CORRESPONDENCE

Phosphate Additives in Food—a Health Risk

by Prof. Dr. med. Eberhard Ritz, Dr. med. Kai Hahn, Prof. Dr. med. Markus Ketteler, Prof. Dr. med. Martin K. Kuhlmann, Prof. Dr. med. Johannes Mann
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Phosphates and Behavioral Abnormalities

In their review article, Ritz et al. described the consequences of hyperphosphatemia caused by phosphate additives in food with regard to increased renal and cardiovascular morbidity and mortality (1).

I want to add that phosphates for some time have been suspected of being associated with behavioral abnormalities. The doctor and children's book author Heinrich Hoffmann described in his character of Fidgety Philip not only a child in whom nowadays attention deficit hyperactivity disorder (ADHD) would be diagnosed, but he also adds that "a normal human being has only 1.5/1000 phosphorus in their brain", and wonders if it should be investigated whether "any fellow who was happy as a lark did not carry two or three times of that amount in his head" (2).

The association of phosphorus and behavioral abnormalities has been the subject of a controversial discussion ever since, and in ADHD, a low-phosphate diet has been recommended. However, only recently, several clinical studies have suggested an association between (organo-)phosphates and ADHD (3, 4).

Bearing in mind the rising incidence of ADHD and increasing numbers of prescriptions for methylphenidate, it would be interesting to study the association between dietary components such as in fast food and processed food with a high phosphate content and a causal association with the development of ADHD.

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Hypophosphatemia Also Increases the Risk

In addition to hyperphosphatemia, hypophosphatemia also increases the cardiovascular risk (1). Low serum concentrations reduce the eNOS activity and lead to insulin resistance, ATP deficiency, and—via lowered 2,3-diphosphoglycerate—to chronic tissue hypoxia causing endothelial damage. Risk factors such as diabetes or obesity are often associated with hypophosphatemia (1, 2).

The causes of clinically relevant phosphate deficiency are not only hypophosphatemic osteomalacia, malnutrition, and sepsis—as mentioned in the section entitled "The risks of hypophosphatemia" – but, in addition to poorly controlled diabetes, also chronic alcohol misuse, major surgery, infections (for example, legionellosis, malaria), COPD, long-term hemodialysis, and treatment with antacids, diuretics, catecholamines, imatinib, and others.

Since serum phosphate accounts for less than 1% of the total phosphate in the body, substantial intracellular phosphate deficiency may exist even in the presence of a normal or even raised serum concentration. Phosphate homeostasis is subject to very complex regulation, whose mechanics have been understood only rudimentarily, which is affected not only by FGF-23, parathormone, and vitamin D, but also by pH, insulin, growth hormone, estrogens, stress hormones, calcium, and magnesium. The cardiovascular risk is probably determined more by an impaired phosphate metabolism than by the very low amount of extracellular phosphate alone. Children, for example, often have much higher serum phosphate concentrations than adults but none the less do not have an increased risk, and in a recent osteoporosis study (3), hypercalcemia was confirmed as a cardiovascular risk factor whereas hyperphosphatemia was not.

The serum concentrations of people with healthy kidneys correlate only minimally with the phosphate content of the ingested food (2); besides, because of their circadian rhythm they fluctuate widely over the course of the day in the individual, and consequently serum phosphate readings, which are usually taken only once a day, are not always representative for the average serum concentration over 24 hours.

It is possible that for a healthy diet, the absolute phosphate content of foodstuffs is less important than, for example, the ratio of calcium to phosphate in the interaction with magnesium and vitamin D.

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In Reply

Professor Maurer mentions the association of phosphate with abnormal behaviors. The mechanism of organophosphates that is being discussed in the context of the development of ADHD is due to the direct effect of these organophosphates and not due to dietary phosphate intake.

Dr Deixler rightly points out that in addition to hyperphosphatemia, hypophosphatemia affects the cardiovascular risk. This is undoubtedly true, and pronounced hypophosphatemia leads to a notably increased risk even in renal patients. The extent to which these rare cases of hypophosphatemia represent the result of reduced dietary intake is currently not known. The question of the extent to which problems such as sepsis, poorly controlled diabetes, alcoholism, etc, are due to a negative phosphate balance or poorly distributed extracellular and intracellular phosphate can currently not be answered.

Dr Deixler rightly also reminds us that the phosphate concentration in the extracellular space probably triggers pathological effects not directly, but perhaps indirectly, owing to intracellular metabolic cascades. This is correct; intracellular phosphate concentration itself is relevant for the problem of vascular calcification. Equally correct is the comment that because of the circadian rhythm, one individual reading of the serum phosphate concentration under non-standardized conditions is not 100% reliable. All the more remarkable is the fact that even in people with healthy kidneys a highly significant relation exists between cardiovascular risk and serum phosphate (that is, in blood samples taken under non-standardized conditions)—another reason for why, in spite of this potential source of error, the association between serum phosphate and cardiovascular risk is relevant.

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