Niacin and Chronic Kidney Disease

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Summary Chronic kidney disease (CKD) is an increasing problem worldwide. The number of end-stage renal disease patients requiring treatment by dialysis is estimated to be increasing by 10,000 patients per year in Japan. Furthermore, an estimated 13 million people are living with CKD in Japan. Various complications are associated with CKD, including cardiovascular disease (CVD). More than one-third of CKD patients die from CVD. Thus, prevention of CVD is a primary concern for the treatment of CKD patients. CKD-mineral and bone disorder (CKD-MBD) is a serious complication that typically leads to CVD. Hyperphosphatemia is thought to be a central-risk factor for CKD-MBD. Therefore, managing hyperphosphatemia is crucial to prevent CKD-MBD and CVD. It is difficult to achieve the target serum phosphate level through dietary modifications alone in patients with hyperphosphatemia, because most foods contain phosphate. Thus, phosphate binders such as calcium carbonate are commonly prescribed to CKD patients with hyperphosphatemia, but these have undesirable side effects. Inhibition of intestinal phosphate transport activity has also been investigated as an alternative approach for controlling serum phosphate levels in CKD patients. Nicotinamide, which is the amide of niacin, can inhibit intestinal phosphate transport. Niacin and related compounds have also been developed as drugs for hyperlipidemia conditions, especially hypertriglyceridemia with low high-density lipoprotein. This type of dyslipidemia is frequently observed in CKD patients and is a modifiable risk factor for CVD. Thus, niacin and related compounds may have utility for the treatment of both hyperphosphatemia and dyslipidemia in CKD patients to prevent CVD.

Key Words hyperphosphatemia, dyslipidemia, chronic kidney disease, cardiovascular disease, sodium-dependent phosphate transporter

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Chronic kidney disease (CKD) is increasing in prevalence worldwide. The number of end-stage renal disease patients requiring treatment by dialysis is estimated to be increasing by 10,000 patients per year in Japan. Furthermore, it has been estimated that about 13 million people are living with CKD in Japan. Various complications are associated with CKD, including hypertension, hyperlipidemia, anemia, hyperphosphatemia, hyperkalemia, osteodystrophy, and uremia. More than one-third of CKD patients will die from cardiovascular disease (CVD), such as cardiac failure, stroke, and myocardial infarction. Thus, the prevention of CVD is a primary concern for the treatment of CKD patients. Over the past decade, epidemiological studies have clarified various non-traditional risk factors for CVD in CKD patients (1). Hypertension and dyslipidemia are well-known traditional risk factors for CVD, while hyperphosphatemia, anemia and albuminuria are non-traditional CKD-related CVD risk factors. It is critical to manage these risk factors in CKD patients to prevent CVD.

Intestinal Phosphate Absorption in CKD Patients

Serum phosphate homeostasis is maintained through intestinal phosphate absorption, renal phosphate reabsorption, and bone remodeling. However, late-stage CKD patients have decreased urinary phosphate excretion, which results in increased phosphate retention, leading to hyperphosphatemia. In addition, increased phosphate retention results in increases in serum parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), which are potent phosphaturic factors. Hyperparathyroidism increases bone resorption, leading to a condition that has been termed renal osteodystrophy. FGF23 is a novel phosphaturic factor that can inhibit both renal phosphate reabsorption and 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) activities in the proximal tubule (2). Elevation of serum FGF23 is typically observed even at the early stages of CKD, and is related to the progression of CKD as well as the development of complications (2). Both PTH and FGF23 can also cause endothelial dysfunction, which is associated with cardiovascular complications. In addition, elevation of the serum phosphate level per se can cause endothelial dysfunction as well as vascular calcification (3). The phenotype relating to the dysregulation of mineral metabolism has been termed CKD-mineral and bone disorder, and is strongly associated with the incidence of CVD and mortality in CKD patients. Therefore, reduc-
ing the phosphate absorption of CKD patients is vital to decrease their risk of CVD.

Dietary phosphate restriction is a straightforward approach to reduce the intestinal phosphate absorption. However, phosphate is present in most foods, especially animal protein-rich foods and processed foods. It is difficult to achieve a sufficient decrease of phosphate intake by the modification of diet alone, and therefore phosphate binders are widely prescribed to CKD patients. Commercially available phosphate binders for the treatment of hyperphosphatemia include calcium carbonate, sevelamer hydrochloride, lanthanum carbonate, and ferric citrate. However, these phosphate binders have some side effects, including gastrointestinal problems and hypercalcemia. Thus, it would be desirable to develop other inhibitors of intestinal phosphate absorption that work by a different mechanism from that of phosphate binders.

**Niacin and Phosphate Metabolism**

Niacinic acid and nicotinamide are converted to nicotinamide adenine dinucleotide (NAD) or NADP, and can act as a coenzyme for numerous enzymatic oxidation-reduction reactions.

In their earlier study, Kempson et al. demonstrated that NAD can inhibit sodium-dependent phosphate transport activity at the renal brush border membrane (4). Recently, Nomura et al. reported that increased nicotinamide and nicotinamide phosphorosyltransferase (Nampt) after partial heparctectomy of rats suppressed the expression levels of both renal and intestinal sodium-dependent phosphate transporters, resulting in hypophosphatemia (5). Nicotinamide is a metabolite of NAD; however, nicotinamide can also be re-converted to NAD by Nampt. Inhibition of Nampt by the specific inhibitor FK866 increased the serum phosphate level and renal phosphate reabsorption.

Nicotinamide has also been identified as an inhibitor of intestinal phosphate absorption. We previously reported that nicotinamide inhibited sodium-dependent phosphate cotransport activity in the rat small intestine (6). There are three types of sodium-dependent phosphate transporter in mammals, type I (NaPi-I), type II (NaPi-IIa, NaPi-IIb, NaPi-IIc), and type III (PiT-1, PiT-2). NaPi-IIb has been identified as a major sodium-dependent phosphate transporter in the brush border membrane of the mammalian small intestine. Eto et al. clearly demonstrated that nicotinamide inhibited intestinal sodium-dependent phosphate transport in adenine-induced CKD rats by decreasing NaPi-IIb expression in the intestinal brush border membrane (7).

Therefore, NAD metabolism plays an important role in intestinal and renal phosphate handling, and presents a possible target for the treatment of hyperphosphatemia in CKD patients.

**Effects of Niacin on Hyperphosphatemia in CKD Patients**

Niacin and related compounds have been utilized as drugs to treat hypertriglyceridemia with a low high-den-


