NOT ALL PHOSPHATE IS CREATED EQUAL: PHOSPHATE TOXICITY BY FOOD SUPPLEMENTS?
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49th ERA EDTA Congress

Not all phosphate is created equal:
Phosphate toxicity by food supplements?

Markus Ketteler

Dear Chairman, dear colleagues what I would like to go to is maybe a kind of a Renaissance of a former therapy form, the phosphate diet and how to approach it in the future.

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I’m thankful to Doctor Nowicki who has already spoken about biomarkers and as he pointed out in his discussion, also phosphate was always considered maybe one of the really major biomarkers for mortality.

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like shown here in the group of Geoffrey Block’s dialysis patients.

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or this is an unpublished German Registry result, wherever you look in dialysis patients high phosphate levels are associated with mortality.

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The reason why we think this is linked to mortality is mainly based on the observation that phosphate probably is not just a passive bystander but is picked up by vascular smooth muscle cells and when intracellular phosphate rises in such cells, the smooth muscle cell phenotype is turned down. These cells turn into an osteoblast which produces Runx2, produces bone proteins, matrix vesicles and thus leads to ossification of the arteries. But now we know that there are other effects like endothelium-dependent relaxation is impaired and so on.

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If we look at pre-dialysis actually, it is remarkable that phosphate levels rise slowly and only late in kidney disease.

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Kestenbaum B et al., JASN 2005

- **Predialysis patients**: Association between phosphate and mortality with high-normal serum levels

but still if you look, for example, at mortality rates in pre-dialysis patients, you see already an association in the range of the high-normal phosphate levels with impaired survival and you see a very high mortality prediction at the stages of hyperphosphatemia in such a cohort.

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We wrote an article recently in a German Physician’s magazine and that was not just based on these observations in CKD patients but also in observations in normal cohorts like this one published by Tonelli originally in 2005 where phosphate levels in the high and the upper-normal range were associated with overall mortality, with cardiovascular events, infarction, congestive heart failure and so on.

This study result, though epidemiologic and observational was confirmed meanwhile by three other large cohort studies.

So how does phosphate normally balance function? In a Western diet we usually ingest something around 20 mg/kg/day and up to about 80% can be reabsorbed in the intestines here.

We can imagine that this all goes into a kind of extracellular phosphate pool and in the case we have a healthy bone, about 3 mg/kg are reabsorbed from the bone or built into the bone so there’s a steady but obviously balanced turnover here.

Two thirds of the phosphate loads are excreted through the kidneys and about one third through the faeces.
Then we have this other player that especially comes into play when kidney function gets impaired because then phosphate, which may be otherwise retained, stimulates directly or indirectly FGF23 release from the osteocytes in the bone and this goes back into the kidney, blocks phosphate reabsorption in the tubulus thus leads to phosphaturia and the excess phosphate gets eliminated day by day. It further suppresses vitamin D activation in the kidney, so 1-α hydroxylation is blocked.

If we look at the tubulus, it appears that FGF23 is requiring an FGFR and klotho and this dimeric receptor is when FGF23 attaches to it inhibiting two sodium phosphate transporters: NPT2a-2c which effectively block this phosphate reabsorption. Interestingly, PTH also affects both transporters but through different signal transduction mechanisms. So we have two potent hormonal systems which protect us from early hyperphosphatemia.
One thing that is also may be of importance is that if we look for example at the FGF23 levels in normal situations where they are around 30-50 mg, we go to early kidney disease and they can probably adaptively increase up to 1000 mg. We look at the dialysis patients where they can go up to 20,000-30,000 mg. So they react kind of to the phosphate load.

What we also have learnt in the last year was that FGF23 by itself may be a harmful hormone, a harmful player in this game leading to LVH potentially and thus, everything that stimulates FGF23 in late stages may be of harm too but we don’t know that direct connection yet.

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How about phosphate balance in ESRD? We know that this is about the same as I showed you previously just on a weekly basis but even if we have a let’s say, phosphate diet compliant patient, we have some problems because the conventional dialysis can only remove about 2700 mg/week. The bone usually is not balanced in its turnover potential, so there is less built in than built away from the bone.

So this study in a compliant patient comes to a deposition or to an excess phosphate of about 200 mg/day but probably 1500-2000 mg is even more realistic.

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This picture by Myles Wolf suggests the new understanding of how CKD-MBD or secondary hyperparathyroidism develops and this is kind of suggesting that in order to prevent thus from hyperphosphatemia FGF23 is the first hormone that rises. Consecutively 1, 25 hydroxylation of vitamin D goes down and then only PTH comes into play.

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So if phosphate is playing significant role here, we must ask ourselves, do we want to interfere here at the beginning of dialysis where we see overt hyperphosphatemia?

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Do we need interfere here where we see the first rises of phosphate above the normal range?

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Or may we have to interfere here when we in the future when may see rises of FGF23? There’s no answer to that yet but this may become a concept in the next years.

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But if we want to interfere, we have several options. We have the option that we give phosphate binders and we all know that phosphate binders do their job, so they lower phosphate in the body and its reabsorption.

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But maybe we come back or consider diets again.

I would just like to show you 2 or 3 more recent studies on that issue, this one by Kopple and Noori’s group, Kalantar-Zadeh’s

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suggesting as you can see here and here, that higher dietary phosphate and especially phosphorous to protein ratios are associated with increased death risk in maintenance hemodialysis patients even after some adjustments.

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Although there are other studies, for example, this one published about the same time by Lynch coming to the conclusion that no restriction may even be better and there were also some adjustments taken here.

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The Association between Prescribed Dietary Phosphate Restriction and Mortality among Hemodialysis Patients

Katherine E. Lynch,1,* Rebecca Lynch,2 Gary C. Curhan,3,4 and Steven M. Brunelli5

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So they say that prescribed dietary phosphorous restriction is not associated with improved survival among prevalent hemodialysis patients and increased levels of restriction may be associated with greater mortality, particularly in some subgroups.

Conclusions: Prescribed dietary phosphate restriction is not associated with improved survival among prevalent hemodialysis patients, and increased level of restriction may be associated with greater mortality particularly in some subgroups.


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Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? 1-4

Christian S Shinaberger, Sander Greenland, Joel D Koppie, David Van Wyck, Rajnish Mehrotra, Cuba P Kovesdy, and Komar Kalantar-Zaeh

So it’s a bit irritating but maybe this study by Shinaberger is from what we think to know about the most telling because what you see here is the relationship between estimated protein intake and survival and between phosphorous and survival.

As you can see here, the lower the protein intake is, the higher the likelihood of death.
On the other hand there is a very strict relationship concerning phosphorous. If you go from such a baseline and treat or change something in the patients, the intervention you can get to the best results is probably that you increase protein intake while at the same time decrease phosphorous intake.

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**REVIEW ARTICLE**

**Phosphate Additives in Food—a Health Risk**

Eberhard Ritz, Kai Hahn, Markus Ketteler, Martin K. Kuhlmann, Johannes Mann

- Phosphate additives (mostly phosphate salts) are intestinally absorbed in up to 100%
- Absorption of natural phosphates (phosphate esters, phytates, phospholipids, phosphoproteins) is estimated in a range of 30 – 60 %
- Restriction of phosphate additives would be feasible without a reduction of the dietary protein content of the ingested food
- Some natural polyphosphates possess protective properties (e.g. pyrophosphate, phytate)
- USA – RDA: 700 mg/day, EAR: 580 mg/day, UL: 4,200 mg/day
  * P = GRAS ("generally regarded as safe")

The question of course is how to achieve that? This could be something that has to do with the phosphate additives in the food. What are phosphate additives? These are mostly phosphate salts and they can be intestinally absorbed in up to 100%.

While the absorption of natural phosphates like phosphate esters, lipids, proteins is estimated to range only in about 30-60% of absorption.

The restriction of phosphate additives would be feasible without a significant reduction of the dietary protein content of the ingested food because this phosphate is not coupled to the protein.

Some natural polyphosphates may even possess protective properties, so we don’t want to restrict them like pyrophosphate or phytate.

In the US, FDA the recommended daily allowance is 700 mg/day. We eat about 1000-1700 mg per day but what is really interesting is that there is an upper suggested level of 4200 mg of phosphate per day which is GRAS which means "generally regarded as safe". I’m not sure whether this is really true.
Food additives are:

- Sweeteners to sweeten foods or in table-top sweeteners;
- Colours adding or restoring colour in a food;
- Preservatives prolonging shelf-life of foods by protecting them against deterioration by micro-organisms;
- Antioxidants prolonging shelf-life of foods by protecting them against oxidation e.g. fat rancidity, colour changes;
- Stabilisers to maintain the physico-chemical state of a foodstuff;
- Emulsifiers to maintain the mixture of oil and water in a foodstuff.

What are food additives? These are sweeteners, colour additives, preservatives, antioxidants, stabilisers or emulsifiers and many are phosphate containing.
These are especially some German food items where you have trouble. The cheese is troublesome so that is something that you would probably like to limit at least.

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**Phosphate Additives in Food—a Health Risk**

We built up a table here and I just wanted to focus on one compound which is fairly well known.
Cola drinks owe their brown colour to phosphate because if no phosphate was added, they would be oxidised into a very dark black colour and that might not be so attractive to the drinker. European regulations allow up to 700 mg/l, so just the daily allowance of phosphate in cola drinks. If this amount of phosphate were added to 1 L of cola, it would already provide 50-75% of this daily allowance. The actual amount of phosphate added to each litre of cola is somewhere around 520 mg. So it’s really a relatively huge dose.

There was a recent study, a very nice one I guess because it was a real world study. This group tested 40 species of Italian cooked ham and actually 20 were labelled with phosphate additives, 20 were without labelled additives and the label was right because what you can see here is that those which had this label contained about 66% more phosphate per gram meat than the other ones. You see here if you just excluded those from the diet, you would have a phosphate reduction with this kind of ham of about 50% in total. So that’s quite impressive.
Another association study but also maybe interesting is this one from the US. Here 3 groups of people each 700-900 per group were stratified concerning their incomes: less than 20,000, more than 50,000 per year. You can see here that they all ingested about the same amount of phosphate per day.

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But if you measured phosphate levels in this otherwise healthy population, you saw by far the highest phosphate levels in those with a lower income. This may be due to the fact that there is more fast-food ingested, more preserved food from supermarkets and so on. So this is another kind of observation.

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A very interesting study was called ‘Look For Phos’. This addressed hemodialysis patients and they received from the study committee a magnifying glass and instructions concerning better choices in fast-food restaurants. They needed this magnifying glass because they needed to read phos on the labelling of food and you can see here that this really required some magnification and glasses.

They were given a hand out like McDonalds, Subway better choices, so no cheese, no cheese, the melting cheese is a big problem here in this regard or subway and they were instructed to eat that way.
This was well published in JAMA and you see here 145 and 134 patients finished that study in the end.

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This intervention led to in the magnifying glass in the intervention group a lowering in the phosphate of 1 mg/dL which is quite significant. There was also some lowering of -0.4 mg/dL in the placebo group. But even if you take the net effect of -0.6 mg/dL, there was no change in phosphate binders or any other intervention here. So it is may be worth looking that way and still keeping the protein intake intact.

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Our article in the German paper was followed by a response by the International Food Additives Council. PAPA: phosphoric acid and phosphates, phosphate industry response to Ritz et al.

They said the conclusion by Ritz et al. that phosphate additives in food are a health risk is not supported either by scientific evidence or by the conclusions of worldwide regulatory authorities. Inorganic phosphates, a source of phosphorous, are one of the most widely used functional food ingredients and have a long history of safe use in food. For decades numerous toxicology studies have focused on the safety of phosphate based food additives.

So we are a bit glad that we provoked such a response of the industry but we also kind of disagree with this statement.
So I leave you alone with this cartoon.

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Sausage is so expensive, boy!
Just be so kind to eat your phosphate
pure today...

I’ll translate this for you, ‘sausage is so expensive boy just be so kind to eat your phosphate pure today’. I think we should refrain from that in the future. Thank you very much for your attention.