lar injury was less and urinary albumin lower in the C3aR null mice, and interstitial macrophage infiltration was reduced as well. The diminished tubulointerstitial injury in C3aR null mice could be related to less glomerular injury and consequent diminution of ischemic injury downstream from sclerosing glomeruli, compared with wild-type mice (which have induction of C3aR in the mesangium as well as the tubular epithelium) and/or could be due to less macrophage infiltration, because macrophages can induce fibrogenesis. The role of the complement system in proteinuria, as in other forms of renal injury, is complex and difficult to define precisely in vivo. In vitro studies allow more precision in defining mechanisms but remove the important influences of the in vivo milieu. Regardless, the studies by Tang et al. provide convincing evidence of a role for C3a in tubulointerstitial changes with proteinuria, elegantly expanding previous observations of a role for other complement components. These studies provide yet another potential target for therapies that might be capable of abrogating both tubulointerstitial and glomerular injury mediated by complement activation in proteinuric states, with the goal of improving long-term outcome.

DISCLOSURES
None.

REFERENCES

See related article, “C3a Mediates Epithelial-to-Mesenchymal Transition in Proteinuric Nephropathy,” on pages 593–603.

Salivary Phosphorus Binding: A Novel Approach to Control Hyperphosphatemia
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Hyperphosphatemia as a complication of chronic kidney disease (CKD) was recognized nearly a century ago. The central role of altered phosphate metabolism in CKD as a cause of secondary hyperparathyroidism and renal osteodystrophy was exposed as part of the elegant experimental studies that provided the basis of the “intact nephron hypothesis.” The association of high serum phosphorus levels and increased mortality of patients with ESRD first noted in 1990 has since been confirmed and extensively studied. There is now considerable evidence, convincing on balance, that elevated serum phosphorus levels are a surrogate marker of cardiovascular disease (coronary, aortic, valvular, and vascular calcification) and hard clinical outcomes (cardiovascular and all-cause hospitalization and mortality) in CKD. Accrued evidence on the systemic complications of altered phosphate homeostasis in CKD has led to the proposal of a new syndrome of mineral and bone disorders (MBD) of CKD, termed CKD-MBD, which encompasses biochemical alterations, bone abnormalities, and vascular calcification. Renewed interest in the detrimental consequences of elevated serum phosphorus and the difficulties of its management in CKD has become the center of much recent debate and controversy fueled, at least in part, by the pharmaceutical industry.

Approximately two thirds of the daily phosphorus intake is absorbed in the small intestines, and normal phosphorus homeostasis is maintained by its subsequent appropriate excretion by the kidney. With decreasing kidney function, the initial adaptive changes for maintenance of normal serum phosphorus gradually become restricted, and hyperphosphatemia occurs at GFR of <30 ml/min per 1.73 m². Available treatments for the control of phosphorus in CKD are restriction of dietary phosphorus intake, the use of phosphorus binders, and in ESRD the increased duration and frequency of dialysis. The dietary control of phosphorus has been difficult and implicated in contributing to mal-

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nutrition and thereby likely associated with increased mortality. The use of phosphorus binders, as with most dialysis therapies, has followed an empiric approach. Complications as a result of aluminum-based binders used initially led to the preferential use of calcium-based binders. The incriminated potential of increased calcium loads in vascular calcification then led to the introduction of noncalcium binders, whose preferential use continues to be debated.

The administration of phosphorus binders in close temporal proximity of meals, the exogenous source of phosphorus load, is the principal route of binder use. Consideration has also been given to the control of endogenous sources of phosphorus released from bone and the recirculation of absorbed phosphorus secreted in gastrointestinal fluids. The administration of binders between meals has been proposed but not studied, emphasized, or fully used. In this issue of *JASN*, Savica *et al.* propose a novel and promising approach to the control of hyperphosphatemia by the binding of salivary phosphorus. This supplemental approach is especially relevant because dietary restriction and the use of binders control hyperphosphatemia only in approximately half of patients with ESRD.

The role of saliva in initiating the digestive process notwithstanding, the salivary glands remain an orphan-child of gastroenterology and increasingly the domain of oral medicine. Knowledge of their function has been slow and remains rather fragmentary. Several of the functions of salivary glands are similar to those of renal tubular epithelia, an association commented on when the kidney was still considered a secretory organ. Salivary gland function is defined as a two-phase secretory process, which begins in the acini by the production of an isotonic fluid. The second phase occurs in the water-impermeable interlobular ducts that drain the salivary fluid, where sodium chloride is reabsorbed with increasing hypotonicity of salivary fluid and the active secretion of potassium, bicarbonate, magnesium, and phosphorus. As a result, compared with serum, the salivary fluid is hypotonic (0.50 to 0.75), low in urea nitrogen and sodium (0.3 to 0.5), and high in potassium (2 to 4×) and phosphorus (>3×), with a pH of approximately 5.6 to 7.0. These ratios are altered asymptotically toward serum levels at increasing rate of salivary flow after stimulation but retain their general proportionality to serum. Most salivary function studies in CKD have been of hemodialysis patients, in whom the reduced rate of salivary flow has been incriminated for increased thirst and oral lesions, whereas salivary composition maintains its relative proportionalities to serum, with a directional correlation to changes in serum concentrations. These changes are reflected in salivary divalent ion concentrations in ESRD as increased magnesium and phosphorus but not calcium content. The normally elevated salivary phosphorus level is nearly doubled in ESRD. It is this feature of saliva that Savica *et al.* capitalize for the control of hyperphosphatemia.

Chitosan, the active ingredient used in binding salivary phosphorus, is an abundant natural polymer glucosamine that is produced industrially by the deacetylation of chitin obtained from crustacean shells. It is a biocompatible compound of low toxicity with a structure that is similar to cellulose and is not cleaved by digestive enzymes—hence, the increasing biomedical applications of chitosan as dietary fiber for weight reduction and control of hyperlipidemia. To this now is added its ability to bind phosphorus.

In the study by Savica *et al.*, chitosan lowers serum phosphorus when used as a chewing gum preparation that contains 20 mg of chitosan and is chewed for 1 h twice daily. Chitosan was used as a supplemental approach to control the serum phosphorus level of 13 hemodialysis patients who continued their usual regimen of phosphate binders with meals and thrice-weekly hemodialysis. The dosage of chitosan used was relatively small (20 mg twice daily) compared with the much larger dosages (1.0 to 1.5 g/d) used for treatment of obesity and hypercholesterolemia. Increased usage, frequency, or dosage of chitosan gum deserves further examination for its potential capacity to control hyperphosphatemia alone rather than a supplement. Furthermore, the role of chitosan ingested with meals for the control of dietary phosphorus and its additional beneficial effect on the lipid profile would be worth exploring. Although in a study of 80 seemingly poorly dialyzed patients who had ESRD and were not on phosphorus binders oral chitosan (450 mg thrice daily) was said not to have an effect on serum phosphorus, the issue deserves further examination.

Of interest is the intriguing persistence of low serum phosphorus levels after 2 wk of discontinuing chitosan. The authors attribute this to a residual effect of chitosan bound to the intestinal tract because of its mucoadhesive properties. Of note, the parathyroid hormone (PTH) levels decreased and remained low during that period. PTH-released phosphorus from bone is a source of hyperphosphatemia and deserves closer scrutiny. The decrement in PTH level was NS in this study, but that may be due to the limitations of the assay and small number of patients. Under any circumstance, the observations of Savica *et al.* using chitosan chewing gum for the management of a clinically relevant and serious problem are most promising. Their preliminary results are impressive but will need further study.

**DISCLOSURES**

None.

**REFERENCES**

Effect of Membrane Permeability on Survival of Hemodialysis Patients

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The biologic plausibility of clinical benefits of high-flux compared with low-flux hemodialysis is supported by observations that numerous molecules with known biologic activities and potentially harmful effects accumulate in the plasma of patients with ESRD and are preferentially cleared by high-flux dialysis. In addition to β₂-microglobulin, which is often used as a plasma marker, examples of these toxic middle molecules include parathyroid hormones, advanced glycation products of various molecular weights, leptin, apolipoprotein C-III, and several molecules that inhibit granulocyte functions. Empirical support for the clinical benefits of high-flux dialysis is provided by observational studies that report associations of high-flux dialysis with reduced mortality; however, the Hemodialysis (HEMO) Study, a randomized trial performed in 1846 hemodialysis patients in the United States between 1995 and 2001, failed to demonstrate a decrease in its primary end point of all-cause mortality (hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.81 to 1.05) with high-flux compared with low-flux dialysis. Nonetheless, because the lower limit of the CI could not rule out an overall hazard reduction of up to 19% and because secondary analyses showed trends favoring high flux for all-cause mortality in patients with >3.7 yr of previous dialysis and for cardiac mortality in the full cohort, the possibility of a moderate benefit of high-flux dialysis could not be excluded definitively.

The seminal report of the randomized comparison of high-flux versus low-flux groups in the Membrane Permeability Outcome (MPO) Study by Locatelli et al. in this issue of JASN provides valuable new information on this important question. Because the precision of estimated HRs depends on the number of outcome events, the precision of the MPO Study, with 162 deaths, was less than that of the HEMO Study, with 871 deaths; however, the MPO Study provides key information on the effect of flux in a different setting. For example, MPO Study patients were more likely than the HEMO Study patients to be white and to use native fistulas and tended to...