to build a consensus on the importance of phosphate and parathyroid hormone (PTH); we'll debate whether phosphate, PTH, or a combination of the two is important in kidney disease. A second objective is to provide treatment guidelines for hyperphosphatemia and hyperparathyroidism, indicating the quality of the evidence supporting the guidelines. We will also identify areas where new research is warranted.

### Pathophysiology of renal secondary hyperparathyroidism

**Elliott:** Let's begin by considering the pathophysiology of secondary renal hyperparathyroidism and the role of phosphate. Regulation of the concentration of calcium and phosphate in extracellular fluid involves the intestines, bones, kidneys, and

the movement of calcium and phosphate between intracellular and extracellular fluid. The bones' massive store of bound calcium and phosphate is released or replenished to protect the animal against a lack or excess of calcium and phosphate in extracellular fluid, including blood. Hormones regulate this movement. When you study a patient's complex endocrine system by evaluating a blood sample, it's difficult to understand what's occurring in this dynamic system—many different factors can influence each other (*Figure 1*, page 4). For example, a decreased ionized calcium concentration and an increased phosphate concentration in the extracellular fluid stimulate PTH secretion, and PTH increases the release of calcium and phosphate from the bones. This stimulates the kidneys to produce more vitamin D, which increases calcium and phosphate absorption from the intestine. Phosphate and calcium are released from the bone to defend against hypocalcemia, and along

with PTH and vitamin D, they influence the kidneys, such that calcium is retained and phosphate is excreted. Vitamin D feedback inhibits PTH synthesis. It also ensures that some nutritional calcium replenishes that which came out of the bone. So PTH and vitamin D together are needed for calcium to be released from and replenished into the bones.

Let's look at the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in human medicine. KDOQI is an educational initiative of the National Kidney Foundation in the United States whose aim is to improve the quality of care of human patients with kidney disease through the development of scientifically rigorous guidelines based on a critical appraisal of the available evidence. These guidelines maintain that phosphate retention occurs early in the course of chronic kidney disease, probably during KDOQI stage I (glomerular filtration rate, or GFR, is normal or decreased; less than 90 ml/min/1.73 m<sup>2</sup>) but certainly by

## A ROUNDTABLE DISCUSSION



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KDOQI stage II (GFR equals 60 to 89 ml/min/1.73 m<sup>2</sup>). This does not mean that the serum phosphate concentration is elevated at that time; in fact, the serum phosphate concentration may actually be low. This phosphate retention is not the only contributor to hyperparathyroidism; the PTH concentration starts to rise when the GFR is 50% of normal or below. Serum phosphate concentrations might be normal or even reduced at KDOQI stages I to III (stage III equals GFR of 30 to 59 ml/min/1.73 m<sup>2</sup>). Whenever there is a reduction in GFR, whole-body phosphate retention is occurring.

Phosphate is filtered and partially reabsorbed in the proximal tubule. The only way to excrete more is to reduce the amount that is reabsorbed in the proximal tubule. This is controlled by PTH, which reduces the transport maximum of phosphate in the proximal tubule and can cause up to 70% of the filtered load to appear in the urine. However, once GFR becomes limited (less than 50% of normal) and dietary phosphate remains the same, phosphate will be retained in the body as intake exceeds the capacity of the kidneys to excrete phosphate. PTH secretion then becomes maladaptive as it brings more phosphate out of the bound stores in the bone. Because the kidneys cannot excrete this phosphate, it accumulates in cells and extracellular fluid. The logical way we can address this problem

and restore the balance is by reducing phosphate intake.

Secondary renal hyperparathyroidism is an extremely common finding in chronic kidney disease; it is evident early in the disease syndrome. Phosphate retention plays an important role in its genesis. Evidence from human medicine shows that this phenomenon decreases the quality of life and increases the risk of mortality.

Secondary renal hyperparathyroidism is an extremely common finding in chronic kidney disease; it is evident early in the disease syndrome.

—Dr. Jonathan Elliott

The questions I have are: Is PTH responsible for this detrimental effect, or is the phosphate overload detrimental? Perhaps PTH is just a good indicator of phosphate overload. How important is this syndrome in causing progressive renal injury in stages I to III of chronic kidney disease, using the International Renal

Interest Society (IRIS) classification (Table 1, page 5)? And how does this syndrome relate to other causes of progressive renal injury, such as hypertension and proteinuria?

**Dr. Larry Cowgill:** Is phosphate or PTH the bad guy? We have dealt with the problem of secondary hyperparathyroidism from the human perspective, in which metabolic bone disease is one of the major clinical problems associated with this syndrome.

In the majority of veterinary patients, I think renal osteodystrophy isn't clinically manifested enough to warrant therapeutic management. We may have to shift our perspective on hyperparathyroidism and hyperphosphatemia from the human concept to what is relevant in our patients.

**Elliott:** Renal osteodystrophy definitely occurs. If you see these animals late enough in the disease process, you can see it radiographically, which presumably means that it has occurred for quite some time.

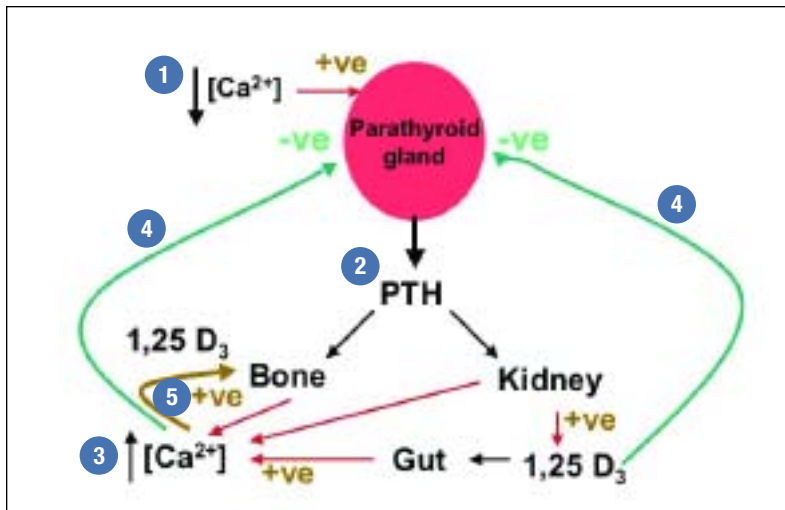
**Cowgill:** But it generally is not clinically manifested.

**Dr. Astrid van Dongen:** Even though practitioners don't see the signs, they shouldn't just forget about the problem. We may not see bone-related disease that often in renal patients, but when we find other evidence of calcium-phosphate imbalance, there is something terribly wrong.

# PHOSPHATEMIA

## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE

Figure 1: Regulation of the endocrine system



1. This schematic diagram shows the sequence of events following a decrease in plasma ionized calcium. For simplicity, this schematic only considers calcium and does not make reference to phosphate.
  1. A fall in extracellular fluid ionized calcium is sensed by calcium-sensing receptors at the level of the parathyroid gland.
  2. PTH is secreted into the blood.
  3. PTH acts on the bone and kidney via active vitamin D<sub>3</sub> (1,25 D<sub>3</sub>) on the intestine to raise extracellular fluid ionized calcium.
  4. The increase in ionized calcium and 1,25 D<sub>3</sub> concentrations act on the parathyroid gland to inhibit PTH secretion.
  5. Raised 1,25 D<sub>3</sub>, over a longer time scale, allows the calcium coming into the body from the intestines to replenish the bone stores with calcium.

### The role of phosphate in chronic kidney disease

**Cowgill:** Let's discuss what clinical problems occur in animals with kidney disease relative to mineral balance or mineral metabolism.

**Elliott:** The main issue is how patients excrete enough phosphate to stay in balance when their GFR drops.

**Cowgill:** If we can't identify any clinical significance to hyperparathyroidism in animals with chronic kidney disease—other than developing bone disease at a late stage—then maybe we don't need to be as concerned about it.

**Elliott:** The problem is that the two are intrinsically linked. In my

experience, if you change phosphate levels, you change PTH levels.

**Dr. David Polzin:** I suspect there is a big difference there. You can have phosphate levels that, while within the normal range, are at the high end of the range, with PTH values remaining quite elevated. I think it really matters which one we focus on to influence the clinical outcome. If we base therapy on PTH, we have to prove that there's a link between the clinical outcome and PTH. We know the clinical outcome is linked to phosphate control.

**Elliott:** So the practical approach is to control phosphate. The difficult concept to sell to practitioners is at what phosphate concentration they

will see benefits. Do we need more clinical studies?

**Dr. Scott Brown:** Recent clinical studies from Minnesota have confirmed the applicability of laboratory studies of models to animals with spontaneous kidney disease.<sup>1,2</sup> Further, we know that structural or functional progression in the remnant kidney model is directly related to serum phosphate concentration in dogs and cats.<sup>3,4</sup> It's thus reasonable to argue that we should restrict phosphate and/or provide an intestinal phosphate binder to control the serum phosphate concentration. And there is enough evidence in other species to suggest that "under control" means a serum phosphate concentration well within the normal range or even in the bottom half of the normal range.

**Elliott:** Our experience in cats has been if we can control phosphate, we can control PTH. To summarize, hyperphosphatemia related to chronic kidney disease warrants treatment and can lead to secondary renal hyperparathyroidism through PTH stimulation.

**van Dongen:** Practitioners should measure phosphate levels and adjust their therapy accordingly. But in an ideal situation, PTH and vitamin D levels should also be checked in addition to phosphate.

**Dr. Maria Josefa Fernandez del Palacio:** I agree with Dr. van Dongen that for practitioners, it would be more practical to measure phosphate levels first because this parameter is usually included in the biochemical panels. As a second step, PTH measurements would be desirable.

**Dr. Greg Grauer:** On the scale of 1 to 10, the quality of evidence for controlling hyperphosphatemia in

**Table 1: Classification of kidney disease in KDOQI vs IRIS stages**

Stage (KDOQI)	Description	GFR (ml/min/1.73 m <sup>2</sup> )	IRIS stage*	Plasma creatinine (μmol/l)**
I	Kidney damage with normal or increased GFR	≥90	I	Feline: <140 Canine: <125 (<1.6 mg/dl)
II	Kidney damage with mild decreased GFR	60 to 89	I to early stage II	Feline: 140 to 249 Canine: 125 to 179 (1.6 to 2.8 mg/dl)
III	Moderately decreased GFR	30 to 59	Later stage II and stage III	Feline: 180 to 439 Canine: 140 to 439 (2.9 to 5.0 mg/dl)
IV	Severe reduction in GFR	15 to 29	Stage IV	Feline and canine: ≥440 (≥5.0 mg/dl)
V	Kidney failure	<15 (or dialysis)	Late stage IV	Not defined but >440 for feline and canine (>5.0 mg/dl)

\* The IRIS classification is based on plasma creatinine and the limitations of this are recognized, particularly in precise definition of kidney function in stages I to III.

\*\* The creatinine concentration values stated above are a guide based on expert opinion.

chronic kidney disease is close to 10. We don't have nearly the same level of evidence for controlling PTH.

**Cowgill:** Despite this, I have a concern about this broad range of early kidney disease occurring with a normal serum phosphate concentration. The only indication that phosphate metabolism is disordered at that disease stage is probably the PTH, which could identify the need for phosphate restriction at an earlier disease stage than the serum phosphate concentration. I am concerned that we are not seeing elevations in the serum phosphate concentration until creatinine levels are 3.5 to 4 mg/dl (310 to 360 μmol/l). Phosphate management could be beneficial at an earlier stage, and practitioners would miss this opportunity if they just focused on serum phosphate

concentration. Monitoring serum PTH levels at IRIS stage II and probably early stage III would likely be beneficial.

**Elliott:** My concern is that practitioners tend to think that if phosphate isn't elevated, they don't need to restrict it. They might feed a renal diet anyway just because the creatinine is elevated. They may misunderstand the reason why that benefits the individual animal—they may think it helps because of decreased protein levels but the decreased phosphate levels in the diet also helps. Another concern is that as phosphate starts to increase, they should target the lower end of the reference range. Practitioners need to recognize that a phosphate in the normal range could still be abnormal in renal patients.

**Cowgill:** Given the lack of a strong correlation between hyperparathyroidism and clinical signs relative to animals with kidney disease, could we say that—at a minimum—PTH serves as a surrogate marker for dysregulation of mineral balance in the face of a normal serum phosphate concentration?

**Dr. Herve Lefebvre:** That's a good point. If the serum phosphate concentration is normal in animals with chronic kidney disease, I'd recommend assessing the PTH to confirm hyperparathyroidism.

**Grauer:** Clinical experience suggests that PTH levels can be elevated in early chronic kidney disease, prior to the onset of hyperphosphatemia. But do we have data showing that treatment of hyperparathyroidism at this stage affects patient outcome?

# PHOSPHATEMIA

## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE

### Q&A: Recommendations for serum phosphate management in chronic kidney disease

#### What should practitioners keep in mind when treating phosphate overload?

- This is a chronic treatment for stable chronic kidney disease patients.
- Stability of chronic kidney disease patients should be demonstrated by serial serum creatinine measurements for two to four weeks. Stability of serum phosphate concentration can also be established over this time.
- Benefits come from long-term control of serum phosphate concentration (for months to years).
- Acute problems of kidney disease patients (*e.g.*, pyelonephritis, severe hypertension) should be managed before introducing methods of managing the serum phosphate concentration.

#### When should chronic kidney disease patients receive treatment for phosphate overload?

Derangements in phosphate homeostasis are commonly associated with chronic kidney disease even at early stages because phosphate accumulates in the body when

the glomerular filtration rate is reduced because of chronic kidney disease.

The following recommendations are based on treating phosphate overload with the objective of reducing the serum phosphate concentration into the recommended range:

- In IRIS stages III and IV, a clinical renal diet is recommended for many reasons, including controlling the serum phosphate concentration (IRIS treatment recommendations).
- In IRIS stage II, dietary phosphate restriction might be considered even if the serum phosphate concentration is in the recommended target range if elevated serum PTH concentrations are documented. However, more research is necessary before specific recommendations can be made on this issue. If serum PTH is not measured, do not restrict phosphate intake for patients with serum phosphate concentrations of less than 4.5 mg/dl (1.45  $\mu\text{mol/l}$ ) (*i.e.*, within the target range for animals with IRIS stage II chronic kidney disease).

#### What is the target serum phosphate concentration that should be achieved with treatment?

The target goals (two months post-treatment) and therefore the degree of phosphate restriction required depend on IRIS stage of chronic kidney disease:

Stage II—target serum phosphate concentration 3.5 to 4.5 mg/dl (1.17 to 1.45  $\mu\text{mol/l}$ )

Stage III—target serum phosphate concentration 3.5 to 5 mg/dl (1.17 to 1.61  $\mu\text{mol/l}$ )

Stage IV—target serum phosphate concentration 3.5 to 6 mg/dl (1.17 to 1.94  $\mu\text{mol/l}$ )

#### How should these targets be achieved and what monitoring procedures should be applied?

The serum phosphate concentration should be controlled by gradually introducing a phosphate-restricted diet. All commercially available renal diets can be used to achieve phosphate restriction because they are all relatively lower in phosphate than standard pet food diets. These renal diets should be introduced gradually over a period of seven days. The greater the proportion of the renal diet fed, the better.

Patients should be reevaluated after four weeks of dietary therapy. If the serum

**Cowgill:** We have lots of canine data showing that in the early stage of disease, treating the phosphate imbalance with dietary reduction corrects the hyperparathyroidism.<sup>5,6</sup> So hyperparathyroidism can serve as a sensitive marker that the mineral balance is abnormal.

**Brown:** There is certainly correlative evidence that PTH may be detrimental, but the confounding problem is that the PTH level is also directly correlated to the degree of phosphate imbalance. If we make clinically relevant recommendations, the logical target is the serum phosphate concentration. To me, the first step is targeting the phosphate level with appropriate dietary

maneuvers, rather than recommending an ancillary test.

**Polzin:** I don't think we have proof of a cause and effect relationship between PTH levels and progression of kidney disease, but we do between phosphate intake and progression. Another issue is that I'm not sure it's possible to identify the phosphate level within stage II, for example, that reliably normalizes PTH levels. If we answer that question, it would be easier to focus on the phosphate level. Then you get into the issue that is confronting the IRIS—we are suggesting that phosphate should be below a number that is well within the normal range. We are essentially changing the normal range in the

renal patient, which practitioners can find confusing.

**Grauer:** Well, we've recently changed what we think is normal and abnormal for hypertension and proteinuria. Maybe we need to do the same for creatinine and phosphate concentrations.

**Polzin:** The implication might be that if you treat a patient appropriately over an extended period of time you could, in fact, just monitor the serum phosphate concentration.

**Elliott:** Yes, as long as you keep the phosphate in the optimal range.

**Grauer:** So should practitioners initiate dietary phosphate restriction

phosphate concentration is greater than 6 mg/dl (1.94  $\mu\text{mol/l}$ ), introduce an intestinal phosphate binding agent, reevaluate after four weeks, and adjust the dose to achieve the target level for the stage of chronic kidney disease.

If the serum phosphate concentration is less than or equal to 6 mg/dl (1.94  $\mu\text{mol/l}$ ) after four weeks, continue dietary therapy for four more weeks. If the target serum phosphate concentration has not been achieved at this time, introduce an intestinal phosphate binder. Reassess after four weeks and adjust the dose of phosphate binder to achieve the target phosphate concentration.

Once the target serum phosphate concentration has been achieved, monitor every two to four months to maintain the phosphate level within the desired range. As chronic kidney disease progresses, the degree of phosphate restriction, dosage of intestinal phosphate binding agent, or both will need to increase. This occurs despite the fact that the target serum phosphate concentration increases as chronic kidney disease progresses from IRIS stages II to IV.

### What intestinal phosphate-binding agents are available?

The available binding agents are:

- Aluminium carbonate
- Aluminium hydroxide
- Aluminium oxide
- Calcium carbonate (+/- chitosan)
- Calcium acetate
- Calcium citrate
- Lanthanum carbonate
- Sevelamer hydrochloride

### How should phosphate-binding agents be used?

The following recommendations are for dosing:

- Starting dose should be 30 to 60 mg/kg.
- Powdered and granular preparations are recommended over liquids and gels, which might affect palatability of the diet.
- The binder must be mixed with the diet.
- Serum phosphate concentration should be reassessed every 4 weeks.
- Increase dose to effect (doubling increments to a maximum tolerable dose) and reassess.
- When using aluminium-containing binders, drug-induced microcytosis, muscular weakness, and

encephalopathy are possible.

- Higher doses of the binder will be required if the animal is consuming low amounts of a clinical renal diet (or a diet relatively higher in phosphate) and as the stage of chronic kidney disease increases.
- Constipation is a potential complication of higher doses of any of the available intestinal phosphate-binding agents.

### What are the recommendations for the serum calcium concentration?

Phosphate and calcium homeostasis are intrinsically linked—both are affected by chronic kidney disease as a response to the accumulation of phosphate in the body as GFR decreases. Thus:

- Serum calcium concentrations should be monitored together with phosphate.
- If the total calcium concentration is elevated, assess ionized calcium concentration.
- In cases where ionized calcium concentrations are elevated, replace calcium-containing phosphate binders with alternatives (aluminium hydroxide, lanthanum carbonate, or sevelamer hydrochloride).

prior to the onset of hyperphosphatemia?

**Brown:** There are data suggesting that using a phosphate-restricted diet at IRIS stages II to III has a beneficial effect on clinical outcome.<sup>1,2</sup>

It's important that we not become trapped in the concept that evidence-based medicine means we only use evidence from prospective clinical trials or that we not extrapolate results of a trial to animals or conditions to which they do not apply. Evidence-based medicine means we highly value randomized, placebo-based, blinded prospective clinical trials—but as nephrologists and veterinarians, if we don't have applicable prospective trials, we are

obligated to rely on the best available evidence. This is really what evidence-based medicine means. Thus, if we have no clinical trials but there are results available from good model studies that are applicable, we base our decisions on those model studies. If we don't have model studies in our species of interest, then we look at studies in other species. Here, evidence in rodents and people clearly shows some benefit of phosphate restriction in normophosphatemic, early-stage kidney disease.

**Polzin:** That is an important point. Evidence-based medicine means looking at the best available evidence. If the best evidence is from people, we should use that.

**Elliott:** So our consensus is that we should monitor the serum phosphate concentration in animals with chronic kidney disease. We may also look at PTH in animals that are normophosphatemic to see whether we need to restrict phosphate. This might be a reasonable marker for phosphate and mineral imbalance.

### Evidence from experimental animal models and clinical cases

**Brown:** The data from multiple laboratory studies on the relationship of phosphate to kidney disease are quite clear: Dietary phosphate restriction, at least in IRIS stages II

# PHOSPHATEMIA

## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE

and III, is protective of renal structure, function, and survival.<sup>3,4</sup>

**Polzin:** A number of studies have been performed on dogs and cats with naturally occurring chronic kidney disease. In these studies, the phosphate-restricted diets in both dogs and cats were associated with significant improvement in survival. In a study examining the effect of diet on survival in dogs with IRIS stages III and IV chronic kidney disease, dogs consuming a phosphate-restricted diet survived approximately three times longer than dogs fed a standard maintenance diet. Similar beneficial effects have been observed in cats with stages II and III chronic kidney disease.<sup>1,2,7</sup>

**Cowgill:** So these data indicate a survival advantage for dietary phosphate restriction, but the advantage was independent of any change in the serum phosphate concentration. The serum phosphate concentration was not a marker or predictor.

**Polzin:** Nor was PTH. What do you think this means in terms of using phosphate or PTH as an endpoint for therapy?

**Grauer:** Well, at one level, it confounds things. But at the practical, everyday level, it creates a nice scenario. We don't deal with renal failure diets that are just sodium-reduced, omega-3 fatty acid-supplemented, alkalized, protein-reduced, or phosphate-restricted. We are looking at the whole package, and the whole package works.

**Elliott:** We need to remember that a phosphate in the top end of the reference range is probably not appropriate for IRIS stage II and stage III kidney disease.

**Cowgill:** Just as creatinine at the top of the normal range doesn't mean that your patient is normal or that there aren't consequences. This whole concept of important parameters being within the normal range is a problem throughout all stages of kidney disease. Practitioners could fail to recognize disease because the levels are within the normal range, when in fact the animal has progressive disease. It is not

The first step in managing patients with chronic kidney disease is to change the diet.

—Dr. Astrid van Dongen

until it extends out of the normal range that you recognize it. If creatinine and other blood values are normal, you can recognize renal disease by identifying other parameters that reflect alterations of renal structure or function.

### Experience from human medicine

**Elliott:** Let's now talk about guidelines for human medicine. I think it would be interesting to contrast those with the experiences and recommendations that practitioners make when managing their patients.

To summarize the study findings, hyperphosphatemia is associated with morbidity and mortality in people with kidney disease. The evidence supports an association between the serum phosphate concentration, both above and below the reference ranges, with poor out-

comes.<sup>8</sup> So the maintenance of a normal serum phosphate concentration is critical for the prevention of abnormalities in PTH metabolism. The KDOQI guidelines for the control of phosphate and PTH are presented in *Table 2*.

### Effective treatment protocols

**Grauer:** Let's look at how hyperphosphatemia and hyperparathyroidism should be managed in chronic kidney disease patients and how we can monitor the effectiveness of treatment (see *Q&A: Recommendations for serum phosphate management in chronic kidney disease*, pages 6 to 7). We determined a serum phosphate concentration of 3.5 to 4.5 mg/dl for stage II, 3.5 to 5 mg/dl for stage III, and 3.5 to 6 mg/dl for stage IV. We discussed monitoring PTH levels, but this is probably not something practitioners will do until we can attribute more significance to the outcome. I think we agree that you start with a renal failure diet, monitor the response, add phosphate binders (if needed), again monitor the response, and then add calcitriol (at least in dogs) if you can't reach your serum phosphate concentration goals with the initial treatments.

### Renal diets

**van Dongen:** The renal diet is different from the maintenance diet in more than one way. So the first step in managing patients with chronic kidney disease is to change the diet as much as possible before even considering a phosphate binder. We have evidence indicating that a complete renal diet with all its differences has a better clinical outcome.

**Brown:** In dogs and cats with chronic kidney disease, no one has compared the efficacy of phosphate

**Table 2: Kidney Disease Outcomes Quality Initiative recommendations for phosphate and PTH levels**

KDOQI stage	Recommended serum phosphate level	Recommended target intact PTH	Strength of evidence
III	0.87 to 1.48 $\mu\text{mol/l}$ (2.7 to 4.6 mg/dl)	35 to 70 pg/ml	Opinion
IV	0.87 to 1.48 $\mu\text{mol/l}$ (2.7 to 4.6 mg/dl)	70 to 110 pg/ml	Opinion
V	1.13 to 1.78 $\mu\text{mol/l}$ (3.5 to 5.5 mg/dl)	150 to 300 pg/ml	Evidence

control with a maintenance diet plus a phosphate binder to a phosphate-restricted prescription renal diet alone. While the results might be similar, there are other nutritional changes in special diets, such as potassium and alkali supplementation, that make them preferable.

Because of the nature of the available data, we don't know if it's just phosphate restriction that is beneficial in the clinical trials. I think it is the phosphate restriction partially, but it could be some combination of dietary factors. To me a logical first step—after the dog or cat is completely evaluated diagnostically and you establish that it has chronic kidney disease—is to recommend a renal diet. Then you follow it for several weeks to determine what is happening to the serum phosphate concentrations before you add a phosphate binder.

**Elliott:** We know that about 40% of the cats put on a renal diet will either not eat enough or not eat at all.<sup>2</sup> Are we recommending that these cats be fed a standard maintenance diet plus phosphate binders?

**Brown:** Yes, but only as a last resort after attempting to feed a renal diet. There are many other benefits to a renal diet, depending on the stage of kidney disease. There is no doubt that if an IRIS stage III or higher

animal is given a high-protein diet, this substantially increases its risk of having a uremic crisis. It is important to recommend that it be introduced to a renal diet in a very controlled and gradual manner. Some experts also say there is a benefit to changes in fatty acid, sodium, and/or protein composition in the renal diets.

**Cowgill:** In your experience, are the 40% of patients that won't eat a renal diet in a higher stage of chronic kidney disease?

**Elliott:** They tend to be cats that have been fed a variety of foods. If they've had prawns, then they just don't look at the renal diet.

**Polzin:** Cats that accept a renal diet generally do well on them. Most of these cats maintain body weight, and their hair coats and body conditions remain good. But problems arise if they fail to consume an adequate number of calories. If you combine lower protein intake with inadequate dietary intake, then you get into trouble.

**Brown:** Yes. Inadequate intake of a protein-restricted diet may pose more of a nutritional risk than inadequate intake of a nonrestricted diet. That is probably true for many nutrients. But when addressing phosphate balance only, there are alternatives to a renal

diet. In early chronic kidney disease, we have already suggested that practitioners can consider a diet mixture with intermediate levels of protein and phosphate plus a phosphate binder if they are worried about hair coat or diet palatability.

**Polzin:** Studies in people have looked at the effect of partial diet compliance. They have documented that partial compliance is superior to noncompliance. In our trials in dogs and cats, we assumed that we'd get partial compliance, so we tolerated up to 20% noncompliance. We kept dietary records, and most dogs and cats were 90% or greater compliant. One way to address the noncompliance issue would be to recommend that clients use as much of a renal-type diet as possible, so at least some of the diet consumed is renal. Our success rate is much higher than yours, which in part reflects that more people in the United States feed a commercial pet food than in Great Britain. You could also formulate a homemade renal diet if the pet would be more likely to eat it.

**Grauer:** How much difference is there between the various renal diets?

**Brown:** I don't see how you can distinguish them for a variety of reasons. For one, depending on how the phosphate level in the diet is

# PHOSPHATEMIA

## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE

expressed and what the caloric content of the diet is, it's difficult to know which diet really provides the lowest phosphate intake per kg of patient. The other variable is that phosphate availability in these diets has never been compared and dietary phytin levels alter phosphate absorption considerably. Furthermore, we should be careful not to simply recommend a phosphate-restricted diet as the best option; we should clearly indicate that a diet formulated for chronic kidney disease is our first preference.

**Elliott:** The renal diets are more than phosphate-restricted; they have other potential benefits and for this category of patient, they are all appropriate. So the renal diet is fed for four weeks and is introduced gradually over one to two weeks by mixing it with the original diet and increasing the proportion over time. Then the animal is reevaluated after four weeks.

### Phosphate binders

**Cowgill:** Let's discuss the management of patients that require more than a renal diet to manage hyperphosphatemia—patients that need phosphate binders. I think the biggest failure in the management of hyperphosphatemia in uremic animals is not necessarily what phosphate binder is prescribed but how it is used. Veterinarians may not have a good understanding of how these drugs should be used; there is no standard dose. You dose to the outcome that you want within reason. The dose is markedly dependent on the diet's basal phosphate content and the timing of the medication with the diet—all potential causes of treatment failure. It is a dietary phosphate binder, so the medication has to be physically coupled with the diet.

Animals with kidney failure don't

eat like young, healthy Labradors—they don't eat all of their food in one gulp. If you administer a pill and the animal eats throughout the day, there is no timing of medication with the diet—and no likelihood that this medication will work. It will work best if mixed with food, but only to the extent that it doesn't adulterate the food so the animal will not consume it. Practitioners should recommend medications that are not flavored. Practitioners may not embrace phosphate management because they don't understand how to effectively prescribe it and, therefore, don't see clinical benefits.

The biggest failure in the management of hyperphosphatemia in uremic animals is not necessarily what phosphate binder is prescribed but how it is used.

—Dr. Larry Cowgill

**van Dongen:** Practitioners also need to be sure that they are dealing with a patient with stable chronic kidney disease. Sometimes it is not easy to be sure about the nature (*e.g.*, acute, extrarenal, a combination, or complicated by ascending infection) of kidney failure on initial consultation. Rather, practitioners should postpone phosphate management until initial treatment, results, and follow-up have confirmed that the renal patient is not deteriorating or improving rapidly, is capable of

maintaining its fluid balance, and is ingesting enough food. You cannot forget the basic steps.

**Elliott:** So our recommendation is that phosphate binders are used for long-term treatment; they aren't a quick fix. This treatment involves long-term phosphate control, which is important in managing patients with chronic kidney failure. And to ensure a good outcome, practitioners need to monitor phosphate levels periodically because these levels can increase even if phosphate binders are administered.

**Cowgill:** I find it amazing how many referrals I get for acute kidney failure. These patients often have a phosphate level approaching or exceeding 25 mg/dl and are being treated with intestinal phosphate binders, despite the fact that the animal was not eating.

**van Dongen:** Or worse, sometimes an animal is referred for kidney disease and a urinary tract infection is also detected during the workup but urine was not checked before referral. These initial steps are important.

**Cowgill:** Historically, the way we have dosed phosphate binders is intrinsically wrong. They should be dosed based on the amount of phosphate in the diet, but we make blanket recommendations of 30 to 60 mg/kg. We need to understand how much phosphate is in the diet and how much phosphate binder—based on its binding capacity—would tie up that phosphate. We know the content of most of the diets animals eat these days, so it's possible to estimate the phosphate intake.

**Elliott:** We also want to encourage monitoring the serum phosphate concentration as part of longitudinal monitoring of animals with chronic kidney disease, which help us adjust

the dose to suit the individual patient. The other factor that influences dose is the stage of kidney disease.

**Dr. Bernhard Gerber:** What starting dose of phosphate binders should practitioners recommend?

**Grauer:** Typically, aluminum hydroxide or calcium carbonate is recommended, starting at 30 mg/kg and increasing to 90 mg/kg or above as needed.

**Polzin:** Two important factors play a role in dosing. First, the dietary phosphate level, even with the same GFR, can profoundly alter the starting dose of phosphate binder. Then there is the concept of proportional reduction in phosphate according to the reduction of GFR, which involves the stage of kidney disease. So with an animal at a certain stage of chronic kidney disease on a particular diet, you can estimate the phosphate intake, which may lead you to a very different starting dose than the standard recommendation. Is there a way to use those two factors together to determine a dosing recommendation? Again, practitioners can become frustrated quickly because the phosphate binder isn't working—they may be looking too soon or the dosing is not optimal. For example, if you use a phosphate binder with a standard diet in an animal that has fairly advanced kidney failure and you start with a 30 mg/kg dose, you may see no response at all. So we should probably do a better job of linking starting dosage to the severity of the disease and providing very explicit follow-up recommendations.

**Elliott:** How stable is this animal before we start treatment? If you take one pretreatment sample for the serum phosphate concentration and a later posttreatment sample shows that

the phosphate has increased or decreased, you don't actually know how stable that animal was initially. The recommendation is that you take two pretreatment samples to evaluate whether this animal presented to you because it suddenly deteriorated and if its second pretreatment sample shows a further deterioration. Quite often, it has improved since the first sample. Then you take a third sample to see whether it really stabilized, and that is what you base your treatment on.

**Cowgill:** There is no rationale for adding a phosphate binder until you have exhausted the limits of dietary phosphate reduction. As you transition the animal to the diet, you have the opportunity for two or three serum phosphate measurements to determine the stability and baseline value. So another thing that isn't done routinely in the first line of hyperphosphatemia management is changing the diet because it isn't as easy as just adding a phosphate binder to an existing diet.

**Polzin:** I'd be surprised if waiting two or three weeks to modify phosphate levels would make any difference in the long-term. The first thing practitioners focus on is decreasing the phosphate level. It doesn't have anything to do with symptomatology, and I doubt starting phosphate binders a few weeks earlier will alter the disease outcome. It makes sense to establish the serum phosphate concentration baseline for the patient first and then determine what to do. Again, you don't want to make abrupt diet changes as most dogs and cats won't accept them. It may be a couple of weeks to months before you can decide to add a phosphate binder. We don't want to present this as an urgent thing.

**Elliott:** Are calcium-containing phosphate binders and the risk of hypercalcemia an issue in veterinary medicine as they are in human medicine?

**Cowgill:** First, I don't think we have necessarily excluded aluminum as an effective phosphate binder in animals. We don't know if animals have the same historical problems with aluminum as people. Do we know that aluminum affects the neurologic system? Do we know that we have aluminum bone disease or aluminum toxicity? As you use higher doses of aluminum-based phosphate binders in animals with more advanced disease, the likelihood of seeing aluminum toxicity is real and needs to be monitored. But at varying stages of chronic kidney disease, you can also see definite effects of hypercalcemia from calcium-based binders.

**Elliott:** The problem I have is that aluminum-based binders have disappeared from the pharmacy shelf.

**Polzin:** It is sometimes difficult for owners and practitioners to get aluminum-based phosphate binders unless it is through a veterinary distributor or university.

**Cowgill:** If you use an aluminum powder, you can sprinkle it on the food. I think gels are a disaster. We have ordered reagent-grade aluminum very economically from suppliers, and you can provide that in a very easy form and mix it with canned or kibble foods. Aluminum hydroxide also works very effectively.

Dosing has become a problem with aluminum because of the difficulties of finding effective preparations. But I think aluminum is still a reasonable choice. People using aluminum binders have years of exposure with no effective means of eliminating the aluminum. I'm not

# PHOSPHATEMIA

## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE

sure we have those same concerns in dogs and cats.

**del Palacio:** Calcium carbonate and calcium acetate are the most common calcium-containing binders. They have replaced aluminum-based salts in people in order to avoid the toxicities secondary to aluminum. However, due to a lower phosphate-binding capacity than aluminum, high doses of calcium carbonate are required to reduce the serum phosphate concentration to acceptable levels. Calcium acetate achieves similar control of the serum phosphate concentration as calcium carbonate at a lower dose of elemental calcium. The main disadvantage of calcium salts reported in people is the associated hypercalcemia and metastatic calcification.

**Elliott:** There are no published clinical studies comparing the available phosphate binders (calcium containing or noncalcium-containing) in veterinary medicine. Anecdotally and by extrapolation from human medicine, one would recommend close monitoring of serum calcium concentrations when using calcium-containing phosphate binders because the risk of hypercalcaemia may be higher than with noncalcium-containing phosphate binders.

Do we know if adding a phosphate binder to a maintenance diet containing a standard amount of phosphate has a chance of success? I have always thought that you need to reduce the dietary phosphate intake, and if you can't get animals to eat a phosphate-restricted diet, adding phosphate binders to their standard food is unlikely to be successful.

**Brown:** In our laboratory study in cats with early IRIS stage II chronic kidney disease, we fed a maintenance diet with standard phosphate

levels but used a phosphate binder (Epakitin—Vetoquinol). It did decrease the serum phosphate concentration; initially mean serum phosphate concentrations were above 5 mg/dl. With the phosphate binder, mean serum phosphate concentration fell to 4.4 mg/dl (Brown SA, Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, Ga.: Unpublished data, 2005). I am not saying that this is the right approach, but you can see an effect of binders. The group means were about 5.1 mg/dl with diet alone vs. 4.4 mg/dl with the binder—this may appear to be a small effect, but it did move cats with chronic kidney disease to within our target range and was statistically significant.

**Grauer:** So this was about a 20% reduction in the serum phosphate concentration. And you fed a maintenance diet?

**Brown:** That might be a fall-back plan if animals won't accept a renal diet. But it is likely that an intestinal phosphate binder will be more efficacious with a renal diet than with a maintenance diet.

**Lefebvre:** One issue with phosphate binders is that they may interact with oral absorption of other drugs that are given to renal patients. If the phosphate binder is mixed with food and the other drug is given at the time of the meal, the absorption of the drug may be decreased.

**Polzin:** How serious would it be if we mix the binder in the food and the animal grazes like many cats and some dogs do? Is this a huge issue?

**Grauer:** You could simply withhold food for two hours after the other medication is administered.

### Monitoring and rechecking phosphate levels

**Elliott:** We now need to make specific recommendations on managing hyperphosphatemia in terms of a staged approach and frequency of monitoring.

**del Palacio:** We often treat dogs with chronic kidney disease secondary to leishmaniasis, which is the main cause of chronic kidney disease in our hospital. Hyperphosphatemia in those dogs is mainly present in advanced stages of kidney disease. Some of these dogs have very high phosphate levels (18 mg/dl) at diagnosis. In our experience, a standard treatment based on stabilization of the patient (*e.g.*, fluids, antiemetics, H2 receptor blockers), ACE inhibitors, calcium channel blockers (if hypertensive), allopurinol (for leishmaniasis), and a phosphate-restricted renal diet helps maintain a serum phosphate concentration of less than 6 mg/dl in most dogs. However, when diet is not well accepted by a dog or phosphate levels remain higher than normal a month later, we introduce an intestinal phosphate binder.

**Gerber:** In Switzerland, we try to reduce serum phosphate concentrations by feeding a renal diet first. Usually we do not achieve total control of phosphate, so we add an aluminum-based phosphate binder, which is still available in Switzerland.

**Brown:** Another concern we should address is the frequency of rechecks for assessing phosphate balance in patients with chronic kidney disease.

**Elliott:** Once you have introduced the treatment—a change in diet and/or phosphate binders—and you recheck the patient in four to six weeks to

ensure compliance, then monitoring every two to three months is frequent enough for IRIS stage II to III.

**Brown:** So ask them to return in one month and then check them every two months?

**Polzin:** Our philosophy is more frequent rechecks in the early stages. Then you can back off depending on how the patient responds. For dogs and cats in stage III, you can recheck them every three or four months. And you can recheck cats less often if they are stable. Dogs and cats in stage IV may require more frequent visits.

**Grauer:** We should not lose sight of the fact that checking early allows us to look at other parameters than just the serum phosphate concentration. It allows us to have a better handle on the stability—or lack thereof—of the disease process.

**Polzin:** If you wait too long between examinations, compliance will fall precipitously. I think three to four months is the longest you can go without having to reintroduce any drug in this situation—including phosphate binders—to clients.

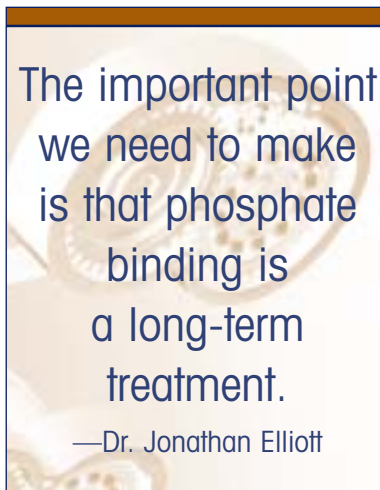
**Grauer:** It depends, too, on whether there are other medications on board. If you have a hypertensive, proteinuric patient on ACE inhibitors, you'll need to look sooner at response, and you may or may not include your serum phosphate evaluation at that time.

**Polzin:** Again, there is a chance you won't see much change in the phosphate level if you evaluate it too soon.

**van Dongen:** You only start evaluating the phosphate level once other parameters have stabilized, such as proteinuria.

**Polzin:** As mentioned earlier, it doesn't have to be solved in the first two weeks of treatment.

**van Dongen:** You have a reason for regular checkups in the beginning. But don't only monitor phosphate levels; also follow-up on clinical signs, the intake of fluids and food (e.g., quantity, quality, amount of renal diet), parameters indicative of renal function itself



(e.g., plasma creatinine, proteinuria, improvement in urine sediment), and underlying or secondary abnormalities, such as hypertension. Phosphate does become important to reevaluate after the patient has stabilized.

**Brown:** I used to recommend monitoring at two-week intervals, but I now realize that's too frequent to reassess the full effects of either diet or a binder on serum phosphate concentration. If you put an animal on a diet, recheck it in one or two weeks, add a binder, and then recheck it in another week or two, soon you may be overdosing the binder and interfering with food intake. So a preferred plan would be to recheck once a month for the first three months. With this approach, once your

patient is stable and eating a recommended diet, you then assess the serum phosphate concentration a month later and make a decision about a binder. Then a month after that, decide about adjusting the binder dose.

**Grauer:** So that begs this question: Should we have different initial starting dosages of binders given during different stages of chronic kidney disease?

**Polzin:** If you start an IRIS stage II animal at the same dose that you start a stage IV animal and your plan is to recheck monthly for three months and then every three to four months, the stage IV animal may not be there by the third month.

**Grauer:** What would you recommend?

**Polzin:** We need to determine different starting doses. There is some logic to reducing the serum phosphate concentration in parallel to the reduction in GFR. So determine the serum phosphate concentration, figure out the binding capacity, get an idea of the dietary phosphate intake, and calculate the appropriate dose to reduce the serum phosphate concentration proportionately. It will vary, depending on the diet and the severity of the GFR reduction.

**Elliott:** So the important point we need to make is that phosphate binding is a long-term treatment.

**Polzin:** And the dose is to effect.

**Elliott:** It's also important to establish the stability of the given disease before starting the intervention. Because it is a long-term treatment, the follow-up and monitoring can be as

# PHOSPHATEMIA

## MANAGEMENT IN THE TREATMENT OF CHRONIC KIDNEY DISEASE

infrequent as once monthly to begin with and then every two months, depending on the stage of disease.

**Grauer:** Would we automatically add a binder to the diet in an initial treatment for an advanced IRIS stage III or IV patient, or would you always assess the effect of diet first?

**Polzin:** I don't think hyperphosphatemia is something you have to fix immediately, so I would start with diet to see what that does. I'd follow the diet until it's stable, which could be two months or more. At that point, you could choose to intervene.

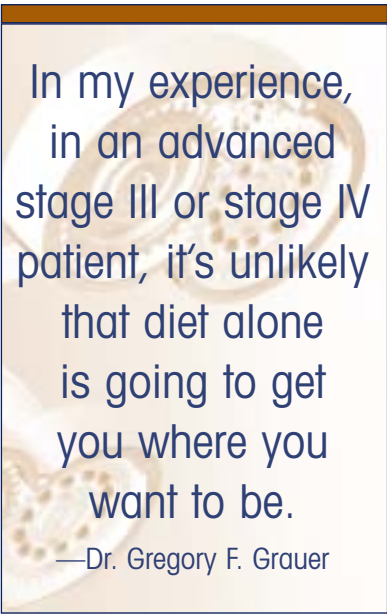
**Elliott:** In one feline study, researchers rechecked the cats at four to seven weeks after a renal diet was introduced and then at four to five months.<sup>9</sup> There was very little change between the initial decrease in serum phosphate concentration after a month or two on the diet. These were cats in IRIS stages II and III. Fourteen cats were fed the renal diet alone or renal diet and aluminium hydroxide, and eight cats were fed a standard maintenance diet.

**Brown:** And this study was on diet alone?

**Elliott:** Primarily. Some of these cats would have been reassessed at points in between, and two were then given phosphate binders because researchers were not happy with the degree of phosphate restriction. I think only two cats out of 14 in the first four to five months needed phosphate binders. These cats tended to be in more advanced stages of kidney disease, so the diet alone was insufficient to control the serum phosphate concentration and PTH. Thus, the degree of phosphate restriction needs to be tailored to the individual cat. A logical way to

do this is with regular reassessment of the treatment response in relation to a defined post-treatment serum phosphate target concentration; practitioners should use stepwise increments of phosphate restriction each month until they achieve effective control.

**Cowgill:** Particularly as you treat these late stage III to stage IV animals, it is problematic to throw all of the therapy at the patient at once. It is more tolerable for the animal and the client in steps, and they are not dealing with four or five medications at the beginning.



In my experience, in an advanced stage III or stage IV patient, it's unlikely that diet alone is going to get you where you want to be.

—Dr. Gregory F. Grauer

**Grauer:** I don't disagree with that. But in my experience, in an advanced stage III or stage IV patient, it's unlikely that diet alone is going to get you where you want to be. So you're right; there are different ways to approach it. These cats or dogs are fragile, so you should change the diet gradually. If you have a phosphate binder that doesn't affect palatability, this might not be a bad time to introduce it so you aren't introducing a subsequent change down the road.

**Polzin:** Do you think step-wise therapy is a problem in terms of serum phosphate concentration adjustment?

**Grauer:** No.

**Cowgill:** What is a dog's life expectancy in early or late stage III or early stage IV? Six or eight months?

**Polzin:** We didn't look at the data in those terms, but that's probably right.

**Cowgill:** So are you going to take two and a half months to get this animal on a low-phosphate diet?

**Elliott:** Should we check dogs that are in the late stages after four weeks and add the phosphate binder then?

**Cowgill:** You may want to be more aggressive with your approach. I don't have evidence, but my feeling would be that hyperphosphatemia may accelerate their demise.

**Elliott:** Could we say that with a certain level of hyperphosphatemia you should treat initially with diet and binders? So what if the serum phosphate concentration is higher than 6 or 6.5 mg/dl (1.94 or 2.10  $\mu\text{mol/l}$ ) after one month?

**Cowgill:** Then you have two options. You could either try to get a greater proportion of dietary phosphate reduction or add a binder.

**Polzin:** You could set two targets: 6 mg/dl (1.94  $\mu\text{mol/l}$ ) at one month, and 4.5 mg/dl (1.45  $\mu\text{mol/l}$ ) at two months. If you are above 6 mg/dl (1.94  $\mu\text{mol/l}$ ) at one month, then you add the binder. If you are below 6 mg/dl, then you keep going.

**Brown:** So you are proposing that at one month, if the animal's serum phosphate concentration is above 6

mg/dl, you would add a binder, bring that animal back in a month, and continue at monthly intervals until you reach stability in the serum phosphate concentration? Ultimately do we still have the same targets that we had before?

**Polzin:** Yes. The serum phosphate concentration target stays the same. Ideally, you would reach it by two months. If you don't, you might consider increasing the binder dose.

**Brown:** By all likelihood, the stage IV animal would be on a phosphate binder at one month.

### Calcium monitoring

**Brown:** Practitioners should also monitor calcium.

**Elliott:** What limits are we putting on calcium? What should we do if we are outside of those limits?

**Polzin:** A lot of these dogs and cats are hypercalcemic, but the hypercalcemia isn't necessarily associated with ionized calcium elevations. Frankly, I am not 100% sure what that means physiologically or pathologically to a patient. It might suggest a higher probability of tissue mineral deposition.

**Grauer:** You have made a critical point. If you see hypercalcemia, you need to analyze ionized calcium levels.

**Polzin:** But is it going to change what you do? Clearly it will if the ionized calcium is elevated, but if it's not, what do you do?

**Brown:** If the animal is hypercalcemic, you should measure the ionized calcium. If the ionized calcium

is in the normal range, you make no adjustments; you just monitor the calcium. But if the ionized calcium is elevated and the animal is taking a calcium-containing phosphate binder, I would switch to a noncalcium-containing binder.

**van Dongen:** If you use a calcium-based binder, it would be wise to monitor the calcium and preferably ionized calcium levels.

### Conclusion

**Elliott:** Our recommendations for serum phosphate concentration management are summarized on pages 6 to 7. This treatment is for stable chronic kidney disease patients, and the benefit comes from long-term control of the serum phosphate concentration. Manage your key problems first before considering the serum phosphate concentration; for example, address pyelonephritis and severe hypertension. Demonstrate stability in the patient with chronic kidney disease by performing serial serum creatinine measurements every two to four weeks. Phosphate restriction can also be addressed at this time.

Control of the serum phosphate concentration should be achieved by gradually introducing a phosphate-restricted diet. All commercially available renal diets can be used to achieve phosphate restriction. These should be introduced gradually over a period of seven days. The greater the proportion of the renal diet fed, the better.

Patients should be reevaluated after four weeks. If the serum phosphate concentration is greater than 6 mg/dl (1.94  $\mu\text{mol/l}$ ) at this time, introduce intestinal phosphate binding agents, reevaluate after another

four weeks, and adjust the dose to achieve the target level for the stage of chronic kidney disease. If the serum phosphate concentration is less than or equal to 6 mg/dl (1.94  $\mu\text{mol/l}$ ) after four weeks, continue dietary therapy for an additional four weeks. If the target serum phosphate concentration has not been achieved at this time, introduce intestinal phosphate binders.

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