Acute Phosphate Nephropathy

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Abstract

Acute phosphate nephropathy (APN) is defined as a clinical state characterized by kidney injury or failure following exposure to oral phosphate solutions for bowel cleaning before colonoscopy. Similar clinical situations were also seen with oral or intravenous phosphate replacement during hypophosphotemia treatment. The exact frequency was unknown but it has been reported more frequently in recent years. The precise mechanism has yet to be defined but hyperphosphatemia and dehydration after high-volume phosphorus uptake are most probable mechanisms. Awareness for risk factors is important. The most important risk factors are age, female gender, hypertension, chronic kidney disease and use of some antihypertensives drugs. Diagnosis is often clinically made but it is essential to see the biopsy findings. There is no effective treatment in acute period and chronic injury develops in most cases.

Key words: acute kidney injury, acute phosphate nephropathy, nephrocalcinosis, oral sodium phosphate

Acute phosphate nephropathy

Colorectal cancer screening with colonoscopy contributed in early diagnosis and removal of precancerous lesions. A good bowel cleansing is mandatory for the success of the process, thereby for detection and recognition of the lesions [1]. However, bowel cleansing is a very laborious and difficult process, and uncomfortable for most patients. Search for a well tolerated, ideal preparation which is safe and effective is still continuing.

In 1990, Vanner et al. developed an oral sodium phosphate solution (OSPS) which was more tolerable than the previous preparations and needed less fluid intake than polyethylene glycol (PEG) [2]. Depending on the effect of hyperosmotic sodium phosphate, it shows its effects by drawing water and electrolytes from plasma into the bowel. Typically OSPS was administered as two doses of 45 ml within 10-12 hours apart and 5.8 grams of elemental phosphorus was administered in total. The phosphorus load during OSPS administration is too high. Acute kidney failure after OSPS use for bowel cleansing was first described in 2003 in a 71 year-old woman. Two weeks after exposure to OSPS, she presented with nonspecific malaise and her serum creatinine level was 4.5 mg/dl (baseline creatinine: 1.0 mg/dl). Renal biopsy showed intratubular deposits containing obstructive calcium phosphate crystalluria and intraluminal nephrocalcinosis [3]. Subsequent observations confirmed the relation between OSPS and kidney injury. In 2004, acute renal failure after bowel cleansing with OSPS was described in five patients. Kidney biopsies showed diffuse tubular injury and abundant tubular calcium phosphate deposits and the researchers named this finding as acute nephrocalcinosis [4]. In a following study, same group pointed out a cause-effect relationship, risk factors, predisposition to chronicity and hyperphosphatemia [5]. This clinical situation which was described as acute nephrocalcinosis initially, has more widely labelled as acute phosphate nephropathy (APN) in the literature. APN is described by Markowitz and Perazella as "a clinicopathological state characterized by acute and chronic renal failure following exposure to oral sodium phosphate (OSP) bowel purgatives" [6].

Etiology and incidence

Calcium phosphate accumulation seen in biopsy reports of documented cases made it easier to put forward a cause and effect relationship. However, biopsy is not a routine procedure of diagnosis in population-based studies. This causes difficulties in determining actual risk factors and incidence of APN. In many observational studies, it could only be possible to obtain information about acute and chronic kidney injury that was apparent after OSPS usage or colonoscopy. In these studies, there were large differences in both inclusion criteria and ways to determine acute renal injury. Therefore study results were incompatible to each other; while OSPS usage was a risk factor for APN [7-10] for some of them, there were not such a relationship in the others [11,12]. In these studies, acute kidney injury incidence ranged from 1.29% to 6.3%. The other methods used for bowel cleansing such as PEG, may also cause renal injury. Hypovolemia and fluid loss were the most important factors in such associations. In studies in which polyethylene and OSPS were compared, a considerable amount of acute kidney injury was observed in patients who used PEG [7,10-12]. Therefore, biopsy
is absolutely required for deciding the actual incidence of acute phosphate nephropathy. Phosphate nephropathy is not only seen in those who use oral phosphate solutions, it can also be encountered after phosphorus tablets or even intravenous usage. Ehrenpreis et al. have pointed to the increasing number of cases in their study in which they documented renal events associated with sodium phosphate tablets [13]. Acute phosphate nephropathy development was shown in a post-transplant hypophosphatemic patient for whom oral phosphate tablets were used for replacement [14]. In a more striking example, intravenous phosphate replacement for hypophosphatemia to a diabetic ketoacidosis patient who was a cadaveric renal transplant donor also caused phosphate nephropathy. In both cases, there were severe impairment of renal function and biopsies showed that both had calcium phosphate crystals [15].

**Pathogenesis and risk factors**

Massive phosphorus intake was claimed to be the major pathogenetic mechanism. Physiologically, phosphate balance is compensated by balancing its intake and excretion. Taking phosphate into body or reabsorption from the kidney is arranged by sodium-dependent phosphate co-transporter proteins (NaPi) [16,17]. NaPi IIa and NaPi IIc that exist in renal proximal tubule, are sensitive to serum phosphate and parathormone levels; and increase in either of them reduces the expression of NaPi IIa quickly. NaPi IIb is more widely available in small intestine, and expression of this protein increases with presence of hypophosphatemia and vitamin D, but this slow process last for days. While phosphate intake is done by absorption from small intestine and renal tubules, excretion is only through the kidneys. Since phosphate absorption is slower to control, hyperphosphatemia caused by too much phosphorus intake, both directly and indirectly, causes an increase in parathormone [18]. This leads to reduction of reabsorption in both proximal tubule and descending loop of Henle, thus, it causes an increase of calcium-phosphorus load reaching to distal tubule. As calcium-phosphorus product increases, precipitation of calcium phosphorus crystals gets easier especially in distal and collecting tubules [19,20]. It is thought that superficial changes on distal tubule epithelium due to hypovolemia constitute a suitable environment for adhesion of calcium phosphate crystals [21]. Acute phosphate nephropathy does not always develop in patients with hyperphosphatemia and this raises the possible contribution of other risk factors and even suggests other pathogenic pathways. In Zager’s study published in 1982, a correlation was shown between the percentage of decrease in glomerular filtration rate (GFR) and degree of hyperphosphatemia in rats which had been given phosphate infusion and developed acute renal failure. Interest-

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**Fig. 1.** Pathogenesis of acute phosphate nephropathy (adapted from reference 6). While the straight lines and arrows show direct pathways, dashed lines represent indirect factors in pathogenesis. NaPi co-transporter: Sodium-dependent phosphate co-transporter proteins
Chronic kidney disease is a major risk factor for all forms of acute kidney injury. Reduction of GFR diminishes renal phosphorus excretion and high phosphorus load remains for intact nephrons that are few in number [10,12]. Age (>50 years) is an important risk factor and hyperphosphatemia is the cornerstone of pathogenesis, it is important to keep OSPS usage at a minimum amount. For years, preperations were used as two times, 45 ml; and after recognition of APN, the administration was changed as 45 ml + 30 ml. The time interval between the doses may also be increased along with, increasing the amount of fluid intake in order to avoid dehydration as a preventive approach. Hypertension [5,7,12,23,24] and some antihypertensive drugs (angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEI), diuretics) [5,7,12,25,26] were seen as risk factors in many case reports and in some epidemiological studies. While adaptation to hypovolemia is supposed to be impaired in patients with hypertension, ARB, ACEI and diuretic use are known to aggravate this situation. Another unwanted effect of the renin angiotensin system blockers is the reduction of bicarbonate absorption in the proximal tubule which makes urine more alkaline, thus increases tendency for calcium phosphorus precipitation [27,28].

Table 1. Risk factors for acute phosphate nephropathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Phosphate intake (oral solution, oral tablet or intravenous)</td>
<td>especially in repeated or excessive doses</td>
</tr>
<tr>
<td>Kidney injury (acute or chronic) or kidney transplantation</td>
<td></td>
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<tr>
<td>Dehydration/volume depletion (true or effective)</td>
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<tr>
<td>Age (&gt;50 years)</td>
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<tr>
<td>Female gender</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Antihypertensive medications (ACE inhibitors, angiotensin receptor blockers, diuretics)</td>
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<tr>
<td>Nonsteroidal antiinflammatory drug use</td>
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<tr>
<td>Diabetes mellitus</td>
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Clinical presentation and diagnosis

Acute phosphate nephropathy may occur in two distinct clinical patterns following ingestion of oral sodium phosphate. First one is acute, symptomatic reversible form and occurs following uptake of large amounts of phosphorus. Sudden onset hypocalcemia may result in death in ones with tetany and cardiac arrest. Kidney dysfunction returns to normal quickly and it mostly doesn’t require a renal biopsy. The second one is the actual form of acute phosphate nephropathy. It may be symptomatic or asymptomatic. It presents with an increase in serum creatinine after days to months from use of oral sodium phosphate solution. The longer the duration between solution use and development of acute kidney injury is, the harder the diagnosis, even it may not be possible to recognise.

Some patients present very late after the exposure with chronic kidney disease. When kidney damage is discovered, serum phosphorus and calcium values are typically in normal ranges. By definition, all patients with phosphate nephropathy should be normocalcemic since hypercalcemia is also one of the causes of nephrocalcinosis. Patients with APN have bland urinary sediment with no cellular casts or crystals. Hematuria and pyuria have been intermittently observed and patients may present with low-grade proteinuria (usually <1 g/day). Because of the lack of unique clinical findings of APN, the diagnosis can only be confirmed by renal biopsy. While acute tubular necrosis findings and interstitial edema are dominant in biopsies taken in the first three weeks, after three weeks, chronicity findings including tubular atrophy and interstitial fibrosis dominate. In both situations, tubular (abandon) and interstitial (less prominent) calcium phosphate deposits are seen [6].

Prevention and treatment

The most important strategy for preventing acute phosphate nephropathy starts with better defining the risk factors and keeping high-risk patients away from all the interventions that require high phosphate load, especially oral phosphate solutions. However, when cases with very high risk can not be foreseen, minimizing the amount of phosphorus, increasing the liquid intake to prevent dehydration, and even increasing the time between oral phosphate solution doses, may be considered as general measures. Most important steps in prevention began in 2006 with the increase of phosphate nephropathy cases in the United States. Its reflection to the clinic was reducing the dose of solution from 90 ml to 75 ml, and increasing the fluid intake. In 2008, the United States Food and Drug Administration announced a warning that phosphorus solutions should not be used over-the-counter for laxative purposes. Shortly thereafter, the best known oral phosphorus solution, Fleet phosphosoda®, was voluntarily withdrawn from the US market. However, in many parts of the world, particularly in Europe, oral phosphate solutions are easily accessible and used for bowel cleansing.

There is no specific treatment of acute phosphate nephropathy. In order to avoid from dehydration, in early diagnosed cases, it may be reasonable to carry out intravenous

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There is no specific treatment of acute phosphate nephropathy. In order to avoid from dehydration, in early diagnosed cases, it may be reasonable to carry out intravenous
fluid replacement. Hemodialysis may be useful in patients whose renal dysfunction and hyperphosphatemia were diagnosed in the early period. However, the newly detected cases are often dominated by chronic process and their treatment is the same as in other causes of chronic kidney damage. In conclusion, regarding the ageing of population along with the increasing enthusiasm for colon cancer screening, nephrologists will face more and more cases of APN. Increased awareness of this situation along with adequate education and vigilance for preventive measures will certainly decrease the burden of both acute and chronic kidney injury in the community. While measures are being taken for prevention, every effort should also be carried out to treat and reverse acute cases.

Conflict of interest statement. None declared.

References