Niacin Lowers Serum Phosphate and Increases HDL Cholesterol in Dialysis Patients

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Background and objectives: Adverse effects complicate the use of drugs that are prescribed for phosphate control in dialysis patients. Alternative treatment options are needed.

Design, setting, participants, & measurements: Nicotinic acid inhibits intestinal phosphate reabsorption and increases HDL cholesterol. This study tested the phosphate-lowering and HDL-increasing effect of Niaspan (prolonged-release nicotinic acid) in patients who were undergoing dialysis. Efficacy, safety, and tolerability of Niaspan were prospectively studied. Twenty dialysis patients, who were receiving a stable dosage of a calcium salt–containing drug for phosphate control, received after a 2-wk washout period Niaspan for 12 wk. Patients were started on 375 mg/d, and the dosage was increased every 2 wk to achieve 500, 1000, 1500, and 2000 mg/d, respectively. Clinical and laboratory parameters were prospectively recorded in patients who tolerated a target dosage of ≥1000 mg/d.

Results: Seventeen patients tolerated ≥1000 mg/d Niaspan (mean dosage 1470 ± 110 mg/d). Niaspan treatment for 12 wk 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 ($P = 0.0005$).

Conclusions: Niaspan effectively lowered serum phosphate levels and significantly increased HDL cholesterol. Niaspan may provide an alternative or adjunctive treatment option in dialysis patients.

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H yperphosphatemia occurs in patients with renal failure and is a consequence of both diminished glomerular filtration and increased tubular reabsorption. Nephrologists have feared hyperphosphatemia for decades because of its participation in hyperparathyroidism and renal osteodystrophy. Perhaps more important, epidemiologic studies in patients as well as experimental animals documented that hyperphosphatemia is also associated with disturbed cardiac histology and increased cardiovascular mortality (1–3). Thus, current National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend targeting serum phosphate values of <1.49 mmol/L (4.6 mg/dl) in patients with stages 3 and 4 chronic kidney disease (CKD) and <1.78 mmol/L (5.5 mg/dl) in patients with stage 5 CKD (4). Unfortunately, no study has yet shown that lowering serum phosphate results in increased survival of patients with renal failure. Because a variety of additional risk factors contribute to the excessive mortality, conceivably additional risk factors need to be targeted to affect mortality. Common treatment options to achieve the K/DOQI phosphate targets include dietary restriction, aluminum hydroxide, calcium salts, and elimination by

dialysis. Alternative drugs are sevelamer hydrochloride, lanthanum carbonate, magnesium salts, and polynuclear iron (5). Authorities continue to debate issues such as treatment effectiveness, bone mineralization defects, encephalopathy, acid/base homeostasis, tablet numbers, costs, and calcium-related adverse effects that are related to the various treatment protocols (6–10).

Calcium's role in the progression of cardiovascular disease is gaining more and more attention as a result of better understanding of mechanisms that control calcification processes (11,12). Although effective and well tolerated, feeding calcium salts may promote coronary artery and aortic valve calcification (13,14); therefore, hyperphosphatemia treatment protocols must carefully balance potential benefits and adverse effects. Moreover, drugs that target additional cardiovascular risk factors, such as dyslipidemia, could have additive benefits. Dyslipidemia occurs in dialysis patients with predominantly abnormal HDL cholesterol levels (15–17).

Nicotinic acid, also termed niacin or vitamin B₃, provides an interesting therapeutic approach to both hyperphosphatemia and low HDL levels in dialysis patients. The rationale stems from the fact that nicotinic acid was shown to inhibit adipocyte lipolysis, resulting in increased HDL levels, and that nicotinic acid metabolites inhibit the Na/Pi co-transport system (18–22). In a proof-of-principle study, we prospectively tested the hypothesis that prolonged-release nicotinic acid (Niaspan; Merck,

Darmstadt, Germany) lowers hyperphosphatemia and at the same time increases HDL levels in dialysis patients.

Concise Methods

Nineteen hemodialysis patients and one peritoneal dialysis patient who were receiving maintenance dialysis were enrolled in this prospective study. The institutional review board approved the protocol, and written informed consent was obtained before study entry. Adherence to the Declaration of Helsinki was ensured.

Before enrollment, all patients were treated for at least 4 wk with stable dosages of calcium salt–containing drugs; two of 18 patients received aluminum-containing drugs. Calcium salts– and aluminum-containing medications were stopped, and after a 2-wk washout period, patients received a starting dosage of 375 mg/d Niaspan. Every 2 wk the dosage was increased to 500, 1000, 1500, and 2000 mg/d, respectively. Patients who did not tolerate the dosage increase remained on the highest tolerated dosage. However, a lower limit of 1000 mg/d Niaspan was established to be included in the data analysis. At enrollment, patients were counseled to take Niaspan at bedtime and to use a nonsteroidal anti-inflammatory drug 1 h before Niaspan in case of flush symptoms. Patient compliance was monitored by weekly pill counts.

Evaluation of BP, heart rate, body weight, and temperature was performed before enrollment and once during the 12-wk treatment period. In addition, hemoglobin, leukocytes, platelets, C-reactive protein, creatinine, glutamic-oxaloacetic transaminase, glutamic pyruvic transaminase, γ-glutamyl-transferase, creatine kinase, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, calcium, phosphate, and intact parathyroid hormone (PTH) were measured in a central reference laboratory at baseline at 1 and 2 wk of washout and weekly during niacin treatment. In particular, PTH was measured using the Eclesys intact-PTH electrochemiluminescence immunoassay and a Roche Modular E170 device (Roche, Mannheim, Germany). Normal values are from 1.6 to 6.9 pmol/L.

Data are means ± SEM. The primary end point of the study was reduction in serum phosphate concentration between end of the washout period and end of the treatment phase. Under the assumption of a 0.5-mmol/L SD and an α of 5%, 15 patients were required to show a 20% reduction in serum phosphate with a power of 80%. As indicated, patients who reached a target dosage of 1000 mg/d were included in the analysis. In patients who ended the study prematurely, the last observation was carried forward. We compared data at the end of washout and end of drug treatment with Wilcoxon matched pair tests. We applied the Friedman test for repeated measurements followed by Dunn post test. $P < 0.05$ indicated statistical significance.

Results

Baseline characteristics of the 20 patients enrolled in this study are listed in Table 1. Six of the 20 patients achieved a maximal dosage of 2000 mg/d, four achieved 1500 mg/d, seven achieved 1000 mg/d, and three only 375 mg/d. According to the lower niacin limit set before the study, three patients who achieved <1000 mg/d were excluded from further analysis and 17 patients were included in the analysis. In these patients, the mean Niaspan dosage at the end of the 12-wk treatment period was 1470 ± 110 mg/d. Eleven patients completed the 12-wk study period; six stopped prematurely after 6 to 10 wk. The

Table 1. Baseline characteristics of dialysis patients ($n = 20$)[a]

Characteristic	Value
Age (yr; mean ± SD [range])	65.4 ± 10.2 (45 to 83)
Gender (male/female)	15/5
Time on dialysis (yr; mean ± SD)	3.8 ± 2.1
Cause of renal disease	
diabetes	5
glomerulonephritis	4
hypertension	8
carcinoma	2
PKD	1
Previous phosphate binder (mean dosage, g/d)	
calcium acetate	4.85 (14 patients)
calcium carbonate	1.6 (4 patients)
aluminium hydroxide	6 (2 patients)
Vitamin D treatment	13/20 patients
Statin treatment (mean dosage, mg/d)	
atorvastatin	20 (1 patient)
fluvastatin	40 (2 patients)
simvastatin	35 (8 patients)
Serum phosphate (mg/dl; mean ± SEM)	5.7 ± 0.4
Serum calcium (mg/dl; mean ± SEM)	9.2 ± 0.2
Intact PTH (pmol/L; mean ± SEM)	22.1 ± 6.4
HDL (mg/dl; mean ± SEM)	44 ± 3.6

[a]PKD, polycystic kidney disease; PTH, parathyroid hormone.

reasons for withdrawal were flush ($n = 3$), unexplained weight loss ($n = 1$), or low BP during dialysis ($n = 2$).

Before the washout period, serum phosphate and calcium concentrations were 5.7 ± 0.4 and 9.2 ± 0.16 mg/dl, respectively. Serum phosphate levels increased whereas calcium decreased during the washout period ($P < 0.05$ for both). With Niaspan, phosphate decreased from 7.2 ± 0.5 to 5.9 ± 0.6 mg/d in the group with the last observation carried forward ($n = 17$; $P = 0.015$; Figure 1). In the 11 patients who completed the 12-wk study period, phosphate decreased from 7.2 ± 0.7 to 5.8 ± 0.75 mg/dl ($P = 0.08$). Changes in serum phosphate, calcium, and intact PTH concentrations are illustrated in Figure 2. Vitamin D treatment was not changed during the study period for patients who received the drug. The strongest decrease in serum phosphate occurred early during treatment ($P = 0.027$ by Friedman test; Figure 2, top). Niaspan had no effect on serum calcium or intact PTH levels during the 12 wk of treatment (Figure 2, middle and bottom). Serum calcium levels were 8.5 ± 0.12 and 8.6 ± 0.08 mg/dl after washout and at the end of the treatment period, respectively. Intact PTH was 31 ± 6.4 pmol/L after washout and 30 ± 5.3 pmol/L after 12 wk of Niaspan treatment.

Niaspan increased HDL cholesterol from 40 ± 3.2 to 59 ± 5.5 mg/dl ($P = 0.0005$). LDL cholesterol levels tended to decrease slightly. Remarkably, triglyceride levels did not change significantly (Figure 3). Statin treatment was not changed during the study period. Adverse events possibly related to Niaspan treatment were flushing ($n = 7$) and diarrhea ($n = 1$). We observed no changes in platelet counts (175 ± 57 versus 172 ± 45 glutamic pyruvic transaminase/L; $P = 0.41$).
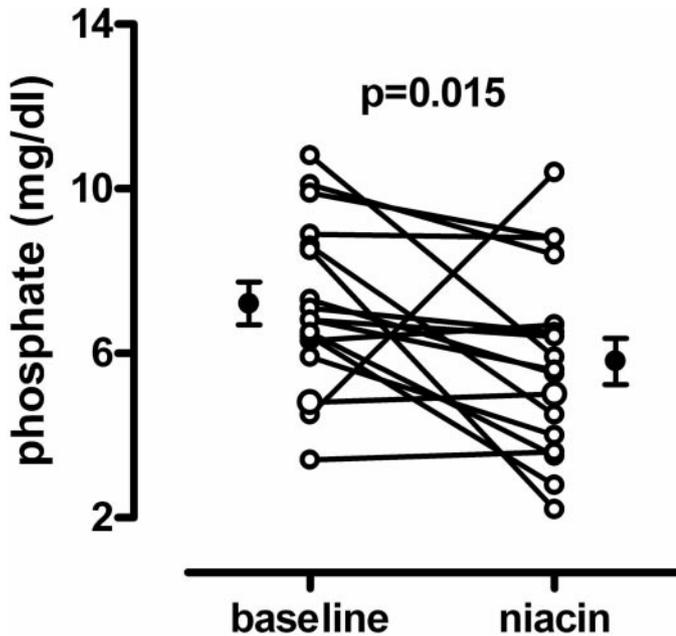

Figure 1. Individual (○) and mean (●) serum phosphate levels at the end of the washout (bsl) and at the end of the Niaspan treatment period in patients who were treated with at least 1000 mg/d Niaspan ($n = 17$). For patients who ended the study prematurely, the last observation was carried forward.
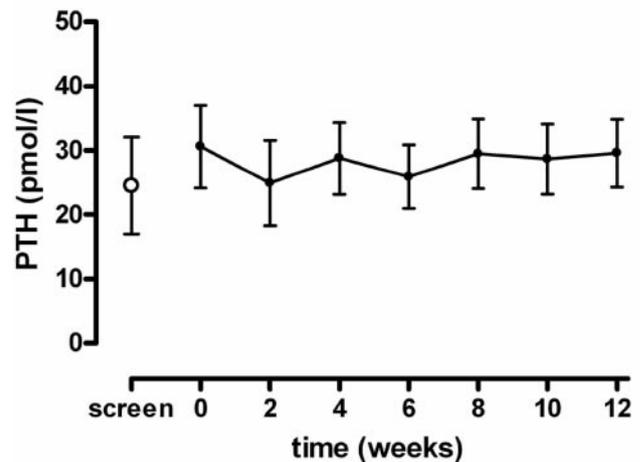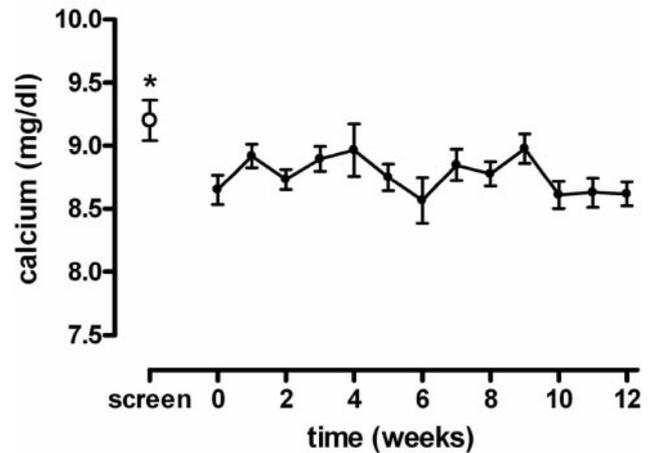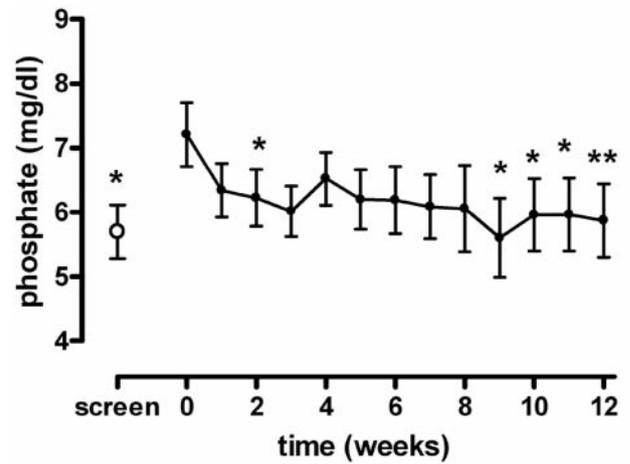

Figure 2. Changes in serum phosphate (top), calcium (middle), and intact parathyroid hormone (PTH; bottom) over time in patients who were treated with at least 1000 mg/d Niaspan ($n = 17$). For patients who ended the study prematurely, the last observation was carried forward. ○, values at the screening visit before phosphate-lowering medications were discontinued. Week 0 was the end of the washout period. *$P < 0.05$, **$P < 0.01$ versus week 0.
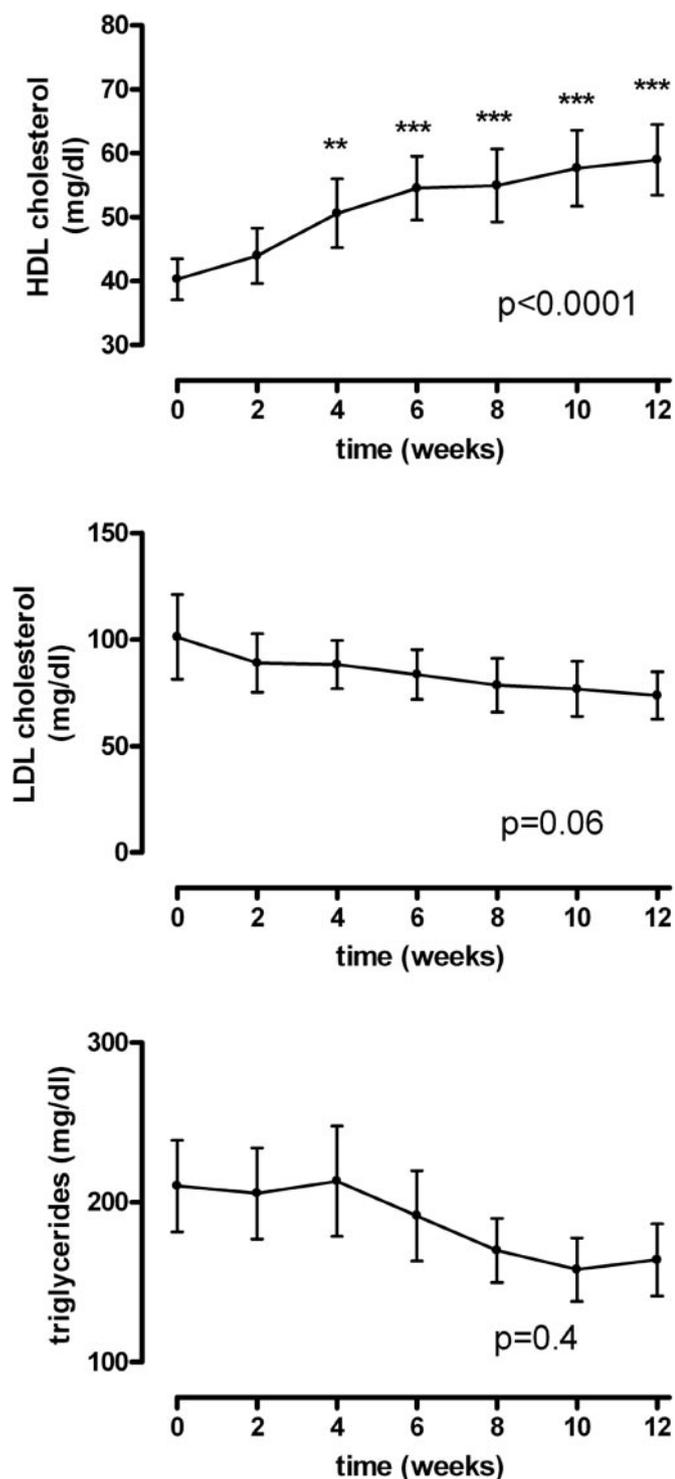
Figure 3. Changes in serum HDL cholesterol (top), LDL cholesterol (middle), and triglycerides (bottom) over time in patients who were treated with at least 1000 mg/d Niaspan (*n* = 17). For patients who ended the study prematurely, the last observation was carried forward. Week 0 was the end of the washout period. **P < 0.05, ***P < 0.01 *versus* week 0.

Discussion

Hyperphosphatemia represents a cardiovascular risk factor associated with CKD, whereas low HDL cholesterol represents a

traditional cardiovascular risk factor applying to the general population as well. Our study provides proof of concept that Niaspan lowers phosphate and increases HDL cholesterol in dialysis patients.

Hyperphosphatemia occurs in patients with CKD usually when GFR falls below 30 ml/min (3). Increased phosphate results from decreased filtration together with an increase in tubular reabsorption. The role of hyperphosphatemia in the development of secondary hyperparathyroidism and renal osteodystrophy has been known for decades; however, observational data demonstrate that hyperphosphatemia is also associated with increased mortality (1,3,23,24). Previously, the significance of the Na/Pi co-transport system for the regulation of the phosphate homeostasis was established (25,26). The apical Na/Pi IIa in the proximal tubules provides the vast majority of the transporter activity in the kidney. PTH and additional mediators that result in internalization of the Na/Pi co-transporter regulate the renal phosphate reabsorption. The list of these so-called phosphatonins is growing and includes fibroblast growth factor-23, frizzled-related protein-4, and the matrix extracellular phosphoglycoprotein. In addition, the Na/Pi IIb co-transporter mediates the intestinal phosphate reabsorption. In animal models of renal failure, the nicotinic acid metabolite nicotinamide downregulated the Na/Pi IIb expression in the jejunum brush border and thereby prevented hyperphosphatemia (21,22). The findings of our study indicate that in addition to nicotinamide, nicotinic acid administration to dialysis patients leads to a significant serum phosphate decrease, presumably by a similar mechanism. We observed that phosphate levels decreased already when patients received the starting dosage of 375 mg/dl for 14 d. We did not perform pharmacokinetic studies; however, Niaspan may accumulate in dialysis patients and relatively low dosages in the range of 500 to 1000 mg/d may be sufficient for the phosphate-lowering effect of the drug. Takahashi *et al.* (27) observed a similar effect on phosphate in hemodialysis patients using nicotinamide instead of the nicotinic acid used in our study. With 1080 mg/d, Takahashi's patients received a similar average dosage of the drug. Data from these two prospective studies suggest that either nicotinic acid or nicotinamide can extend our arsenal of phosphate-lowering drugs. Niaspan may be used alone or as an additive, for example to reduce the load of calcium salts in dialysis patients. The latter seems to be of particular interest because calcification of coronary arteries and cardiac valves occurs particularly in dialysis patients who are treated with calcium-containing phosphate binders (13,14).

The Canadian pathologist Rudolf Altschul (18) observed approximately 50 yr ago that gram doses of nicotinic acid lowered plasma cholesterol. In contrast, nicotinamide, a nicotinic acid–derived metabolite, did not affect plasma lipid levels. The difference is explained by the fact that nicotinic acid but not nicotinamide serves as a ligand for the recently discovered nicotinic acid receptor (28). The nicotinic acid receptor is a high-affinity Gi protein–coupled receptor (GPR109A) expressed in adipocytes, spleen cells, and macrophages (19,20). GPR109A, also called HM74A in humans and PUMA-G in mice, lowers cAMP levels and thereby inhibits adipocyte lipol-

ysis. Several studies established that nicotinic acid—but, again, not nicotinamide—results in elevation of HDL cholesterol in patients. In fact, nicotinic acid is the most effective measure to increase HDL levels. A placebo-controlled trial demonstrated that 1000 mg/d Niaspan led to a significant increase in HDL cholesterol in patients with type 2 diabetes (29). Niaspan also increased HDL in patients who were already being treated with statins and slowed the progression of atherosclerosis in these individuals (30). Low HDL, type 2 diabetes, and progressive atherosclerosis are important issues contributing to morbidity and mortality of dialysis patients (15–17). Our findings indicate that Niaspan significantly increased the HDL values in dialysis patients. This impressive increase was progressive during the entire study period and occurred already at a very low dosage of 375 mg/d. Takahashi *et al.* (27) observed a similar increase in HDL with nicotinamide treatment in their study; however, we are puzzled by their finding given that nicotinamide is not a ligand for the nicotinic acid receptor. The data suggest that nicotinic acid receptor–independent effects were responsible for the HDL effect. In any case, our data indicate that Niaspan, in addition to lowering phosphate, strongly increased HDL cholesterol levels in dialysis patients.

Adverse events as a result of nicotinic acid or its derivatives are mainly flush, gastrointestinal symptoms, and increases in serum uric acid levels (31). In fact, flush, although harmless, may limit patient compliance. Recently, experimental data from Benyo *et al.* (32) suggested that GPR109A-mediated Cox-1–dependent prostaglandin generation in immune cells of the skin is responsible for the flushing response. Prolonged-release preparations, such as the one used in our study, reduced but did not completely eliminate flush; therefore, we advised our patients to take a nonsteroidal anti-inflammatory drug 1 h before Niaspan administration and to take the drug at bedtime. Seven patients still experienced flush, which precluded dosage escalation. Diarrhea may also occur with nicotinic acid or nicotinamide. In the study by Takahashi *et al.* (27), 7.8% of the patients experienced diarrhea, whereas Delanaye *et al.* (33) reported in a letter that five of six patients included in an open-label study developed diarrhea. The authors pointed out that all patients received additional calcium binders, a fact that may have facilitated this adverse event. However, diarrhea was no problem in our patients on Niaspan (one of 20). Rottembourg *et al.* (34) pointed out that five of six dialysis patients who were treated with 1000 mg/d nicotinamide developed significant thrombocytopenia. We did not observe significant changes in platelet count in our patients who received Niaspan or find increases in uric acid values.

Conclusions

Our study suggests that Niaspan could be a useful drug for phosphate control in dialysis patients. The strong increase in HDL values may be a beneficial side effect. Larger and longer term controlled trials are needed to establish the optimal dosage and the clinical significance of Niaspan treatment. Niaspan may be combined with other phosphate binders to achieve K/DOQI targets. Pharmacokinetic studies will be necessary to establish the appropriate dosage and drug disposition.

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