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BRIEF REPORT

Niacin as potential treatment for dyslipidemia and hyperphosphatemia associated with chronic renal failure: the need for clinical trials

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ABSTRACT

Niacin has profound and unique effects on lipid metabolism. In addition to increasing high-density lipoprotein cholesterol, it is also known to decrease total cholesterol, low-density lipoprotein cholesterol, and triglyceride. Interestingly, the plasma concentration of lipoprotein(a) [Lp(a)], which has been suggested to play a role as an independent risk factor for coronary heart disease, is also decreased by niacin. Therefore, it is not surprising that in the literature it was given unique description as broad-spectrum lipid drug. Its impact is referred to as desirable normalization of a range of cardiovascular risk factors. However, its clinical use is limited due to harmless but unpleasant unique side effect of cutaneous flushing. Interestingly, recent experimental and clinical studies suggest the potential benefit of niacin as a treatment of dyslipidemia and high plasma phosphate associated with chronic kidney disease (CKD). Both dyslipidemia and high serum phosphate levels are shown to be associated with higher cardiovascular mortality. Furthermore, niacin administration improves renal tissue lipid metabolism, renal function and structure, hypertension, proteinuria, and histological tubulointerstitial injury. Further studies are required before the use of niacin for the treatment of both dyslipidemia and hyperphosphatemia with CKD advocated.

Keywords: niacin; chronic renal failure; dyslipidemia; hyperphosphatemia; kidney

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INTRODUCTION

Chronic kidney disease (CKD) is known to be associated with accelerated process of atherosclerosis. Importantly, cardiovascular disease (CVD) is the main cause of morbidity and mortality in kidney transplant recipients. Recent studies suggested the potential benefit of lipid lowering medication in preventing cardiovascular events in CKD and transplant population.[1,2] In particular, statin was shown to be of effective in reducing low-density lipoprotein (LDL) cholesterol. It is worth mentioning that an evidence of potential benefit of lipid-lowering medication started to emerge from clinical trials. In large post hoc analysis of three large trials, pravastatin treatment showed to reduce the decline in renal function in patients with moderate CKD (GFR 30–60 mL/min). Importantly, pravastatin reduced CVD in diabetic patients irrespective of the presence or absence of CKD.[3] Interestingly, the Assessment of Lescol in Renal Transplantation (ALERT) study demonstrated that fluvastatin significantly reduces cardiac deaths and myocardial infarction in renal transplant recipients.[4] These studies demonstrated that patients with CKD would derive benefit from lipid-lowering medication. However, refractory dyslipidemia and difficulty in lowering LDL to target were reported with CKD and renal transplant. The Second United Kingdom Heart and Renal Protection (UK-HARP-II) study showed that the addition of ezetimibe to simvastatin was safe and effective in treating dyslipidemia with CKD. Furthermore, the combination of ezetimibe and statin was also effective and safe in treating dyslipidemia associated with renal transplant.

On the contrary, ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 – HDL and LDL Treatment Strategies) enrolled patients who had coronary heart disease or a coronary heart disease risk equivalent, who were receiving long-term statin therapy, and in whom an LDL cholesterol level under 2.6 mmol/L and an HDL cholesterol level under 1.3 mmol/L for men or 1.4 mmol/L for women had been achieved. The patients were randomly assigned to receive extended-release niacin (target dose, 2000 mg/day) or

ezetimibe (10 mg/day). The primary end point was the between-group difference in the change from baseline in the mean common carotid intima-media thickness after 14 months. The trial was terminated early, on the basis of efficacy, according to a prespecified analysis conducted after 208 patients had completed the trial. The mean HDL cholesterol level in the niacin group increased by 18.4% over the 14-month study period to 1.3 mmol/L ($p < 0.001$) and the mean LDL cholesterol level in the ezetimibe group decreased by 19.2% to 1.7 mmol/L ($p < 0.001$). Niacin therapy significantly reduced LDL cholesterol and triglyceride levels; ezetimibe reduced the HDL cholesterol and triglyceride levels. As compared with ezetimibe, niacin had greater efficacy regarding the change in mean carotid intima-media thickness over 14 months ($p = 0.003$), leading to significant reduction of both mean ($p = 0.001$) and maximal carotid intima-media thickness ($p \leq 0.001$ for all comparisons). Paradoxically, greater reductions in the LDL cholesterol level in association with ezetimibe were significantly associated with an increase in the carotid intima-media thickness ($r = -0.31$, $p < 0.001$). The incidence of major cardiovascular events was lower in the niacin group than in the ezetimibe group (1% vs. 5%, $p = 0.04$ by the χ^2 test). The authors concluded that the use of extended-release niacin causes a significant regression of carotid intima-media thickness when combined with a statin and that niacin is superior to ezetimibe.[5] Importantly, niacin is the only available treatment known to increase HDL-C besides lowering cholesterol, LDL-C, and TG. The plasma concentration of lipoprotein Lp(a), which has been suggested to play a role as an independent risk factor for coronary heart disease, is also decreased by niacin.[6] Ganji et al. showed that in cultured human aortic endothelial cells, niacin increased nicotinamide adenine dinucleotide phosphate [NAD(P)H] levels by 54% and reduced glutathione (GSH) by 98%. Niacin inhibited (a) angiotensin II (ANG II)-induced reactive oxygen species (ROS) production by 24–86%, (b) LDL oxidation by 60%, (c) tumor necrosis factor α (TNF-α)-induced NF-κB activation by 46%, vascular cell adhesion molecule-1 (VCAM-1) by 77–93%, monocyte chemotactic protein-1 (MCP-1) secretion by 34–124%, and (d) in a functional assay TNF-α-induced monocyte adhesion to HAEC (41–54%). The authors concluded that niacin inhibits vascular inflammation by decreasing endothelial ROS production and subsequent LDL oxidation and inflammatory cytokine production.[7]

NIACIN AND RENAL DYSLIPIDEMIA

Interestingly, niacin administration was tested in animal models of chronic renal failure (CRF) (induced by 5/6 nephrectomized) by Cho et al. CRF resulted in hypertension, proteinuria, renal tissue lipid accumulation, upregulation of scavenger receptor A1 (SR-A1), acyl-CoA cholesterol acyltransferase-1 (ACAT1), carbohydrate-responsive element binding protein (ChREBP), fatty acid synthase (FAS), acyl-CoA carboxylase (ACC), liver X receptor (LXR), ATP-binding cassette (ABC)A-1, ABCG-1, and SR-B1, and downregulation of sterol responsive element binding protein-1 (SREBP-1), SREBP-2, HMG-CoA reductase, PPAR-alpha, fatty acid binding protein (L-FABP), and CPT1A. Niacin therapy attenuated hypertension, proteinuria, and tubulointerstitial injury, reduced renal tissue lipids, CD36, ChREBP, LXR, ABCA-1, ABCG-1, and SR-B1 abundance and raised PPAR-alpha and L-FABP. Their conclusion is that niacin administration improves renal tissue lipid metabolism and renal function and structure in experimental CRF.[8] The same authors conducted the same experiment in the same an animal rat model looking at impact of niacin in renal histology. The untreated CKD rats exhibited azotemia, hypertension, hypertriglyceridemia, proteinuria, glomerulosclerosis, tubulointerstitial damage, upregulation of MCP-1, plasminogen activator inhibitor-1 (PAI-1), transforming growth factor (TGF)-beta, cyclooxygenase (COX)-1, COX-2, and NAD(P)H oxidase [NOX-4, gp91(phox), p47(phox), and p22(phox) subunits], and the activation of NF-kappa B (IkappaB phosphorylation). Niacin administration reduced MCP-1, PAI-1, TGF-beta, p47(phox), p22(phox), COX-1, and NF-kappa B activation, ameliorated hypertension, proteinuria, glomerulosclerosis, and tubulointerstitial injury. Although niacin lowered serum creatinine and raised creatinine clearance, the differences did not reach statistical significance. Their conclusion is that niacin supplementation helps to attenuate histological injury and mitigate upregulation of oxidative and inflammatory systems in the remnant kidney.[9] Administration of 1000 mg nicotinic acid for 8 months in 9 patients on dialysis was associated with marked improvement of hyperphosphatemia and dyslipidemia. The phosphorus levels reduced reaching a significant value at 8 months: initial 6.46 ± 0.53, 4 months 4.37 ± 0.63 ($p > 0.05$), and 8 months 3.94 ± 0.76 ($p < 0.01$); the product Ca $\times$ P obtained important reductions at 4 and 8 months; the total cholesterol and triglyceride was significantly reduced at all periods, not being so for the LDL, although the HDL elevated to significant values at 8 months. There were no significant modifications in the LDL cholesterol, intact PTH, hemoglobin, platelet count, hepatic function tests alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin), coagulation tests prothrombin time (PT), partial thromboplastin time (PTT), uric acid, glycemic control, albumin, creatinine, blood urea nitrogen (BUN), % transferring saturation, ferritin, folic acid, and vitamin

B12. No patient presented collateral or clinical effects of importance, being the adherence to the medicament 100%. The authors recommended that nicotinic acid is efficient, very well tolerated, and economical in comparison with others drugs, which makes it ideal for the treatment of patients with hyperlipidemia and refractory hyperphosphatemia to the classical treatments.[10]

NIACIN AND HYPERPHOSPHATEMIA

Phosphorus retention develops in CKD when the GFR fails below 25 mL/min. High serum phosphate levels have been shown to be associated with higher mortality for all causes, cardiovascular mortality, and vascular and vascular calcification.[11,12] It was estimated that for each 1 mg/dL of serum phosphate increase in CKD, the risk of having myocardial infarction increases by 35%.[13] Cheng et al. conducted a prospective, randomized, double-blind, placebo-controlled crossover trial for the assessment of the safety and efficacy of niacinamide (belongs to the family of nicotinamide but lacks the ability to lower cholesterol and LDL) treatment for 8 weeks in hemodialysis patients with phosphorus levels ≥ 5.0 mg/dL. Vitamin D analogues and calcimimetics were held constant; phosphorus binders were not changed unless safety criteria were met. Thirty-three patients successfully completed the trial. Serum phosphorus fell significantly from 6.26 to 5.47 mg/dL with niacinamide but not with placebo (5.85–5.98 mg/dL). A concurrent fall in calcium–phosphorus product was seen with niacinamide, whereas serum calcium, intact parathyroid hormone, uric acid, platelet, triglyceride, LDL, and total cholesterol levels remained stable in both arms. Serum HDL levels rose with niacinamide (50–61 mg/dL but not with placebo). Adverse effects were similar between both groups. Among patients who were ≥ 80% compliant, results were similar although the decrease in serum phosphorus with niacinamide was more pronounced (6.45–5.28 mg/dL) and the increase in HDL approached significance (49–58 mg/dL). The authors recommended that in hemodialysis patients, niacinamide effectively reduces serum phosphorus when coadministered with binders and results in a potentially advantageous increase in HDL cholesterol.[14] Furthermore, niacinamide may effectively reduce phosphorus levels in peritoneal dialysis (PD) patients already receiving standard phosphorus-lowering therapies. Young et al. carried an 8-week, randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of niacinamide (750 mg twice daily) to reduce plasma phosphorus levels in 15 PD patients (8 niacinamide, 7 placebo). Phosphate binders, active vitamin D, and cinacalcet were kept constant during the study. The niacinamide treatment group experienced an average 0.7 ± 0.9 mg/dL decrease in plasma phosphorus and the placebo-treated group experienced an average 0.4 ± 0.8 mg/dL increase. The treatment effect difference (1.1 mg/dL) was significant ($p = 0.037$). No significant changes in HDLs or LDLs or triglycerides were demonstrated.[15] Different studies showed potential benefit of niacin as treatment of hyperphosphatasemia and summary is provided in Table 1. Niacin has been shown to increase fecal phosphate excretion but not urinary phosphate excretion. Its basic mechanism of action lies on the inhibition of activity of expression of the sodium-phosphate cotransporter protein (Na–Pi–2b) at the duodenum and jejunum (this accounts for approximately 50% of gastrointestinal phosphate absorption).[10] This in agreement with the study by Restrepo Valencia and Cruz, in which niacin administration for 8 months at a dose of 1000 mg/day reduces phosphate from 6.46 to 3.94 mg/dL (~40% reduction in plasma phosphate level).[10] It is worth mentioning that almost all studies of phosphorus-lowering agents fail to adequately describe two important characteristics of the patient population studied – that is, (1) the presence or absence of residual renal function and the amount of urinary phosphorus excretion and (2) dietary phosphorus intake.

In summary, recent experimental and clinical studies suggest the possible utility of niacin (nicotinic acid, vitamin B3) and its metabolite nicotinamide not only as a means of lowering phosphate levels in dialysis patients but also as a means of treating hyperlipidemia associated with CKD. Although the possibility of taking just one or two pills a day, which do not have to be taken with meals, is very attractive, caution is warranted before moving forward with niacin for treating dyslipidemia and lowering phosphate levels and in CKD patients until it is certain that they are effective, well tolerated, and safe. Taking all these factors into consideration, it is possible to suggest that a clinical trial designated to investigate the potential benefit of niacin as a treatment for hyperlipidemia and hyperphosphatasemia in CKD is now warranted.

CONCLUSION

Niacin has been widely used in the management of dyslipidemia and atherosclerotic coronary heart disease. Besides its lipid-lowering actions, niacin possesses potent antioxidant and anti-inflammatory properties. Further niacin showed potential benefit in lowering high plasma phosphate in CKD patients. Importantly, administration of niacin with statin

TABLE 1. Different studies with favorable outcome of niacin as potential treatment for hyperphosphatemia in patients on dialysis.

Study	Main outcome
Muller et al.[16]	Niaspan treatment in 17 patients on dialysis for 12 weeks decreased serum phosphate values from 7.2 ± 0.5 to 5.9 ± 0.6 mg/dL ($p < 0.015$). In contrast, Niaspan did not affect serum calcium levels. A significant increase in HDL cholesterol from 40 ± 3.2 to 59 ± 5.5 mg/dL (34%) was also observed with Niaspan($p = 0.0005$).
Sampathkumar et al.[17]	34 patients on hemodialysis for a mean period of 8.7 months. A single dose of extended-release nicotinic acid (375 mg) tablet was given with meal. Repeat measurements of serum calcium, phosphorus, and alkaline phosphatase were carried out after 8 weeks. Serum phosphorus levels changed significantly from a pretreatment level of 7.7 ± 1.5 mg/dL to posttreatment level of 5.6 ± 1 mg/dL ($p < 0.001$). There was no significant variance across age groups, sex, disease categories, and dialysis duration. The calcium level increased from 8.1 ± 1.0 to 8.5 ± 1.0 mg/dL ($p < 0.015$). The serum alkaline phosphatase level decreased significantly from 107 ± 66 IU/L to 82 ± 46 IU/L ($p < 0.001$). There was a significant reduction of calcium phosphate product from 63.1 ± 15.1 mg^2 to 48.7 ± 10.9 mg^2/dL^2 ($p < 0.001$).
Takahashi et al.[18]	65 hemodialysis patients with a serum phosphorus level of more than 6.0 mg/dL after a 2-week washout of calcium carbonate were enrolled in this study. Nicotinamide was administered for 12 weeks. A 2-week posttreatment washout period followed the cessation of nicotinamide. The serum phosphorus concentration increased from 5.4 ± 1.5 to 6.9 ± 1.5 mg/dL with the pretreatment washout, then decreased to 5.4 ± 1.3 mg/dL after the 12-week nicotinamide treatment ($p < 0.0001$), and rose again to 6.7 ± 1.6 mg/dL after the posttreatment washout. No significant changes in serum calcium levels were observed during nicotinamide treatment. Median serum iPTH levels increased with pretreatment washout from 130.0 (32.8–394.0) pg/mL to 200.0 (92.5–535.0) pg/mL and then decreased from the maximum 230.0 (90.8–582.0) pg/mL to 150.0 (57.6–518.0) pg/mL after the 12-week nicotinamide treatment ($p < 0.05$). With nicotinamide, HDL-C concentrations increased significantly and LDL-C decreased from 78.9 ± 18.8 mg/dL to 70.1 ± 25.3 mg/dL ($p < 0.01$); serum triglyceride levels did not change significantly.
Musso et al.[19]	15 patients on peritoneal dialysis treated with single dose of nicotinic acid 500 mg daily for 6 months. The authors concluded that this dose was not effective in reducing hyperphosphatasemia in peritoneal dialysis patients.

showed significant reduction of atherosclerosis. Taken together, it is possible to suggest that niacin may have the potential to be an effective medication in treating dyslipidemia and high phosphate associated with CKD. Currently, two important ongoing clinical trials looking at the effect of simvastatin with niacin. AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) is designed to test whether the drug combination of extended-release niacin plus simvastatin is superior to simvastatin alone, for delaying the time to a first major CVD outcome over a 4-year median follow-up in patients with atherogenic dyslipidemia. HPS2-THRIVE trial (Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events) will look at combining niacin with a new drug (MK-0524A) that minimizes niacin's side effects (chiefly facial flushing) can drive down still further the risk of serious heart attacks and strokes among people already taking statin treatment. These two trials will enhance our understanding of niacin and its impact on CVD and ultimately further analysis may reveal an exciting role for niacin in renal function.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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