Salivary Phosphate Secretion in Chronic Kidney Disease

Vincenzo Savica, MD, *† Lorenzo Calò, MD, ‡ Domenico Santoro, MD, *
Paolo Monardo, MD, † Antonio Granata, MD, * and Guido Bellinghieri, MD *

Background: Hyperphosphatemia is an important contributor to cardiovascular calcification in chronic renal failure (CRF) patients. Cardiovascular calcifications are responsible for the high morbidity and mortality in patients undergoing hemodialysis (HD). Despite dietary phosphate reduction and treatment with phosphate binders, serum phosphorus level, as recommended by K/DOQI guidelines, is achieved only by 50% of dialysis patients. Thus it is necessary to identify other therapeutic approaches to reducing serum phosphate. Phosphate may be secreted in the saliva, which is then swallowed, and this provides a source of endogenous phosphate and thus contributes to the hyperphosphatemia in CRF.

Patients and Intervention: This study evaluated salivary phosphate in 68 HD patients and 110 subjects with various degrees of CRF, compared with 30 healthy subjects. Saxon’s test confirmed normal salivary secretion volume in all subjects. Salivary and serum phosphate and calcium and serum parathyroid hormone were measured.

Results: Both HD and CRF patients had significantly higher salivary phosphate levels compared with healthy control subjects. In the latter group of patients, salivary phosphate correlated positively with serum creatinine ($P < .0001$) and the glomerular filtration rate ($P < .0001$).

Conclusions: These results suggest that the level of salivary phosphate may provide a better marker than serum phosphate for the initiation of treatment of hyperphosphatemia in CRF and HD patients. The results may also offer a new horizon in the therapy of hyperphosphatemia by establishing measures to bind salivary phosphate in the mouth, and before saliva is swallowed.

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groups of CRF patients: one group undergoing dialysis treatment, and another with various degrees of renal failure undergoing conservative treatment. Results were compared with the salivary phosphate contents of healthy volunteers.

Methods

The patients studied were divided into two groups: the first consisted of 68 ESRD patients from the Nephrology and Dialysis Unit of Papardo Hospital (Messina, Italy) (47 males and 29 females; mean age, 61.6 years SEM ± 9.4 years; treated for 4 hours three times a week with bicarbonate dialysate and polysulfone dialyzers; these were the HD patients). The second group included 110 patients (59 males and 51 females; mean age, 58.1 years SEM ± 7.9 years) with various degrees of CRF undergoing conservative treatment, randomly selected from the outpatient clinic by the Nephrology and Dialysis Unit at Papardo Hospital. Thirty healthy subjects (18 males and 12 females; mean age, 52.3 years SEM ± 6.4 years) from the medical and paramedical staff of our division were used as controls.

Inclusion criteria were age >18 years, and a minimum of 1 year of hemodialysis treatment for dialysis patients. Exclusion criteria for all subjects consisted of acute infections, malignancy, inflammatory processes, symptoms of dry mouth, and the presence of clinical signs of autonomic nervous-system impairment according to our previously reported protocol.14 We also excluded patients with Sjögren’s syndrome. All patients and controls were checked for normal salivary function, using the Saxon test15 at enrollment, and all HD patients were treated with the phosphate binder sevelamer at a dose of 3.2 to 4.8 g/day. All patients gave informed consent before participation, and the study was approved by our Institutional Review Board. Serum phosphorus, calcium, and parathyroid hormone (PTH) were measured from fasting predialysis blood samples in HD patients. In CRF with conservative treatment and in control subjects, blood samples were collected from an antecubital vein. After rinsing of the mouth with deionized water, 2 mL of saliva were collected by direct suction from the oral vestibule, using an automatic pipette. After centrifugation of the sample, serum and salivary calcium and phosphorus concentrations were measured by a spectrophotometric assay, using a flex reagent cartridge (Dade Behring, Inc., Newark, NJ). The serum PTH concentration was evaluated using the Immulite 2000 intact PTH, solid-phase, two-site chemiluminescent enzyme-labeled immunometric assay (Diagnostic Product Corp., Los Angeles, CA), with normal values ranging between 7.0 and 53.0 pg/mL.

Statistical analysis of the data was performed on a Macintosh G5 computer (Apple Computer, Cupertino, CA) using the Statview II statistical package (Brain-Power, Inc., Calabasas, CA). The distribution of the data was established using the Kolmogorov-Smirnov test. A normal distribution resulted only for PTH. Given the skewed distribution of serum and salivary calcium and phosphorus in HD patients, a logarithmic transformation was performed before statistical analysis. Data are expressed as geometric means with logarithmically transformed CIs, and were analyzed using the nonparametric Wilcoxon-Mann-Whitney rank sum test. Values at the 5% level or less (P < .05) were considered statistically significant. Regression analysis was used in HD patients to identify relevant relationships between levels of salivary phosphate and serum phosphate, whereas in CRF patients undergoing conservative treatment, relationships between levels of salivary phosphate, serum phosphate, creatinine, and the glomerular filtration rate (GFR) were evaluated. Multiple regression analysis was performed in all subjects, to verify independent predictors.

Results

In HD patients, the serum and salivary calcium levels were 8.73 (95% CI, 8.4 to 8.98) and 7.21 (95% CI, 6.5 to 7.91) mg/dL, respectively. In these patients, the serum and salivary phosphorus levels were 5.56 (95% CI, 5.24 to 5.91) and 30.27 (95% CI, 26.5 to 34.58) mg/dL, respectively. The level of parathyroid hormone was 143.63 ± 99.41 pg/mL. In control subjects, the salivary phosphorus level was 12.1 (95% CI, 10.5 to 14.73) mg/dL.

Considering the upper limit of CIs for mean salivary phosphate as the cutoff in control subjects (14.73 mg/dL), 62 of 68 subjects (91.17%) had an increased level of salivary phosphate. In HD patients, salivary phosphorus was significantly higher compared with healthy controls, at 30.35 (26.0 to 34.6) versus 12.1 (10.58 to 14.73) mg/dL (P < .0001), respectively. The salivary phosphorus
levels of HD patients correlated significantly ($P < .0001$) with serum phosphorus levels. Multiple regression analysis confirmed that only serum phosphorus was significantly and independently correlated ($P < .0001$) with salivary phosphorus.

In CRF patients, salivary phosphorus was higher versus controls: 31.2 mg/dL (10.3–95.6 mg/dL) versus 12.1 mg/dL (10.58–14.73 mg/dL) with $P < .0001$, while serum phosphorus was 3.70 mg/dL (2.1–6.8 mg/dL) in CRF patients versus 3.50 mg/dL (2.3–4.6 mg/dL) with $P = .013$ in controls. Moreover, in CRF patients salivary phosphorus was positively correlated with serum phosphorus ($r = 0.42$, $P < .0001$) and with serum creatinine ($r = 0.72$, $P < .0001$), while a negative correlation was found between salivary phosphorus and GFR ($r = 0.72$, $P < .0001$). No significant correlation between salivary phosphorus and serum phosphorus, creatinine, and GFR was found in the control group.

**Discussion**

Therapeutic strategies in CRF patients and in ESRD patients undergoing periodic dialysis are oriented to decrease the excess morbidity and mortality from cardiovascular disease. Cardiovascular calcifications are known to contribute to the increased morbidity and mortality of ESRD and HD patients, and hyperphosphatemia is recognized as promoting these complications.

To date, pharmacologic therapeutic strategies for hyperphosphatemia in ESRD patients include the use of phosphate binders free of calcium and metals which, together with reduced dietary phosphate intake, joint dialysis to remove excess phosphorus from the blood. Considering that the mean daily phosphate ingestion with food is 1000 mg (7000 mg/week), that the absorption involves about 4,200 mg per week, and that dialysis removes 800 mg during each session (2400 mg for three sessions per week), each dialysis patient has 1800 mg as a positive balance of phosphate weekly. These considerations support the finding that despite actual therapeutic measures, a relevant percentage of patients undergoing periodic HD have serum phosphate levels higher than those recommended by the K/DOQI guidelines.

Therefore, it is important to identify new methods of intervention and other possible therapeutic approaches to reduce phosphate levels in the blood. Moreover, CRF patients undergoing conservative treatment also have increased salivary phosphate secretion, which is correlated with serum creatinine and a degree of reduction in GFR, which suggests in turn the effect of a hypothesized salivary phosphate compensatory secretion abolished by the ingestion of saliva and its subsequent absorption in the intestinal tract. Salivary phosphate secretion as a compensatory effect of the kidney's reduced capacity to excrete phosphorus may create a vicious circle involving salivary phosphate secretion and fasting phosphate absorption, thereby worsening hyperphosphatemia. The demonstration that the salivary phosphate secretion in our patients was increased in HD patients could help open an important path toward a possible additive approach to the management of hyperphosphatemia, by breaking the vicious circle caused by the absorption of increased salivary phosphate. In fact, with knowledge of the salivary phosphate balance in CRF and in HD patients, it may be possible, for example, to bind salivary phosphate secretion in the mouth, thus contributing to the reduction of its absorption and therefore further reducing the serum phosphate concentration. The possible therapeutic implications, as suggested by the results of our study, need further investigation, both to identify substances with potential use as salivary phosphate binders, and to evaluate the identified substances in a clinical setting. In conclusion, the present results achieved in CRF and HD patients could offer new challenges in the therapeutic approach to hyperphosphatemia.

**References**