Source and amount of dietary phosphorus and its effects on renal health

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Phosphorus is an important major mineral and an essential nutrient. One major function is of structural nature concerning the strength of bones and teeth in the form of calcium apatite. The majority of the body‘s phosphate is therefore found in these tissues. On the other hand, phosphorus has important functional significance: it is involved in the energy metabolism via energy-rich phosphates or nucleotides such as ATP. It is also crucial for the body as component of enzymes and DNA etc. and affects the cation-anion-balance. The regulation of phosphorus is closely linked to the calcium homeostasis via factors such as PTH, vitamin D and calcitonin. The major element phosphorus is consumed and used by the body in the form of phosphates deriving from orthophosphoric acid. This is why phosphorus and phosphate might be used as a synonym.

A way to differentiate between phosphates from plant and animal tissue on one hand and from mineral salts on the other is to group them in organic and inorganic phosphates with organic phosphates originating from plant and animal tissues and inorganic from rock. Even though it is scientifically or rather chemically not completely correct, e.g. for calcium apatite from bones being organic, this classification is commonly used. Organic phosphate sources are contained also in protein of different origin, so we find them in muscle tissue, eggs, dairy products but also fruits, vegetables and cereals. Inorganic phosphates or phosphate salts on the other hand are added to processed food and feed in order to supply the nutrient phosphorus but for the most part for technical reasons. Phosphate additives have many different effects and are widely used to increase palatability, for water binding, preservation, to manipulate texture and colour of the product and other purposes. The appropriate authorities even recommended the use of phosphate salts instead of sodium and nitrite in the 1980’s. For decades, the use of inorganic phosphates were thought to be safe as excessive amounts are excreted renally. This led to the classification as GRAS (generally recognised as safe) substances, meaning declaration of their use on the label of a food, beverage or feed product is not always mandatory. Where the phosphorus concentration of a product is labelled, it gives the amount (or minimum amount) of total phosphorus. In other words, there is no way to find out if or how much inorganic phosphates were added. This would be necessary to estimate the availability of the total amount of phosphates in a product and therefore its suitability. Reason therefore is that the solubility of the phosphate in the chyme is a precondition for the absorption, i.e. solubility is the major factor affecting the magnitude of bioavailability of the phosphorus source in question. A method from agricultural sciences adapted to determine the solubility of phosphates in food and feed was published in 2018 (Lineva et al.): the amount of total phosphorus will be subdivided into four different fractions based on their solubility in water or weak acid solution. The amount of phosphorus soluble in water after 1 minute is considered highly soluble and therefore readily available directly after ingestion. Applying this method, a recent study has demonstrated to what extend phosphate excess happens when feeding commercial complete diets and snacks (Dobenecker 2021). It is commonly accepted, that the amount of phytate bound phosphates in plants effect the degree

of phosphate absorption because of its low digestibility in monogastric species. However, the amount of absorbed phosphate might not be as low as expected due to microbial fermentation in the hindgut. Recently, Calvo and Uribarri (2021) were able to demonstrate that considerable amounts of phosphate might be absorbed even in the colon. It is also important to know that in contrast to humans, cats and dogs do not adapt to different amounts of both elements in their diet. They absorb fixed percentages irrespective of the ingested amount (Mack et al. 2015). This makes sense, as carnivores normally ingest bones from prey animals, and thus consume large amounts of calcium and phosphorus on a regular basis. Low intake of these elements is combined with low food intake and even starvation when there is little or no prey available. In this case, it makes no sense to spend energy on increasing efficacy of gastrointestinal mineral absorption by synthesizing carrier.

In fast growing animals, a deficient intake of phosphates may lead to signs such as inappetence, reduced body weight gain, dry and scaly skin and fur as well as reduced fitness and strength, probably because of reduced energy stores in the form of ATP (Kiefer-Hecker et al. 2018a,b). Muscle will disintegrate in the course and bone resorption leads to reduced bone mass. However, much more frequent and concerning is the excessive supply with phosphorus. An increased phosphate burden for the body is linked to increased bone resorption, vascular calcification and renal dysfunction, to name only some consequences. These effects are long known and were already demonstrated nearly a century ago (Mackay and Oliver, 1935). 40 years ago, Schneider and co-workers induced nephropathy in dogs by adding inorganic phosphates for a couple of weeks (1980). Various other researcher caused secondary hyperparathyroidism with bone loss and soft tissue calcification in dogs by adding inorganic phosphate to dog rations. In cats, less than quadruplicating the recommended daily intake led to reduced renal efficacy (Pastoor et al. 1993). It was possible to verify the results in a study by demonstrating a significantly reduced creatinine clearance, glucosuria and haematuria in cats after adding inorganic phosphate to their diet (Dobenecker et al. 2017). In contrast, a phosphate excess with balanced calcium to phosphorus ratio by adding organic sources such as bone meal did not affect parameters of renal efficacy and phosphorus homeostasis in cats and dogs (Schaschl et al. 2014, Dobenecker et al. 2021). A study in cats demonstrated that there are differences even within the group of inorganic phosphates (Dobenecker et al. 2018). The absorbed and renally excreted amount of phosphorus should be considered when evaluating the effects of diets. Haut et al. (1980) stated that the degree of renal damage correlates with the amount of phosphorus excreted per nephron. A high extracellular phosphate concentration is harmful and leads to cell death and soft tissue calcification. As both, a loss of functional nephrons during chronic kidney disease and a high dietary phosphate burden increase the phosphorus load per nephron, the occurrence of adverse effects during those trials are explainable. To help answer the question if early CKD and a prolonged excessive oral phosphate load are comparable in this respect, a study in dogs was performed which looked into the effects of an increased oral phosphate load on regulatory elements of the phosphate homeostasis. In young healthy beagle dogs, addition of inorganic phosphates (balanced Ca/P ratio) led to significant effects on the serum concentrations of phosphate, calcium, parathyroid hormone (PTH), FGF23 and markers of bone resorption while the same amount of phosphorus from organic sources showed the same kinetics as a balanced control diet. A disruption of phosphorus homeostasis can be the reason for soft tissue calcification,

adverse effects on the kidneys, cardio-vascular events and increased bone resorption. The aspect of an end organ resistance to FGF23 has to be taken into account because FGF23 levels increased for extended time, i.e. more than 24 hours, after feeding soluble inorganic phosphates to dogs. A recent study in fattening pigs (Dobenecker et al. 2021) demonstrated that addition of soluble inorganic phosphates for 3 months caused reduced weight gain, a higher concentration of phosphorus in the urine, a higher kidney weight, a high degree of nephrocalcinosis as well as degeneration, fibrosis and inflammation of the kidneys.

But how about phosphate intake in patients with chronic kidney disease (CKD)? An accepted principle in dietary treatment of CKD patients is to keep serum phosphorus within normal ranges as long as possible. At least in diagnosed patients this means, that excessive phosphate intake especially from highly soluble sources should be avoided. However, we have to accept that due to late diagnosis a considerable number of individuals with considerable restrictions of renal efficacy, i.e. still undiagnosed patients, exist in the population. These individuals should receive even less inorganic phosphates than those with their full renal capacity, but the majority will be fed with the average complete diet probably containing considerable amounts. As even commercial diets for renal patients contain high amounts not only of total phosphorus but also of highly soluble phosphates (Dobenecker 2021), choosing the best fitting diet is not an easy task. There is no way to determine the amount of inorganic phosphates in a product based on the given information. The declaration of source and amount of phosphate additives would be helpful even though other characteristics such as the concentration of other minerals as well as the cation anion balance need to be considered when evaluating a diet. Especially the concentration of calcium, potassium and sodium in a diet are possible effectors, even though a wide Ca/P ratio does not prevent a high absorption rate of highly soluble phosphates (Herbst and Dobenecker 2020; Böswald et al. 2020). It is definitely advisable to avoid inverse Ca/P ratios and to adjust the ratio to between 1.3 to 2 to 1. Potassium and other elements important for the phosphate homeostasis should be supplied in sufficient amounts. A high water intake and consequently a high urine volume might reduce the concentration of phosphate in the tubules. Moreover, seniors and especially CKD patients should be monitored at regular intervals. In human medicine, a prolonged serum phosphate concentration in the upper quartile of the reference range qualifies as a warning sign for early CKD.

More research is needed to better understand all factors involved in order to formulate safe diets for our pets. Furthermore, there should be efforts to develop alternative additives, e.g. digests, with similar properties, if necessary, as well as guidelines for how to dietetically treat CKD patients individually (taking into consideration serum P, dietary P sources, serum Ca, dietary supply with Na, K, protein etc. pp.).

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