Niacin for phosphate control: A case of David versus Goliath

Phosphate control in chronic kidney disease (CKD) is important, given the far-reaching adverse cardiovascular effects of even minor elevations of serum phosphorus (P). In this issue of IJN, Zamanifar *et al*. have shown that a single tablet of low-dose niacin (100 mg/day) brings about phosphorus reduction of similar magnitude to the popular phosphate binders in common use. This adds up to the already available evidence base emanating from diverse populations across the world attesting to the efficacy of niacin with a unique phosphorus transport blocking action.

Niacin, more commonly known as Vitamin B3, is a water-soluble vitamin with a recommended daily allowance of 0.3 mg/kg/day. It gets converted *in vivo* to niacinamide via hepatic amidation pathway. The latter is a component of nicotinamide adenine dinucleotide; a coenzyme involved in mitochondrial redox reactions. While both niacin and niacinamide reduce serum phosphorus levels, niacin has the additional potentially beneficial property of raising serum high-density lipoproteins (HDL) levels.

A stroke of serendipity led to the discovery of niacin's phosphorus reducing effect. Shimoda *et al*., showed that when niceritol (a niacin analog) was given to hemodialysis patients for hyperlipidemia, serum phosphorus levels dropped.[1] In 2006, our study on extended-release niacin as a phosphorus reducing agent was published.[2] Subsequently multiple studies across the world have confirmed the potent effect of niacin and analogs on reducing serum phosphorus levels in patients with CKD as shown in Table 1.

Small intestinal phosphate absorption occurs through a paracellular mechanism involving tight junctions and an active transcellular mechanism involving the type II sodium-dependent phosphate cotransporter Npt2b (SLC34a2). The former was long considered as the major route of phosphorus absorption. Recent evidence shows that NPt2b mediated transport contributes to 75% of phosphorus absorption.[6] Niacin and analogs specifically inhibit this transport process.

In our multipronged strategy to retard the progression of CKD, we are forced to practice polypharmacy. CKD patients are ranked high among those reeling under high pill burden due to the use of phosphorus binders.[7] This inevitably leads to drug noncompliance and poor health-related quality of life. The study by Zamnifer *et al*. highlights a remarkable property of niacin in that phosphorus control could be achieved with a single dose. By adding it to our repertoire, a dose reduction of other phosphorus binders is possible.

Pleotropic benefits of niacin

The modification of Diet in Renal Disease (MDRD) study showed that low HDL level was predictor of progression of CKD. Multiple studies pointed toward such an association between elevated triglycerides and low HDL levels.[3] Niacin is the only available agent with proven benefit of increasing HDL levels. HDL has multiple subfractions with varied roles. The HDL2 subfraction has beneficial anti atherogenic activity whereas HDL3 subfraction is proinflammatory.[8] CKD results in higher HDL3 levels which are corrected by niacin therapy. Under experimental conditions, niacin reduces oxidant stress by inhibiting release of myeloperoxidase, monocyte chemoattractant-1, tumor necrosis factor-alpha, nuclear factor-κB, and vascular cell adhesion molecule-1 from cultured human aortic endothelial cells thus contributing to improved endothelial health.[9]

Niacin-induced flushing is often cited as a significant impediment to its continued use. However, a recent analysis showed that extended-release niacin was associated with an acceptably low incidence of flushing.[10] A recent meta-analysis involving 5 randomized controlled

Table 1: Magnitude of phosphorus reduction after niacin therapy in studies across populations

Investigators	Patient population	Pre- and post-niacin therapy phosphorus levels in mg%	*P*
Sampathkumar *et al*.[2]	Hemodialysis	Pre-7.7 post-5.6	<0.0001
Restropo *et al*.[3]	Hemodialysis	Pre-6.5 post-4	<0.04
Muller *et al*.[3]	Hemodialysis	Pre-7.2 post-5.9	0.015
Ahmadi *et al*.[3]	Hemodialysis	Pre-7.3 post-5.9	0.004
Bostom *et al*.[3]	Diabetes+CKD 3	Pre-3.6 post-3.2	0.001
Streja *et al*.[3]	CKD	Pre-3.4 post-3.2	0.001
Vasantha *et al*.[4]	Hemodialysis	Pre-6.8 post-4.5	<0.001
Edalat-Nejad *et al*.[5]	Hemodialysis	Pre-6.9 post-5.9	0.004
Zamnifer *et al*.	Hemodialysis	Pre-6.7 post-4.4	0.004

CKD: Chronic kidney disease

trials with niacinamide called into question its reported association with thrombocytopenia.[11]

Pharmaceutical industry driven large-scale studies are unlikely to be undertaken given the low-cost of niacin. David is up against the formidable Goliath of players promoting costly noncalcium containing phosphorus binders. It is time that international bodies like Kidney Disease, Improving Global Outcomes (KDIGO) take a call on usefulness of niacin as a low-cost, effective, and low pill burden agent for phosphorus reduction in CKD with multiple pleotropic benefits.

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