ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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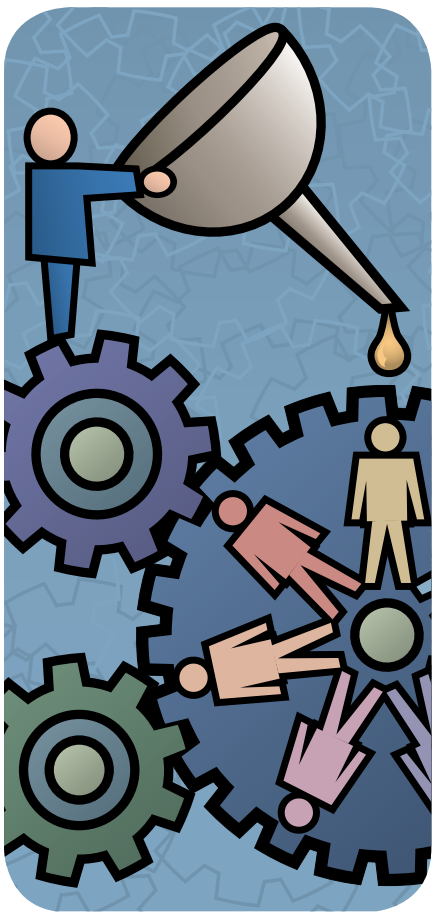

Physiology, epidemiology, and genetics confer susceptibility to the early stages of tissue injury from diabetes. See our special section on diabetic nephropathy, starting on p. 7.

New Questions on Old Drug for Hyperkalemia

Nephrologists Have Used Kayexalate for Decades—But Does It Really Work?

By Timothy O'Brien

To practicing nephrologists, few drugs are more familiar than sodium polystyrene sulfonate (SPS) (Kayexalate). Generally given in a premixed preparation with sorbitol, Kayexalate is widely used for the treatment of elevated potassium levels, with millions of doses prescribed every year. Despite recent safety concerns—including reports of colonic necrosis, leading to a safety warning from the U.S. Food and Drug Administration—SPS plus sorbitol continues to be available and prescribed.

Prompted by this new attention to an old drug, Richard Sterns, MD, of Rochester General Hospital, University of Rochester School of Medicine and Dentistry, NY, reviewed 50 years of published data on the use of SPS for hyperkalemia and reached some surprising conclusions. "We found no rigorous scientific evidence showing that ion exchange resins are effective in ridding the body of excess potassium," said Sterns. "We also found some evidence showing that, on rare occasions, they can be harmful.

"We suspect that if ion exchange resins were introduced today, they would not be approved." The invited commentary by Sterns—with co-authors Maria Rojas, MD, Paul Bernstein, MD, and Sreedevi Chennupati, MD—appears in the May *Journal of the American Society of Nephrology*.

Grandfathered drug predates modern drug approval process

Sodium polystyrene sulfonate is an ion exchange resin designed to exchange sodium for potassium in the colon. It may be given orally or by enema. Because of its poten-

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High Hopes for Kidney Drug Development During 2010

By Cathy Yarbrough

The U.S. Food and Drug Administration (FDA) in the first quarter of 2010 approved liraglutide (Victoza®), the first once-daily human glucagon-like peptide-1 (GLP-1) analogue for the treatment of type 2 diabetes in adults. Several other compounds in the pipeline may also advance the prevention and treatment of kidney disease. Whether 2010 will be a banner year for drug development is unknown. But if the benchmark is 2009, the GLP-1 analogue already has enabled 2010 to keep pace.

Last year the FDA approved only one drug—saxagliptin (Onglyza)—relevant to diabetes, hypertension, or kidney disease. This DPP-4 inhibitor, which stimulates the pancreas to make more insulin after eating a meal, was one of the 26 new compounds approved by FDA in 2009. Saxagliptin is marketed by AstraZeneca and Bristol-Myers Squibb. The companies also have another potential type 2 diabetes drug in development (see below).

Liraglutide (Victoza®) for type 2 diabetes

Liraglutide (Victoza®) was approved by the FDA on Jan. 25 for the treatment of type 2 diabetes in adults, but

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Please see Brief Summary of Prescribing Information on adjacent page.

Reference: 1. Renvela [package insert]. Cambridge, MA: Genzyme Corp; 2009.

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New Questions

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tial to cause severe constipation, SPS is usually given with sorbitol, a widely used over-the-counter osmotic laxative.

The Kayexalate name is still widely used, even though generic preparations are most commonly given. "Kayelate has become synonymous with SPS—it's kind of like Kleenex or Xerox," said Sterns. "When Kayexalate is written, what's given is a premixed preparation of the SPS resin in sorbitol."

Because it has FDA approval, one would assume there's adequate evidence supporting its effectiveness. However, Kayexalate was approved in 1958—four years before passage of Kefauver-Harris Drug Amendments. Under the 1938 Federal Food, Drug, and Cosmetic (FD&C) Act, drug manufacturers were required to demonstrate only that their products were safe. After the Kefauver-Harris Amendments, manufacturers had to provide scientific evidence that their products were effective as well as safe.

But drugs like Kayexalate, which had already been approved under the FD&C Act, were "grandfathered" and allowed to remain on the market—as long as their composition and labeling were unchanged. Thus Kayexalate never underwent the formal evidence review process required for drugs introduced after 1962.

Sterns and colleagues looked at the historical data on Kayexalate, including the FDA files. "The Agency did go back and review Kayexalate and rule that it was effective, but it was based on what today would be considered anecdotal evidence," said Sterns. The evidence included a 1961 paper by Scherr et al (*N Engl J Me*d 1961; 264:115–119), which reported that 23 of 30 patients had at least a 0.4 mEq/L drop in plasma potassium during the first 24 hours on Kayexalate. To this day, the paper by Scherr et al. remains the largest published experience with Kayexalate. Based on the Scherr report and a few others—including observations of patients who actually become hypokalemic while receiving Kayexalate—the FDA concluded that the drug was effective.

What about sorbitol?

The efficacy evidence on sorbitol is even sketchier—another 1961 paper concluded that "sorbitol alone is as effective as a combination" in lowering serum potassium. Yet for decades, the FDA-approved labeling recommended that Kayexalate be given with sorbitol. At many hospital pharmacies, SPS plus sorbitol is the only form of binding resin stocked.

Until recently, administering SPS in sorbitol was viewed as "a pretty benign treatment," according to Michael Emmett, MD, of Baylor University Medical Center in Dallas. "Sorbitol is a very convenient vehicle for suspending the SPS. It became the standard operating procedure years ago, with very little data. I think many people assumed that even if the combination was not particularly effective for reducing potassium, it wasn't hurting anything either."

But over the past few years, the FDA has received several reports of serious bowel injuries, including colonic necrosis, in patients receiving SPS plus sorbitol. Sterns, like other nephrologists, was aware of the reports of bowel injury. "The perception, mine included, was that this occurred primarily in very sick people—often in transplant patients, or following surgery, or after Kayexalate in sorbitol enemas—because that was the way that it had originally been reported. But last year, there was a report that was quite disturbing in the *Southern Medical Journal*, which suggested that this was more common than had been previously thought."

That paper, by C.E. McGowan, et al. (*South Med J* 2009; 102:493–497), reported 11 confirmed cases of intestinal necrosis temporally associated with administration of SPS. "This report also showed that colonic necrosis could occur in people who were not that ill," said Sterns. "Some were patients who were just admitted for some reason and found to be hyperkalemic—often mildly hyperkalemic—and then subsequently developed colonic necrosis."

The reports have prompted a re-evaluation of the risks versus benefits of Kayexalate suspended in sorbitol. "We're at the point now where people have really begun to question if this drug is potentially dangerous," said Emmet. "If it doesn't do much, then why are we using it?"

In September 2009, the FDA issued a warning against concomitant administration of Kayexalate with sorbitol—although the combination product remains on the market. Sterns spoke to the manufacturers of the most widely used generic preparation of SPS plus sorbitol. "They actually make some good points," said Sterns. "They have received very few reports, actually just one report, of an adverse event. And they use a smaller concentration of sorbitol than most of the cases in the literature that have described harm."

That preparation contains 33 percent sorbitol, whereas the reports of adverse events have come in patients receiving 70 percent sorbitol. Sterns added, however, that at least some of the patients in the *Southern Medical Journal* report had received the lower concentration of sorbitol.

So which patients are at risk of developing this potentially life-threatening complication, and at which concentration? "I think it's safe to say that we just don't really know for sure," said Sterns.

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Kidney News

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High Hopes

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only in combination with diet, exercise, and other diabetes medicines. The Novo Nordisk drug was not approved as a first-line treatment because of "safety concerns"; the FDA described clinical trial data suggesting that the drug may be associated with pancreatitis. Laboratory animal data indicated that rare type medullary thyroid cancer may be associated with liraglutide. In addition to requiring additional studies to better understand the risks associated with liraglutide, the FDA called for a Risk Evaluation and Mitigation Strategy to include a patient medication guide and a communication plan.

Novo Nordisk's phase III clinical trials evaluated liraglutide as monotherapy and in combination with commonly prescribed treatments. According to the company, liraglutide achieved better or equivalent lowering of blood glucose than drugs such as sulphonylureas and thiazolidinediones. Weight gain was not associated with liraglutide use.

GLP-1 analogues stimulate the release of insulin from the pancreatic beta cells only when blood sugar levels are high. Byetta, marketed by Amylin and GlaxoSmithKline, is a member of this family of diabetes medications that requires twice-daily dosing. A longer-acting form of Byetta is under FDA review, with a decision expected later this year.

Dapagliflozin: potential first in class SGLT2 inhibitor

In the pipeline is another type 2 diabetes drug, Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor that targets an insulin-independent pathway. Inhibiting SGLT2 forces the kidneys to put glucose into urine, where it is excreted, thereby lowering blood glucose. If given the green light by FDA, Dapagliflozin will be first in class SGLT2 inhibitor for the treatment of diabetes. AstraZeneca and Bristol-Myers Squibb reportedly are on track to seek the agency's approval to market the drug.

According to BioCentury, Dapagliflozin is not the only SGLT2 inhibitor in the pipeline for type 2 diabetes therapy. Dapagliflozin, however, is the first SGLT2 inhibitor to reach clinical testing, and is the first for which phase III data have been publicly reported. At the European Association for the Study of Diabetes (EASD) annual meeting last October, scientists said that the drug produced early and substantial reductions in blood glucose and body weight when added to metformin therapy. After 24 weeks of treatment, glycated hemoglobin levels declined 0.7 percent to 0.8 percent with dapagliflozin. In the placebo group, the decline was 0.3 percent ($p < 0.05$).

According to *MedPage Today*, Hannele Yki-Jarvinen, MD, of the University of Helsinki in Finland, who co-chaired the EASD session at which the phase III data were presented, commented that Dapagliflozin "looks wonderful, glucose goes down, blood pressure goes down." But, she added, "I wonder if this degree of decrease in glucose levels actually improves insulin action and insulin secretion. Those are the type of things we would like to influence with the drug."

Also developing an SGLT2 inhibitor is Lexicon Pharmaceuticals, Inc., which has completed phase II studies of its compound, LX4211. According to BioCentury, Lexicon's phase II data included the unexpected benefit of reducing triglycerides.

"The impact on triglycerides suggests there is more going on here than just the effects from glucose excretion in the urine," said Lexicon's Brian Zambrowicz.

Anti-inflammatory for chronic kidney disease

By the second quarter of 2010, the results of a phase IIb clinical trial of a synthetic triterpenoid for the treatment of chronic kidney disease in patients with type II diabetes may be available. The results will determine whether bardoxolone, an anti-inflammatory drug, will proceed to phase III. In two previous phase II trials, bardoxolone significantly improved kidney function in type 2 diabetic patients with advanced chronic kidney disease (CKD), according to the drug's developer, Reata Pharmaceuticals, Inc.

Bardoxolone inhibits the transcriptional activity of NF-kappa B (NF-kB) and signal transducer and activator of transcription 3 (STAT3). It activates the Nrf2 gene, which controls the production of over 250 antioxidant and detoxification proteins. Activation of Nrf2 protects tissues by increasing cellular antioxidant content and suppressing the inflammatory signaling pathways that play a role in promoting type 2 diabetes and its complications, including CKD.

In 90 percent of patients in the previous phase II studies, the estimated glomerular filtration rate increased from baseline. According to Reata, significant improvements also occurred in other markers of renal function, glycemic control, and cardiovascular disease. The observed increases in GFR suggest that bardoxolone may be able to delay or prevent the initiation of dialysis in diabetic patients.

In a *FierceBiotech* article about Bardoxolone, Reata CEO Warren Huff is quoted as saying, "The regulatory agencies recently gave us feedback that they would take IIb as pivotal, particularly if GFR was improved from baseline." According to the article, Reata soon will launch a confirmatory phase III trial, putting Bardoxolone on track for FDA review in 2011.

New Questions

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"We need to be more rigorous in looking for this complication."

Amid safety concerns, efficacy still unknown

Meanwhile, there are still no convincing data to answer the most pressing question: Does Kayexalate lower high potassium levels? When they started their review, Sterns and colleagues knew that Kayexalate was a grandfathered product that hadn't been subjected to the rigorous efficacy evaluations required for today's new drugs. "But what I had not realized was that there's no evidence this preparation increases fecal potassium losses—even in animals," said Sterns. "And in humans, there are no controlled data."

Emmett's group has performed research showing no change in serum potassium levels in end stage renal disease patients with normokalemia or mild hyperkalemia receiving SPS alone or SPS plus sorbitol. "This really casts doubt that Kayexalate was doing very much at all," according to Sterns.

Another review (*Nephrol Dial Transplant* 2003; 2215–2218) has questioned the theoretical basis of Kayexalate's potassium-lowering effect. "Based on in vitro binding characteristics of Kayexalate, the only favorable location for this exchange of Na+ for K+ in the gastrointestinal tract is in the colon," according to Kamel Kamel, MD, of the University of Toronto. However, the amount of K+ that is delivered to the colon is small: about 5 mmol/day.

"In humans, active secretion of potassium in the gastrointestinal tract occurs in the recto-sigmoid portion of the colon," said Kamel. "One possible theoretical benefit to the use of cation-exchange resins is that, if they were to lower the potassium concentration in luminal fecal water, the net secretion of potassium by the colon would be enhanced." However, Kamel pointed out that several other cations are available in the colon to exchange for resin-bound sodium.

"Even if patients with ESRD had an adaptive increase in colonic potassium secretion, and if resins were effective in lowering the potassium concentration in fecal water and hence stimulate this process, stool volume would be limiting," Kamel added. "There are data to show that the addition of resins does not significantly enhance the excretion of potassium beyond the effect of diarrhea induced by osmotic or secretory cathartics."

Research needed—but other options available

Despite the lack of data, Kayexalate continues to be prescribed and administered. "We've looked at our local practice patterns, and I don't think they're unique," said Sterns. "The administration of Kayexalate has become a pretty monosynaptic reflex to the finding of hyperkalemia—even in patients who have only mild renal impairment and would be better managed with just diuretic and by stopping potassium-sparing agents."

Emmett agrees that giving Kayexalate is still a reflex for many physicians. "You see a potassium level that's very high, and you generally throw the whole kitchen sink at the patient … three or four different things, one of which is Kayexalate. And then the potassium comes down, and nobody knows exactly which of these various therapies was most important in achieving that result."

"The risk to a single patient is unlikely to be very high," according to Sterns. "But because of the large number of Kayexalate doses given every year, I think we're exposing an awful lot of people to potential risk." Sterns and colleagues recommend that physicians "exhaust other alternatives" for treatment of hyperkalemia before turning to ion exchange resins.

Emmett noted that there are other good options for the acute treatment of hyperkalemia, including intravenous insulin and glucose, inhaled beta-2 agonists, and even sodium bicarbonate—"which may or may not be very effective but is probably safe," according to Emmett. "Diuretics are also useful, if the patient has reasonable kidney function. If kidney function is very poor, then dialysis is the most effective way to reduce the potassium concentration urgently."

A randomized trial would be needed to demonstrate the safety and efficacy of Kayexalate, and SPS plus sorbitol, in the treatment of hyperkalemia—although it is unclear who would perform such a study. "A good start might be a study in experimental animals, which has never been done," said Sterns. "And of course, a controlled trial to show increased fecal excretion."

Given the other effective options, Emmett questions whether the issue of Kayexalate effectiveness is really all that pressing. Of the various options for acutely lowering potassium, "Kayexalate is clearly the least powerful," he said. "I don't think patients would be harmed or physicians would be very upset if a recommendation came out that it should not be a component of the treatment regimen to acutely reduce plasma potassium levels."

Kayexalate Timeline

- Late 1940s to early 1950s: Initial studies of medical applications of synthetic cation-exchange resins.
- 1958: Kayexalate approved for treatment of hyperkalemia under the FD&C Act.
- 1961: Study by Scherr et al in 30 patients—still the largest published experience with Kayexalate. Recommendations to give Kayexalate with sorbitol because of potential for severe constipation.
- 1962: Kefauver-Harris Amendments passed; Kayexalate receives "grandfathered" drug designation.
- 1982: Premade preparation of Kayexalate plus sorbitol approved for commercial distribution—still the most widely used preparation.
- 2005: Reports of serious bowel injuries associated with Kayexalate plus sorbitol. FDA recommendation for administration with sorbitol removed.
- 2009: FDA issues warning against giving Kayexalate with sorbitol. Premixed product (containing 33% sorbitol) remains on market.

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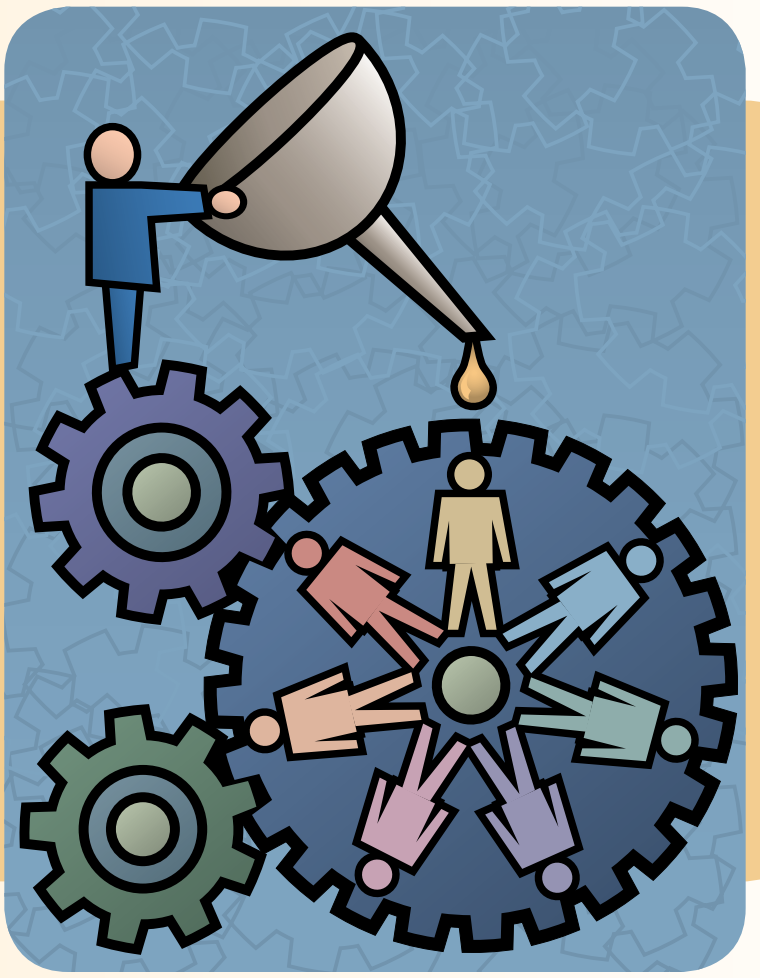
Diabetic Nephropathy

The impact of diabetic kidney disease on the health of the U.S. population is staggering. More than 23 million Americans have diabetes, which is the leading cause of chronic kidney disease and end stage renal disease in this country.

In this issue, we review our current understanding of the physiologic, epidemiologic, and genetic factors that influence the pathogenesis and susceptibility to the early stages of tissue injury related to diabetes. Also discussed are the goals of conservative therapy in patients with established diabetic kidney disease and a review of the principles related to dialysis modality selection for those with advanced disease requiring renal replacement therapy. Finally, we review the issues and challenges of managing new-onset diabetes after kidney transplantation and other solid organ transplant groups of patients.

Ira Davis, MD, is medical director, global clinical affairs, Baxter Healthcare Corp. Renal Division in McGaw Park, IL.



Does dialysis modality matter in diabetic patients with end stage renal disease?

By Anjali Bhatt Saxena and Rajnish Mehrotra

By the end of 2007, over 500,000 Americans were afflicted with end stage renal disease (ESRD), and almost 368,000 patients were undergoing dialysis therapy. Diabetes remains the most common cause of ESRD and accounts for over one-half of all new dialysis patients in the United States. Diabetic dialysis patients have poorer outcomes in general compared to nondiabetics. As a result, clinicians and researchers alike are searching for ways to improve outcomes of these patients.

The basic question of whether dialysis modality *per se* affects the survival of ESRD patients has been debated since the introduction of peritoneal dialysis (PD) for the treatment of ESRD. This issue is particularly important for diabetics because several observational studies have shown a higher risk for death among older diabetic patients treated with PD. Indeed, based on the results of some observational studies, some have questioned whether it is ethical to offer PD as an option for older diabetics.

There are many theoretical advantages and disadvantages to both hemodialysis (HD) and PD (Table 1). Special consideration should be given to diabetics with ESRD since these patients have more severe vascular disease and a higher risk for infection than their nondiabetic counterparts. For diabetics with ESRD, PD may provide certain advantages over HD (Table 2). On the other hand, valid concerns about the adverse effects of glucose-based peritoneal dialysis solutions, including the risks of weight gain and worsened hyperglycemia, may limit PD utilization in diabetics.

Many researchers have sought to answer the question of which dialysis modality is superior. A randomized controlled trial (RCT) would most reliably examine whether any differences in outcomes of patients treated with HD or PD are attributable to the dialysis modality *per se*, but the existing body of literature is unfortunately lacking in RCTs. The Netherlands Cooperative Study of Dialysis (NECOSAD) is the most recent attempt to perform such an RCT. In this study, 735 of 773 eligible patients refused to be randomized to either HD or PD, thus leaving a study group of only 38 patients—far too few from which to make meaningful conclusions. In the absence of RCTs, data examining the effects of dialysis modality are limited to those originating from either observational or prospective cohort studies.

The observational studies examining survival differences between HD and PD patients over the past two decades are heterogeneous in design but manifest a common theme: PD provides an early survival advantage that varies in magnitude and duration depending on patients' age, diabetic status, and presence of co-morbidities. Interestingly, during the same period of time, eight prospective cohort studies have been published on this topic, five of which report no difference in survival outcomes between the two modalities. Specifically with regard to diabetics with ESRD, most studies suggest that younger

Table 1. Potential advantages and disadvantages of in-center hemodialysis and peritoneal dialysis

In-center hemodialysis	Peritoneal dialysis
Advantages	
Effective removal of waste products	Schedule flexibility, easier to travel
Care given by trained professionals	Few risks of dialysis-associated cramps
Regular contact with other patients	Clinic visits limited to 1–2x a month
Rapid correction of electrolyte imbalances	Patient and/or family involved in care
No equipment to store at home	No need for needles or vascular access
Treatment usually occurs only three times a week	Steady state therapy, gentler ultrafiltration
Disadvantages	
Vascular access surgery required	Permanent external catheter; "body-image" problems
Use of large needles	No "off" days
Schedule inflexibility	Risk of peritonitis
Must travel to center three times a week	Risk of weight gain from glucose in dialysate
Cramping with ultrafiltration	Must store dialysis equipment and supplies at home
Risk of bacteremia (with tunneled catheter)	Need for self-monitoring of care

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Dialysis modality

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Table 2

Potential benefits of peritoneal dialysis in diabetics who suffer from more severe vascular disease

- Gentler and more gradual ultrafiltration, greater hemodynamic stability
- Vascular surgeries not required for dialysis access
- Better preservation of residual kidney function
- Minimal rapid shifts in electrolytes (potassium, calcium)

diabetics with no additional co-morbidity have a survival advantage while older diabetics with additional co-morbidity have a survival disadvantage when treated with PD. In other subgroups of diabetics, there appears to be no difference in outcomes between patients treated with either of the two dialysis modalities. In these studies, however, the reported statistical differences in hazard ratios translates into small differences in more clinically relevant measures such as life expectancy of patients treated with HD or PD.

It must also be mentioned that most published studies examining the effect of dialysis modality on survival have drawn their cohorts from patients incident before the year 2000. These older cohorts lacked the benefits of more recent advances in PD such as improvements in connectology, catheter exit-site antibiotic prophylaxis protocols to reduce infection risk, and increased awareness of the importance of solute clearances and careful volume management. All of these PD advances have probably contributed to improvements in PD outcomes, but their benefit has not been well captured in the literature.

A comparison of patient and technique survival in incident HD and PD from 1996 to 2003 has shown that the outcome of incident PD patients progressively improved whereas that of HD patients remained unchanged during the same time period. These improvement trends have continued over the past five years, and a more recent analysis of patients starting dialysis in 2002–04 in the United States shows no significant differences in outcomes between modalities, even among older diabetics treated with either HD or PD.

What can we learn from this varied literature? One must first remember that observational studies, although having the advantage of large patient numbers and therefore excellent statistical power, depend on information gathered from previously existing patient databases that contain limited details about the clinical condition of individual patients. This limitation makes it difficult to know whether reported differences in these studies are truly an effect of dialysis modality or whether they result from unaccounted differences between the patient groups (HD and PD). Such observational studies are also subject to inaccuracies as a result of nonrandom allocation of patients into two dialysis groups and in most parts of the world, do not necessarily reflect patient choice. Thus, despite the use of advanced statistical analyses, one has to be careful in attributing any differences in outcomes of patients treated with different therapies to the dialysis modality itself.

Given the lack of strong and conclusive data favoring one dialysis modality over another plus the differential changes in outcomes of patients treated with HD and PD over time in the United States, it appears reasonable that neither dialysis modality should be automatically excluded for any diabetic patient with advanced CKD; rather, careful evaluation of medical factors are likely best addressed on an individual level.

The diabetic patient who ultimately starts HD should take care to limit interdialytic fluid gains and rapid electrolyte shifts, and venous dialysis catheters should be avoided as far as possible. A diabetic starting PD should be prescribed a regimen that minimizes the use of hypertonic glucose-based solutions. Perhaps more importantly, patient preference should play a major role in the decision-making process, but it necessarily requires dialysis education to be provided in a timely and complete manner. Ultimately, the life-saving benefits of dialysis are of no use if the patient is miserable for lack of being given a choice in their dialysis lifestyle.

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Disclosures: Rajnish Mehrotra has received research grant support, served as an ad hoc consultant, and received honoraria from Baxter Health Care. Anjali Saxena has served as an ad hoc consultant to Baxter Health Care.

Goals of Therapy for Patients with Diabetic Nephropathy

By Jamie P. Dwyer

Many therapies exist to treat diabetic kidney disease (DKD). Some have been proven to delay the progression of chronic kidney disease (CKD), while others have not been rigorously tested in a controlled way. This article summarizes the major clinical findings that direct DKD treatment and outlines the progress of ongoing trials whose results will direct care.

Glycemic control

Intensive glycemic control reduces albuminuria in type 1 diabetes. The Diabetes Complications and Control Trial (DCCT) randomized 1441 type 1 diabetics (age 13–39) without cardiovascular (CV) disease and with normal kidney function to intensive (A1c < 6.05) versus conventional (A1c ~9.0) glycemic control. Only 73 individuals had microalbuminuria at the start of the study.

Participants were followed for a mean of 6.5 years. Intensive glycemic control reduced the occurrence of microalbuminuria by 39 percent and overt proteinuria by 54 percent. There were nearly three times as many severe hypoglycemic episodes in the intensive control arm as in the conventional arm. There was no reduction in CV events in the DCCT (probably a result of the cohort's youth), but these same subjects were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. EDIC showed a 42 percent reduction in any CV event 10 years after both groups had similar glycemic control (implying that the CV effect of intensive glycemic control persisted after control was loosened).

In type 2 diabetes, however, the results are not as clear. An early study (the University Group Diabetes Program [UGDP]) tested the efficacy of tolbutamide, insulin, phenformin, or placebo, and showed no renal, microvascular, or CV benefit, with increased CV death in the tolbutamide arm. The much larger UK Prospective Diabetes Study (UKPDS) tested sulphonylurea or insulin versus dietary control, and showed no renal benefit, a 25 percent microvascular benefit, and no CV effect, although some subgroups showed a possible effect at 10 years. Three large trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], and the VA Diabetes Trial [VADT]) (Table 1) have collectively studied nearly 23,000 individuals. CV effects ranged from no benefit to increased risk, and there was variable renal benefit and a significant proportion of hypoglycemia in the intensive groups.

Evidence supports intensive glucose control as renoprotective therapy in type 1 diabetes. The therapy may also benefit patients with type 2 diabetes who are early in the course of disease, who can achieve glycemic control easily, and who are less prone to hypoglycemia. Current evidence does not support extremely aggressive control of hyperglycemia in all patients with type 2 diabetes.

Single-agent inhibition of the renin-angiotensin system (RAS)

Treatment of type 1 diabetic nephropathy with angiotensin converting enzyme inhibitors (ACE-I) clearly protects against deterioration in renal function. Captopril 25 mg TID was shown to reduce the composite outcome of death, dialysis, or kidney transplantation by 50 percent (relative risk reduction [RRR]; absolute risk reduction [ARR] 9.7 percent, number needed-to-treat [NNT] 10 subjects, for four years). This trial included 409 patients with baseline urinary protein excretion ≥ 500 mg/day and serum creatinine (SCr) ≤ 2.5 mg/dL.

Treatment of patients with type 2 diabetes and early nephropathy (in this case, microalbuminuria) with the angiotensin receptor blocker (ARB) irbesartan has been shown to prevent progression to overt proteinuria. Irbesartan 300 mg daily versus placebo reduced the onset of overt

Table 1. Intensive glucose control in type 2 diabetes, showing no compelling benefit

	ACCORD	ADVANCE	VADT
Population	*n* = 10,251 with CV event or risk	*n* = 11,140 with CV event or risk factor	*n* = 1791 with poor BP control
Age (y, mean)	62	66	60
DM duration (y)	10	8	11.5
On insulin at baseline (%)	39 / 8.1%	1.5 / 7.2%	54 / 9.4%
Hemoglobin A1c, baseline	8.1%	7.2%	9.4%
A1c target (%)	<6.0% vs. 7–7.9%	<6.5% vs. routine care (achieved 6.3% vs. 7.0%)	6.9% vs. 8.4% (1.5% difference)
Primary outcome	Increased total and CV mortality in intensive group	No benefit on CV outcomes, reduction in microvascular events	No benefit
Renal outcome	No benefit	Albuminuria reduced 21%	No benefit
Hypoglycemia (%)	16.2	2.7	21.2

proteinuria by 65.1 percent (RRR), with ARR 9.7 percent (NNT 10 subjects, for 2 years). Irbesartan 150 mg was not statistically significantly different from placebo (in other words, dose mattered).

The treatment of patients with overt proteinuria with irbesartan or losartan has been shown to reduce the composite outcome of doubling of SCr, end stage renal disease, or death, in two large prospective clinical trials (Irbesartan Diabetic Nephropathy Trial [IDNT] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL] study) (Table 2).

Evidence from multiple clinical trials demonstrates that in patients with type 1 or type 2 diabetes and early or late nephropathy, treatment with drugs that inhibit the RAS clearly improves renal outcomes.

Lipid lowering

Multiple small clinical studies have addressed the question of whether improving lipids can delay the progression of kidney disease. No large prospective trials have been done to test this hypothesis adequately. The best available evidence is a meta-analysis that showed that lipid lowering reduced renal outcomes in patients with kidney disease. The effect of these medications, however, may be independent of their lipid-lowering effects.

Blood pressure (BP) control

Despite current guidelines (which urge a BP goal < 130/80 mm Hg for patients with CKD), there are no well-powered, randomized trials that demonstrate in their primary analyses a benefit to this level of BP control. The lack of such trials is dire in the case of DKD, because the results of the study that form the basis of the guidelines (the Modification of Diet in Renal Disease [MDRD] study) enrolled only 25 subjects with diabetes (essentially, excluding them).

No one doubts that an extremely high blood pressure can cause rapid loss of kidney function in DKD. Early studies showed improvement in loss of GFR with lowering BP. In addition, many observational studies or trials in which achieved BP is reported have demonstrated a continuous benefit of lowering BP (e.g,. the Heart Outcomes Prevention Evaluation [HOPE] trial). IDNT—albeit not designed for this specific outcome—showed a decreasing CV risk with achieved systolic blood pressure (SBP) (from > 180 to 120), but those individuals who achieved SBP < 120 had *increased* CV risk, on par with those who achieved SBP > 180. In other words, more may be less with respect to BP control in DKD.

Pending the results of ongoing clinical trials, including the BP study of ACCORD, current recommendations are to target BP < 130/80 in patients with DKD. This goal must be individualized, however. Results in nondiabetic adults or children are difficult to generalize to adults with diabetes.

Lifestyle modifications

Smoking cessation, weight control, and increased physical activity should be encouraged. It is known that smoking and obesity increase the rate at which kidney disease progresses. For all the other reasons we tell our patients to stop smoking, perhaps "It may keep you from going on dialysis" will be the motivator to get them to quit.

Combination therapies

Multiple small and potentially underpowered studies using surrogate outcomes (e.g., proteinuria) have inconsistent results, but generally support improvement with ACE-I + ARB, or suprapharmacologic doses of ACE-I or ARB in diabetic nephropathy. Only a few trials have addressed the question of what combinations of inhibitors of the RAS are successful at preventing outcomes. The results of the Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in nondiabetic renal disease (COOPERATE) trial have been called into question and an official retraction has been published; it is therefore excluded from discussion.

The Aliskiren in the eValuation Of proteinuria In Diabetes (AVOID) trial studied the effect on proteinuria of adding aliskiren or placebo to losartan in type 2 diabetic nephropathy: 599 subjects with type 2 diabetes, hypertension, urinary albumin:creatinine ratio 0.3–3.5 g/g (0.2–3.5 g/g if taking agents that blocked the RAS), and estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2 were studied. Aliskiren reduced proteinuria at 24 weeks, but the trial was not long enough to assess the effect of aliskirin on the progression of CKD or CV events. Patients treated with combination therapy developed hyperkalemia (K ≥ 6.0 mEq/L) more often (4.7 percent versus 1.7 percent).

The ONgoing Telmisartan Alone and in combination with Ramipril Global EndpoinT (ONTARGET) trial studied 25,260 patients with ramipril, telmisartan, or both, for the effect on the composite primary (CV) outcome, namely death from a CV cause, myocardial infarction, stroke, or hospitalization for heart failure. There was no difference in the primary outcome among the three arms. The renal substudy showed less worsening of proteinuria with combination therapy, but GFR decreased more in the combination arm compared to the single-agent arms (by about 2 mL/min/1.73 m^2). Additionally, there was a significant increase in the renal endpoint (dialysis, doubling of SCr, or death) in the combination arm compared to single-agent arms. The biggest contributor to this endpoint was the need for acute dialysis (28 cases in combination, 13 and 20 in the single-agent arms).

It may be that the risk-benefit profile for certain combinations of RAS blockade does not apply to all combinations. Many combinations are limited by hyperkalemia, which is more problematic in the "real world" than in a clinical trial.

Future studies

Several ongoing studies may address current uncertainties in the management of diabetic nephropathy. The Department of Veterans' Affairs NEPHROpathy iN Diabetes (VA NEPHRON-D) Study is testing whether the combination of the ACE-I lisinopril and ARB losartan is superior to losartan alone to delay the progression of CKD. Approximately 1900 patients will be recruited until 2013.

The ALiskiren Trial In Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) Study is testing whether dual RAS blockade with aliskiren and an ACE-I or ARB reduces CV and renal morbidity and mortality. It aims to recruit 8600 patients followed for four years.

Finally, the BP companion study to ACCORD will help elucidate the target BP for diabetic nephropathy caused by type 2 diabetes.

Conclusions

The cornerstone of the treatment of diabetic nephropathy is delaying the progression of CKD. Control of hyperglycemia and blood pressure, and use of RAS blockade are accepted therapies. Combination therapies and very strict BP control are not, as yet, entirely proven, but ongoing trials will address the limitations of currently completed studies.

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Table 2. Landmark "single-agent" clinical trials in type 2 diabetic nephropathy with overt proteinuria

	IDNT	RENAAL
Population	*n* = 1715, with hypertention and urinary protein excretion ≥0.9g/d	*n* = 1513, with urinary protein excretion ≥ 0.5g/d
Age, years (mean [range])	58.9 (30–70)	60.0 (31–70)
Urinary albumin excretion (g/d, median)	1.9	1.2
SCr (mean, mg/dL)	1.7	1.9
Hemoglobin A1c, baseline	8.2%	8.4%
Primary outcome (RRR*, %)	20 (irbesartan vs. control)	16 (losartan vs. control)
Doubling of Scr (RRR, %)	25	33
ESRD (RRR, %)	28	23

*RRR: relative risk reduction.

Genetics of Diabetic Nephropathy

By John R. Sedor

Are common causes of progressive kidney disease regulated by genes?

Many common diseases, including nephropathy, cluster in families, and genetic variants seem likely to regulate disease pathogenesis (1). Until recently, convincing evidence that common disease genes exist has been lacking. Much of the difficulty in identifying genes for common diseases, such as diabetic nephropathy, sporadic FSGS, and nephrosclerosis, arises from the genetic architecture responsible for common diseases, which differs from that of Mendelian disorders.

Most of us learned about Mendel and his peas in medical school. The success of gene mapping for Mendelian disorders, such as polycystic kidney disease, is common knowledge to nephrologists and other physicians. Mendelian traits have a simple correspondence between the gene and the disease phenotype, and mapping strategies have been highly successful in identifying genetic causes of disease with understandable patterns of inheritance.

In contrast, complex traits, like chronic kidney disease, do not have recognizable inheritance patterns, a finding that has made gene mapping more difficult. The frequency of the causal variant in the population and the size of its contribution to the disease phenotypes (the effect size) determine optimal gene mapping strategies (Figure 1). Investigators exploring genetic causes of common diseases still have not reached consensus on the underlying genetic architecture for these disorders.

Two models are dominant. The "common disease, common variant" hypothesis proposes that common diseases are caused by genetic variations having a frequency greater than 5 percent in the population. The functional effects of these variants impair but do not prevent protein function. An illustrative analogy would be that these common variants cause a light bulb to dim, but not go out. Case-control mapping strategies should be successful in identifying causal variants if this hypothesis is correct.

The competing hypothesis is that common diseases are caused by rare variants with moderate effect sizes that generate dysfunctional proteins with little or no wild type function. In this model, common diseases would be caused by a multitude of rare variants in multiple genes. Current mapping strategies are unlikely to identify these gene variants but new technologies—such as exon and whole genome sequencing—seem likely to identify causal rare variants. These two hypotheses are not mutually exclusive. Age-related macular degeneration has been associated with a common variant that causes an amino acid substitution in a complement regulatory protein. In contrast, rare genetic variants have been found to regulate blood pressure and dyslipidemia phenotypes.

Genes and diabetic nephropathy

Over the past decade, many studies have reported association of variants in biologically plausible candidate genes for diabetic nephropathy using case-control analytic strategies. However, few of these candidate gene associations have been replicated owing to study population heterogeneity, small sample sizes, inconsistent phenotype criteria between studies, and incomplete knowledge of disease pathophysiology.

In addition to candidate gene association studies, families with diabetic nephropathy have been collected for linkage analysis in both the United States and Europe (1). In contrast to focus on specific genes, linkage analysis is unbiased; no specific gene is hypothesized to be causal. Consistent linkage signals across studies, composed of African American, American Indian, and European populations, have been identified on chromosomes 3q, 7p, 10p, and 18q (1,2).

Further mapping of the 18q regions subsequently identified carnosinase 1, a gene that encodes an enzyme whose substrate inhibits ACE activity and advanced glycation end product formation, as a diabetic nephropathy susceptibility gene. Variants within the engulfment and motility 1 (*ELMO1*) gene, whose protein regulates cell migration and matrix and TGFβ expression, have been associated with diabetic nephropathy phenotypes and are located within the linkage signal on 7p. The linkage signal on 3q has been attributed to variants with adiponectin (*ADIPOQ*), which encodes an adipose-tissue-derived protein with anti-diabetic, anti-atherogenic and anti-inflammatory functions, and *NCK1* (3), a gene that encodes an adapter protein NCK1 that links actin and nephrin in podocyte foot processes.

More recently, genewide association analysis (GWA), another unbiased strategy. has been applied to gene mapping for common disease. This approach uses a group of patients with disease and controls numbering in the thousands and takes advantage of the technical advances in genotyping platforms, which incorporate genetic variants from the International HapMap Project, an atlas of common genetic similarities and differences in human beings of differing ancestries. These studies have reproducibly identified common variants with highly statistically significant associations with common disease phenotypes, although the underlying biology responsible for the association can be obscure.

The first GWA data for diabetic nephropathy have now been reported by the Genetics of Kidneys in Diabetes (GoKinD) consortium, which included over 800 patients with Type 1 diabetic nephropathy as cases and 800 diabetic patients without nephropathy as controls (4). In this study, the most significant associations were within noncoding regions or close to the genes *CHN2* (encodes chimerin 2 located on chromosome 7p, a region identified in linkage analyses, noted above, *FRMD3* (encodes a FERM domain-containing protein), and *CARS* (encodes cysteinyl-tRNA synthetase). An intergenic region on chromosome 13q was also associated with diabetic nephropathy.

The GOKinD results highlight a strength of the GWA approach: the results point to novel pathways not previously considered as causal for diabetic nephropathy. Although the biology responsible for the association of these genes with diabetic nephropathy has yet to be discovered, these results were replicated in a prospective cohort from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Results from ongoing association studies from the Family Investigation of Diabetes and Nephropathy (FIND) and Finnish Diabetic Nephropathy Study consortia should be available soon.

Genes and other causes of chronic kidney diseases

Using ancestry mapping, two consortia—the U.S. National Institutes of Health (NIH) FSGS Genetic Study and FIND—reported that common variants in *MYH9*, a gene that encodes a ubiquitous intracellular motor protein, myosin 2a, are associated with nondiabetic but not diabetic nephropathy in African American patients (5). The NIH patient sample included individuals with idiopathic or HIV-1-associated FSGS; the FIND group included African American nondiabetic ESRD patients. Much of the excess risk for kidney disease in African American patients can be explained by four genetic variants within *MYH9* noncoding regions, suggesting these common variants have large effect size (Figure 1). The findings have been replicated in multiple, independent African American populations. The mechanism(s) by which MYH9 gene variants cause nondiabetic kidney diseases in African American patients is under intense study, as are approaches to apply this finding to patient care.

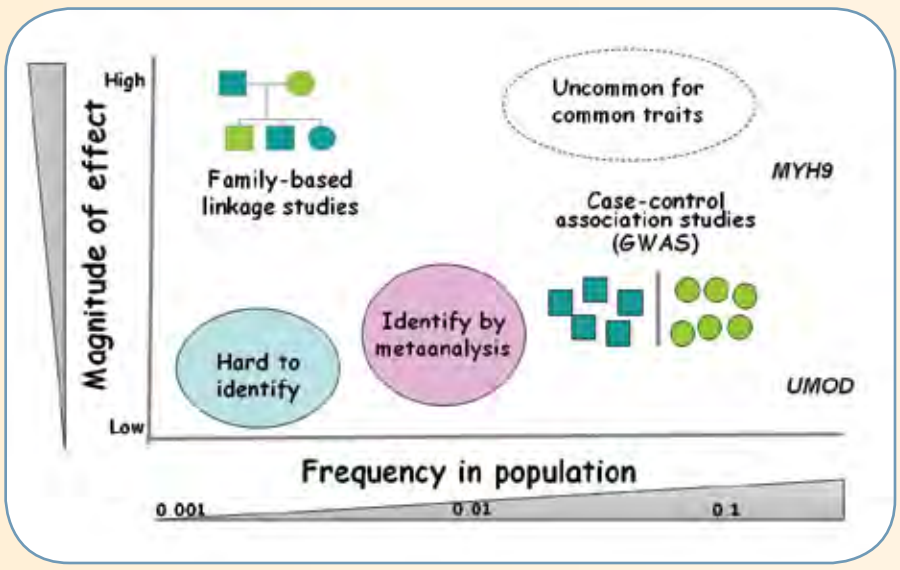
Finally, the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium reported that all-cause CKD, defined as estimated GFR less than 60 mL/min, was associated with common genetic variants in noncoding regions of the gene that encodes Tamm-Horsfall protein (THP) or uromodulin (*UMOD*) (6). Uromodulin/THP provides a protein scaffold for the urinary casts used to diagnose kidney diseases in the clinic. Patients with diabetes were included in this sample. Interestingly, UMOD mutations cause medullary cystic disease and familial hyperuricemic nephropathy, suggesting both common and rare variants with the same gene may regulate different phenotypic presentations of kidney diseases. However, in contrast to MYH9 variants, *UMOD* variants only explain a small percentage of the variability in the CKD phenotype (Figure 1). A subsequent study from CHARGE has shown urinary uromodulin levels can predict development of nephropathy.

Will studies of common kidney disease genetics impact patient management?

The last seven years have been a time of breathtaking discovery and technical advancement in human genetics: The human genome sequence was reported in 2003. The atlas of common genetic variation in individuals of different ancestries—the Hap Map—was completed in 2005. The 1000 genomes project, which will expand our understanding of the range of human genetic variation, is about to publically release its first data set.

The kidney community is actively applying the most advanced gene mapping strategies to understand the underlying

Figure 1. Relationship between the frequency of a genetic variant in the population, its effect size, and gene mapping strategy



The variants with the *MYH9* gene, which have been associated with kidney diseases in nondiabetic African American patients, may be an example of common variants that explain a significant amount of the excess risk for kidney diseases in this population. In contrast, similar to findings for other GWA of other common diseases, *UMOD* variants, although robustly associated with all-cause CKD, only account for a small amount of heritability. (Modified from Rich, SS. Genetics of diabetes and its complications. *J Am Soc Neph* 2006; 17:353).

genetic architecture of common kidney disease, especially diabetic nephropathy. Understandably, both nephrologists and kidney disease patients are hopeful these findings will lead to new therapies and tests that identify individuals at risk for kidney disease progression.

Although novel pathways that potentially regulate the pathogenesis of diabetic nephropathy and other chronic kidney diseases are being identified, much work needs to be done. The common variants associated with most common diseases including kidney disease only explain a small percentage of overall risk. We need to understand the mechanisms responsible for the missing heritability. Although genetic tests are marketed directly to consumers, studies of their clinical validity and utility, which are required of all other laboratory tests, must to be established. Of equal importance, we must understand how our patients will respond to genetic risk information for kidney diseases. Despite these issues, I am confident that studies of genetic causes of kidney and other common chronic diseases will positively impact personal and public health and help stem the worldwide epidemic of chronic diseases (7).

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The Risk of Posttransplant Diabetes Mellitus in Renal Transplant Recipients

By James T. Lane

New-onset diabetes after transplantation (NODAT) affects up to 50 percent of nondiabetic patients post-kidney transplant depending on the type of study (retrospective versus prospective), the patient population, frequency of sampling, posttransplantation complications, the immunosuppression regimen, duration of follow-up, and diagnostic criteria. The 2003 International Consensus Guidelines (1) unified the diagnosis and brought NODAT in line with the more commonly used American Diabetes Association (ADA) criteria for diabetes diagnosis, namely more than one fasting glucose ≥ 126 mg/dL. Although this brief review focuses on NODAT after kidney transplantation, this condition follows all forms of solid organ transplantation.

Pretransplant risk factors for NODAT, similar to those for type 2 diabetes, include older age, increased body mass index, positive family history of type 2 diabetes, hepatitis C infection, cytomegalovirus (CMV) infection, and genetic factors. No conclusive gender differences have been demonstrated. NODAT was also associated with TCF7L2 polymorphism, another factor shared with type 2 diabetes. Autosomal dominant polycystic kidney disease associates with insulin resistance and hyperinsulinemia, and may increase risk. Children also experience NODAT, although not at the same rate as adults.

Several posttransplant factors increase risk for NODAT including the use of certain types of drugs for immunosuppression, marked weight gain after transplant, and the inflammatory response surrounding transplant. It was hoped that movement away from glucocorticoids as a cornerstone of immunosuppression would reduce glucose intolerance; however, alternative drugs produce additional risk. Calcineurin inhibitors, including both cyclosporine and tacrolimus, are strongly associated with NODAT (2). These agents impair insulin secretion and damage pancreatic islets, increasing apoptosis of B-cells. Tacrolimus increases insulin resistance in animal studies. Sirolimus is also diabetogenic with insulin resistance as the likely cause.

NODAT produces more than long-term microvascular risks; it also increases cardiovascular death and decreases graft survival (3). Cardiovascular risk is not related to degree of hyperglycemia; even mild levels of hyperglycemia increase risk above and beyond what is seen with chronic kidney disease alone.

Given the need for renal replacement therapy, but sobered by the risk of NODAT to patient and graft survival, how should we proceed? Patients first need to know about NODAT. Very often patients anticipate the benefits of renal transplantation without considering the risks and are not necessarily willing to think about negative outcomes. Patients appropriately informed about NODAT may be able to minimize weight gain following the transplant through appropriate counseling. A thorough history can identify the mentioned risk factors for NODAT. An oral glucose tolerance test prior to transplant will identify patients with preexisting impaired glucose tolerance. There should be an ongoing strategy to monitor glucose, especially the fasting glucose, posttransplant. Monitoring one to two times per week is not unreasonable. Elevated glucose levels early in the posttransplant period predict NODAT later on. In our patient population, NODAT peaked at three months after kidney transplant; monitoring has to be in place to address this time course. When NODAT is diagnosed, early referral to a diabetes educator for counseling and glucose monitoring is essential.

Patients with the highest risk of NODAT may warrant immunosuppressive regimens with less diabetogenic potential while weighing the risk of acute rejection. Antibody induction therapy, an area of interest at our center, may allow for lower levels of diabetogenic immunosuppressive drugs and less inflammation at the time of transplantation (4).

A recent retrospective study investigated NODAT, type of immunosuppression, and observed hypomagnesemia in renal transplant recipients (5). Hypomagnesemia occurs in the immediate posttransplant period in association with calcineurin-inhibitor therapy and was an independent predictor of NODAT. It is not known whether more aggressive magnesium replacement may prevent NODAT.

The use of HbA1c has recently been adopted by the ADA to diagnose diabetes, but its utility in the transplant population remains unclear. Pretransplant HbA1c levels may be falsely decreased related to uremia. Because it reflects hyperglycemia over several months, it is not sensitive posttransplant, especially for onset of disease within the first few months. HbA1c remains a helpful test to follow patients after three to six months.

Medical therapy for NODAT is similar to that for type 2 diabetes, with some exceptions. Unlike usual type 2 diabetes, metformin as a first-line single agent is controversial because of the risk of lactic acidosis in patients with reduced renal function or in patients at risk for rapid decline in renal function. Sulfonylureas have been used with success, but they have the potential to increase weight and cause hypoglycemia. Thiazolidinediones (TZDs) have been used with success, have less hypoglycemia potential as monotherapy than other agents, but should be used with caution in patients with congestive heart failure or in patients with increasing edema. TZDs can also cause marked weight gain. Exenatide is not an ideal drug in the post-kidney transplant patient since it may cause nausea. However, we have used DPP-IV inhibitors in patients with mild hyperglycemia with good results. Finally, many of these patients require insulin therapy. HbA1c goals recommended by the ADA should be followed. Additional cardiovascular risk factors, such as hypertension, hyperlipidemia, and obesity need to be concomitantly addressed.

Challenges remain for the prevention of NODAT and the threat it poses to patients and their transplanted organs, but we can reduce risk and ensure early diagnosis. Potential interventions undergoing prospective study may prevent NODAT. Until that time, NODAT is a formidable opponent in the quest to improve the lives of patients requiring transplantation.

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Type 1 Diabetes Mellitus:
The Relationship of Clinical and Renal Structural Changes

By Julia Steinke

Diabetic nephropathy (DN)—the progressive decline in renal function usually accompanied by proteinuria, hypertension, and declining glomerular filtration rate (GFR)—is a major complication of longstanding diabetes. After 15–25 years of diabetes, approximately 25–40 percent of patients with type 1 diabetes mellitus (T1DM) will ultimately develop signs of renal involvement. According to the USRDS database, diabetic nephropathy is the single most important cause of end stage renal disease (ESRD) in the United States, Japan, and Europe. Most importantly, much of the renal injury from diabetes occurs in clinical silence before the majority of symptoms or laboratory findings suggestive of DN become evident.

Early abnormalities such as microalbuminuria or hypertension may occur as early as seven years after onset of diabetes but typically take longer to develop. The first detectable renal structural change is an increase in glomerular basement membrane (GBM) width and is followed by an increase in the fraction of the glomerulus occupied by the mesangium, composed of mesangial matrix and cells (Table 1). GBM width has been found to be one of the earliest changes that occur in patients with T1DM, even prior to the onset of overt clinical signs of renal injury, such as microalbuminuria. GBM widening is not only the earliest and most obvious abnormal finding among renal structural parameters, but the most prevalent abnormal finding among morphometric measures regardless of duration of diabetes (Table 1). On the other hand, there is very little change in the mesangial measures for the first 10–15 years of diabetes duration with a rapid increase thereafter (Figure 1).

The expansion of the mesangium is predominantly due to accumulation of mesangial matrix with less contribution from the mesangial cells. With advanced disease, progressive renal functional loss ensues due to glomerular collapse and sclerosis, and by capillary lumen obliteration resulting from massive mesangial expansion. Interstitial fibrosis and tubular atrophy at these later stages of the disease process may also contribute to functional loss. Other renal lesions include afferent and efferent arteriolar hyalinosis and capsular drops that are virtually pathognomenic of diabetes and have been reported rather early in the disease process. The combined effects of glomerular basement membrane thickening, mesangial expansion, glomerular sclerosis, tubular atrophy, and interstitial fibrosis all contribute to eventual loss of renal function in progressive stages.

The typical clinical course of diabetic nephropathy has been described as the initial onset of microalbuminuria and hypertension with the later development of overt proteinuria and finally decline in renal function. The first clinical signs of renal injury can be expressed by changes within "normal limits" of measurable parameters. For example, subtle increases in blood pressure—within the range of normal detected by 24-hour blood pressure monitoring—often precede the development of microalbuminuria. Further blunting of the normal 10 percent decline, commonly referred to as "dipping," in nocturnal blood pressure becomes more pronounced as microalbuminuria and proteinuria develop. Blood pressure changes may develop in parallel or even precede rises in albumin excretion. Hypertension itself is a promoter of GFR decline in patients with diabetic nephropathy.

Although the prevalence of hypertension in patients with T1DM and normal albumin excretion is no different than that in the general population, it is significantly higher in T1DM patients with either microalbuminuria or overt proteinuria. Higher prevalence of elevated systolic and diastolic blood pressure has even been reported in the adolescent population with T1DM and microalbuminuria compared to age-matched normoalbuminuric patients. However, even subtle increases in nocturnal mean arterial blood pressure, detected with 24-hour ambulatory blood pressure monitoring, in normoalbuminuric T1DM patients are an important indicator of renal structural injury. The current literature certainly supports the use of renin angiotensin blockade in patients with microalbuminuria to slow progression to proteinuria, but there is a lack of support for such treatment in those without any clinical evidence for renal injury such as elevated albumin excretion.

Type 1 diabetes is associated with early and prolonged glomerular hyperfiltration, i.e., a glomerular filtration rate (GFR) above normal limits. The presence of hyperfiltration in young patients with type 1 diabetes has been reported to increase the risk of developing microalbuminuria later on, independent of glycemic control and blood pressure. However, this relationship of GFR and microalbuminuria remains controversial as reduced GFR below the lower limit of normal (<90 mL/min/1.73 m^2) has been reported to be associated with more advanced glomerular lesions despite normal urinary albumin excretion. Therefore, it appears that the reliability of GFR as an indicator of clinically detectable injury without the use of a renal biopsy to compare is debatable.

Morphometry studies have demonstrated the importance of renal biopsy data when clinicians are evaluating microalbuminuria and renal function. It appears that mesangial changes are most closely correlated with renal function. The disproportionate increase in mesangium relative to the expansion in glomerular volume is closely correlated with a decrease in the GBM filtration surface density and thereby is related to a decline in GFR. This mesangial expansion is closely related not only to diminished GFR but to the development of microalbuminuria and hypertension.

Improvement in glycemic control, measured by glycated hemoglobin (HbA1c), in as little as three years has also shown to be correlated with slowed renal injury. The beneficial results of optimal glycemic control clearly have a sustained effect in the decreased incidence of microalbuminuria as well as decreased rates of other microvascular injury, such as retinopathy and neuropathy, as shown in the Diabetes Control and Complications Trial (DCCT) and the follow-up of this study in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. The EDIC study showed that, despite a decreased difference in mean HbA1c between the two treatment groups, there was less progression in urinary albumin excretion in those who had been tightly controlled in the previous DCCT study. Based largely on the results of these studies, aggressive glycemic management has become the cornerstone of recommendations made by the American Diabetes Association.

Multiple studies have shown improved glycemic control can contribute to slowed progression of renal morphological changes. Recently, blood glucose fluctuations have been reported as being an additional factor influencing accelerated rates of renal complications related to diabetes. Emerging data suggest that complications in T1DM may be closely associated with glycemic excursions perhaps through oxidative stress and glycation changes. The influence of glucose control on structure was perhaps best demonstrated by the pivotal report of reversal of GBM width changes back to normal occurring a decade after pancreatic transplantation in T1DM patients. There appears to be no question that better glycemic control is an important element in the prevention and even the resolution of renal injury.

Type 1 diabetes mellitus remains one of the leading causes of ESRD. Patients who develop ESRD from diabetes are at higher risk of mortality and associated microvascular morbidities. There have been tremendous strides in our understanding of the progression of renal disease in type 1 diabetes mellitus as well as the risks that may impact this rate of progression, such as the profound importance of maintaining strict glycemic control. However, there are other considerations such as gender, genetics, and renal hemodynamics that clinicians should also consider when evaluating a young person with diabetes and renal structural changes. We have only begun to understand the multitude of factors that may influence the varying trajectories of renal injury.

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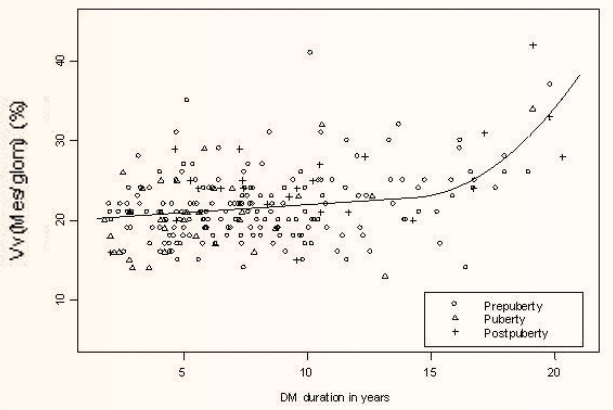
Table 1. Percentage of abnormal morphometric parameters in relation to duration of diabetes

		Duration of type 1 diabetes			
Variable	**Abnormal value***	**2–8 years**	**8–14 years**	**14–20 years**	**All durations**
n		144	74	25	243
GBM (nm)	>445	23	50	68	36
Vv(Mes/glom)	>0.25	10	16	48	16
Vv(MM/glom)	>0.11	15	31	68	25
Vv(MC/glom)	>0.13	3	3	12	4

Duration data are percent. * >95th percentile of normal, nondiabetic control subjects.

Abbreviations: GBM, glomerular basement membrane; Vv(Mes/glom, fraction of the glomerulus occupied by mesangium; Vv(MM/glom), fraction of glomerulus occupied by mesangial matrix; Vv(MC/glom), fraction of glomerulus occupied by mesangial cells [Drummond K, Mauer M. The early natural history of nephropathy in type 1 diabetes: II early renal structural changes in type 1 diabetes. *Diabetes* 2002; 51:1580–1587].

Figure 1. Mesangial fractional volume as a function of disease duration in three subgroups defined by age at onset of type 1 diabetes



Abbreviation: Vv(Mes/glom), morphometry measurement indicating the fraction of glomerulus occupied by the mesangium [Drummond K, et al. Effects of duration and age at onset of type 1 diabetes on preclinical manifestations of nephropathy. *Diabetes* 2003; 52:1818–1824].

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN News

ASN Launches Distance Learning

The American Society of Nephrology (ASN) continues to broaden its commitment to education and to the kidney professionals who help ASN lead the fight against kidney disease. ASN now offers distance learning opportunities that make it possible for nephrologists to advance their professional education anytime, anywhere.

ASN's Board Review Course & Update (BRCU) online mirrors the BRCU offered annually in San Francisco. Internationally renowned speakers lecture and participate in case presentations and panel discussions that blend physiology and pathophysiology with clinical discussions. BRCU is the primary preparatory course for the American Board of Internal Medicine's (ABIM) initial certification and maintenance of certification examinations in nephrology; each section is patterned after the ABIM nephrology examination blueprint (maximum 70 AMA PRA Category 1 credits).

On April 14, 2010, ASN launched ASN Renal WeekEnds (RWE) Online. This comprehensive overview of Renal Week 2009 presents breakthroughs in research, as well as clinical and translational medicine summarized by experts in the field. Now ASN members can access key presentations on acute kidney injury, kidney transplantation, hypertension, end stage renal disease, glomerular disorders, and clinical nephrology from the office, at home, or while traveling (maximum 9.5 AMA PRA Category1 credits).

These new offerings are just the beginning. ASN will expand its distance learning education programs and offer opportunities for members to update their professional skills at their convenience and pace. Check the ASN website for announcements about new distance learning programs. To access all ASN's distance learning opportunities, visit the ASN website at http://www.asn-online.org/education_and_meetings/distance-learning/

Policy Update

ASN Presents Remarks at Key CMS Meeting on ESA Usage

ASN was among a small group of invited presenters at the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting to review available evidence on use of erythropoieis-stimulating agents (ESAs) to manage anemia in patients with chronic kidney disease (CKD). MEDCAC provides independent guidance and expert advice to CMS on specific clinical topics.

Presenting on behalf of ASN, Wolfgang Winkelmayer, MD, ScD, FASN, delivered remarks at Centers for Medicare and Medicaid Services (CMS) headquarters in Baltimore last month.

"We derive from the available evidence that current ESAs may be dangerous if used for overly aggressive treatment targets compared with practices that are compatible with current treatment guidelines," Winkelmayer said. "Continued access to these medications is required, however, to give patients with CKD a fair chance at first receiving and then maintaining the function of a kidney transplant. Swift action is needed to support comparative effectiveness research that closes the evidence gap in the optimal role of ESAs in the treatment of relatively severe anemia and to more modest treatment targets while maintaining these patients transfusion-free."

ASN members Rajiv Agarwal, MD, MBBS, FASN; Daniel Coyne, MD; and Joseph Messana, MD, served as a guest panelists on the MEDCAC panel considering presenters' remarks and reviewing evidence.

Read a copy of the society's remarks at ASN's website at http://www.asn-online.org/policy_and_public_affairs/patient-care.aspx.

State Initiatives to Manage Diabetes on the Rise

States have taken several steps to ensure that diabetes patients are appropriately managed by private and public insurers alike. Forty-six states require insurers to have some sort of coverage for diabetes management. Typically this coverage includes direct treatment, as well as diabetes equipment and supplies. The National Conference of State Legislatures has put together an interactive map to highlight private insurance mandates, public insurance coverage, and state-based public prevention programs. The map and associated tables can be accessed at http://tiny.cc/ncsl. The site also includes related legislation and links to state laws and regulations.

Looking for diabetes prevention and control programs in your state? The Centers for Disease Control has a list of links to state programs that can be accessed at http://tiny.cc/cdc249.

Want to know how much diabetes is costing your state? The American Diabetes Association can tell you at http://tiny.cc/statecost.

The Centers for Medicare and Medicaid Services included diabetes prevention for the Quality Improvement Organization's (QIO) 9th Statement of Work. QIOs work on a state level to improve health care services delivered to Medicare beneficiaries. Five states or jurisdictions were chosen to participate in the "Every Diabetic Counts" Program, an initiative to reduce health disparities among diabetes patients through diabetes self-management education: the District of Columbia, Georgia, Louisiana, Maryland, and New York. QIOs in these states are responsible for monitoring statewide diabetes rates and education efforts, and must submit the number of patients who complete self-management training on a monthly basis. To follow the progress of these and other Medicare Quality Improvement state initiatives, check out: www.cms.hhs.gov/qualityimprovementorgs/. To view and download the "Every Diabetic Counts" toolkit, visit http://tiny.cc/EDC.

Read a copy of the society's remarks at ASN's website at http://www.asn-online.org/policy_and_public_affairs/patient-care.aspx.

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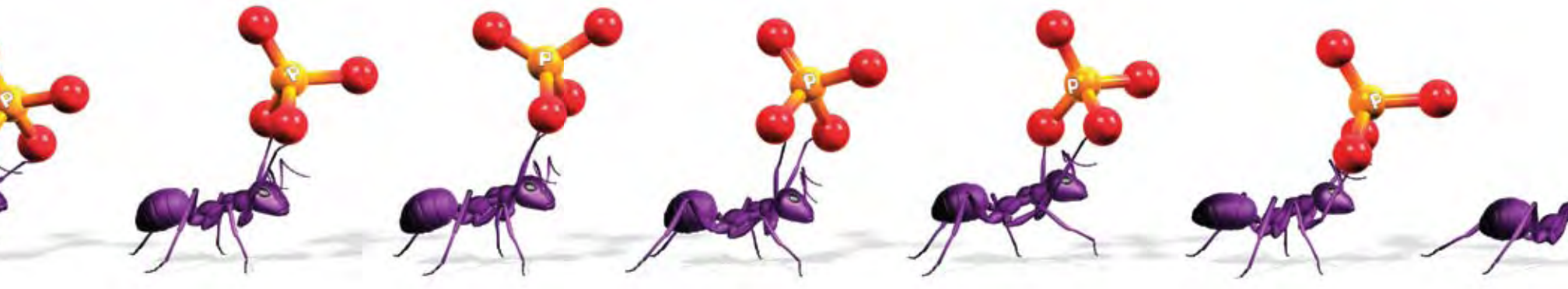

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FOSRENOL is indicated to reduce serum phosphate in patients with end stage renal disease.

Important Safety Information

• Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease, or bowel obstruction were not included in FOSRENOL® clinical studies. Caution should be used in patients with these conditions • There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years • FOSRENOL® tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. To aid in chewing, tablets may be crushed. Intact tablets should not be swallowed • No adequate and well-controlled studies have been conducted in pregnant women. FOSRENOL® is not recommended for use during pregnancy • The safety of lanthanum carbonate excreted in human milk is unknown. Caution should be exercised when FOSRENOL® is administered to a nursing woman • The use of FOSRENOL® in the pediatric population is not recommended • The most common adverse events for FOSRENOL® were gastrointestinal events, such as nausea and vomiting, and they generally abated over time with continued dosing. Gastrointestinal adverse events, such as nausea, diarrhea, and vomiting, were the most common type of event leading to discontinuation • Most common treatment-emergent adverse events were gastrointestinal (such as nausea and vomiting), dialysis graft complication, diarrhea, headache, and dialysis graft occlusion • Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent

Please see Brief Summary of Full Prescribing Information on adjacent page.

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FOSRENOL® (lanthanum carbonate)

Shire

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

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INDICATIONS AND USAGE
FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease.

CONTRAINDICATIONS
None known.

PRECAUTIONS
General:
Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in FOSRENOL® clinical studies. Caution should be used in patients with these conditions.

Diagnostic Tests:
Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

Long-term Effects:
There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years.

Information for the Patient:
FOSRENOL® tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. To aid in chewing, tablets may be crushed. Intact tablets should not be swallowed.
Notify your physician that you are taking FOSRENOL® prior to an abdominal x-ray (see **PRECAUTIONS, Diagnostic Tests**).

Drug Interactions:
Lanthanum is not metabolized.
The absorption and pharmacokinetics of FOSRENOL® are unaffected by co-administration with citrate-containing compounds (see **CLINICAL PHARMACOLOGY: In Vitro/In Vivo Drug Interactions**).
An *in vitro* study showed no evidence that FOSRENOL® forms insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril in simulated gastric fluid. In studies in healthy volunteers, FOSRENOL®, when administered 30 minutes in advance, did not alter the pharmacokinetics of oral warfarin, digoxin, or metoprolol. However, it is recommended that compounds subject to reduced absorption when co-administered with antacids (e.g. aluminum-, magnesium-, or calcium-based) should not be taken within 2 hours of dosing with FOSRENOL®. Examples of relevant classes of compounds where antacids have been demonstrated to reduce bioavailability include antibiotics (such as quinolones, ampicillin and tetracyclines), thyroid hormones, ACE-inhibitors, statin lipid regulators and anti-malarials.
The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken together with FOSRENOL® in a single-dose study in healthy volunteers. It is recommended that oral quinolone antibiotics are not taken simultaneously with FOSRENOL®.
The bioavailability of levothyroxine was decreased by approximately 40% when taken together with FOSRENOL®. Consequently, thyroid hormone replacement therapy should not be taken simultaneously with FOSRENOL® and monitoring of TSH levels is recommended in patients receiving both medicinal agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg of the salt per kg/day [2.5 times the maximum recommended daily human dose (MRHD) of 5725 mg, on a mg/m^2 basis, assuming a 60-kg patient] revealed no evidence of carcinogenic potential. In the mouse, oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.
Lanthanum carbonate tested negative for mutagenic activity in an *in vitro* Ames assay using *Salmonella typhimurium* and *Escherichia coli* strains and *in vitro* HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2000 mg/kg (1.7 times the MRHD), and in micronucleus and unscheduled DNA synthesis assays in rats given IV lanthanum chloride at doses up to 0.1 mg/kg, a dose that produced plasma lanthanum concentrations >2000 times the peak human plasma concentration.
Lanthanum carbonate, at doses up to 2000 mg/kg/day (3.4 times the MRHD), did not affect fertility or mating performance of male or female rats.

Pregnancy:
Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. The effect of FOSRENOL® on the absorption of vitamins and other nutrients has not been studied in pregnant women. FOSRENOL® is not recommended for use during pregnancy.
In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

Labor and Delivery
No lanthanum carbonate treatment-related effects on labor and delivery were seen in animal studies. The effects of lanthanum carbonate on labor and delivery in humans is unknown.

Nursing Mothers:
It is not known whether lanthanum carbonate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSRENOL® is administered to a nursing woman.

Geriatric Use:
Of the total number of patients in clinical studies of FOSRENOL®, 32% (538) were ≥ 65, while 9.3% (159) were ≥ 75. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients.

Pediatric Use:
While growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of FOSRENOL® in this population is not recommended.

ADVERSE REACTIONS
The most common adverse events for FOSRENOL® were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.
In double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to FOSRENOL® and placebo, respectively, for 4-6 weeks of treatment, the most common events that were more frequent (≥5% difference) in the FOSRENOL® group were nausea, vomiting, dialysis graft occlusion, and abdominal pain (Table 1).

Table 1. Adverse Events That Were More Common on FOSRENOL® in Placebo-Controlled, Double-Blind Studies with Treatment Periods of 4-6 Weeks.

	FOSRENOL® % (N=180)	Placebo % (N=95)
Nausea	11	5
Vomiting	9	4
Dialysis graft occlusion	8	1
Abdominal pain	5	0

The safety of FOSRENOL® was studied in two long-term clinical trials, which included 1215 patients treated with FOSRENOL® and 943 with alternative therapy. Fourteen percent (14%) of patients in these comparative, open-label studies discontinued in the FOSRENOL®-treated group due to adverse events. Gastrointestinal adverse events, such as nausea, diarrhea and vomiting were the most common type of event leading to discontinuation.
The most common adverse events (≥5% in either treatment group) in both the long-term (2 year), open-label, active controlled, study of FOSRENOL® vs. alternative therapy (Study A) and the 6-month, comparative study of FOSRENOL® vs. calcium carbonate (Study B) are shown in Table 2. In Table 2, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 0.9 years on lanthanum and 1.3 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.71.

Table 2. Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B

	Study A %		Study B %	
	FOSRENOL® (N = 682)	Alternative Therapy Adjusted Rates (N=676)	FOSRENOL® (N=533)	Calcium Carbonate (N=267)
Nausea	36	28	16	13
Vomiting	26	21	18	11
Dialysis graft complication	26	25	3	5
Diarrhea	23	22	13	10
Headache	21	20	5	6
Dialysis graft occlusion	21	20	4	6
Abdominal pain	17	17	5	3
Hypotension	16	17	8	9
Constipation	14	13	6	7
Bronchitis	5	6	5	6
Rhinitis	5	7	7	6
Hypercalcemia	4	8	0	20

OVERDOSAGE
There is no experience with FOSRENOL® overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg. In clinical trials, daily doses up to 4718 mg/day of lanthanum were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. Given the topical activity of lanthanum in the gut, and the excretion in feces of the majority of the dose, supportive therapy is recommended for overdosage.

DOSAGE AND ADMINISTRATION
The total daily dose of FOSRENOL® should be divided and taken with meals. The recommended initial total daily dose of FOSRENOL® is 1500 mg. The dose should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum phosphate levels should be monitored as needed during dose titration and on a regular basis thereafter.
In clinical studies of ESRD patients, FOSRENOL® doses up to 3750 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.
Tablets should be chewed completely before swallowing. To aid in chewing, tablets may be crushed. Intact tablets should not be swallowed.
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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Journal View

Does Soda Intake Affect Kidney Disease Risk?

High consumption of sugar-sweetened soft drinks is associated with an increased prevalence—but not incidence—of hyperuricemia and chronic kidney disease (CKD), according to a study in *Kidney International*.

The study included 17,745 participants in the Atherosclerosis Risk in Communities study, who provided baseline data on their consumption of sugar-sweetened sodas. About 5 percent reported drinking more than one soda per day. Based on serum creatinine and uric acid measurements, 37 percent of participants met sex-specific criteria for hyperuricemia while 3.1 percent had prevalent CKD.

On multivariate analysis, individuals who drank more than one soda per day had an increased prevalence of hyperuricemia, compared to those who drank less than one soda per day: odds ratio 1.31. The prevalence of CKD was increased for participants who drank more than one soda per day and who had a serum uric acid level of greater than 9.0 mg/dL: odds ratio 2.59.

A longitudinal analysis was performed using three- and nine-year follow-up data. The results showed no association between soda consumption and the incidence of hyperuricemia or CKD. Soda consumption was unrelated to incident CKD risk, regardless of whether hyperuricemia was present at baseline or developed during follow-up. Consumption of diet soda was unrelated to prevalent or incident hyperuricemia or CKD.

Rising rates of obesity, metabolic syndrome, and CKD have occurred at a time of increasing consumption of high-fructose corn syrup—most of it in soft drinks. Two recent studies have linked sweetened soda consumption to albuminuria and elevated serum creatinine. Both of these studies focused on prevalence and neither looked at the effects of elevated uric acid.

The new study finds increased rates of prevalent hyperuricemia among Americans who drink more than one sugar-sweetened soda per day. Prevalence of CKD is increased for heavy soda drinkers with hyperuricemia. However, there are no similar associations on longitudinal analysis of incident hyperuricemia and CKD. "[O]ur findings add to but in no way close the heated discussion over the potential dangers of sugar-sweetened soda," the investigators conclude [Bomback AS, et al. Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. *Kidney Int* 2010; 77:609–616].

No Increase in Mortality for Living Kidney Donors

At medium-term follow-up, there is no increase in the overall risk of death for Americans who become living kidney donors, concludes a study in the *Journal of the American Medical Association*.

The study included 80,347 people who became live kidney donors in the United States between 1994 and 2009, reported to the Organ Procurement and Transplantation Network through the United Network for Organ Sharing. Donors were followed up for a median of 6.3 years. Survival was compared with a cohort of 9364 matched participants from the third National Health and Nutrition Examination Survey (NHANES III), excluding those with contraindications to kidney donation.

The number of live kidney donors increased significantly over the years—in 2008, there were 5968 donors. The rate of death within 90 days after nephrectomy was 3.1 per 10,000 donors, and remained stable throughout the 15 years covered by the registry. This was so despite an increased number of donors over age 50. Surgical mortality was higher for men than women, 5.1 versus 1.7 per 10,000 donors; and for black donors than white donors, 7.6 versus 2.6 per 10,000. The strongest risk factor for mortality was hypertension: 36.7 versus 1.3 per 10,000 donors.

Despite the increase in 90-day mortality, live kidney donors had long-term mortality similar to or lower than that in the matched NHANES III cohort: at 12-year follow-up, mortality was 1.5 percent versus 2.9 percent, respectively. This remained so on stratification by age, sex, and race.

Living kidney donation is an increasingly important source of organs for transplantation. Although donation appears safe, continued follow-up is essential to gather accurate information on the expected outcomes.

This registry study finds no increase in mortality among living kidney donors at a median follow-up of 6.3 years, compared to a closely matched population cohort. Certain groups have increased surgical mortality; potential donors should be counseled accordingly. While calling for more research on the physiologic changes after nephrectomy, the authors conclude that living kidney donation is a "reasonable and safe" approach to increasing the number of kidneys for transplantation [Segev DL, et al. Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010; 170:959–966].

eGFR Reporting Increases Nephrologist Visits for CKD

In Alberta, implementation of estimated glomerular filtration rate (eGFR) reporting by laboratories has been followed by an increase in initial visits to nephrologists for chronic kidney disease (CKD), according to a study in the *Journal of the American Medical Association*.

Alberta laboratories began reporting eGFR in 2004. A time-series analysis included more than 1.1 million adult outpatients who had at least one outpatient serum creatinine measurement, with follow-up from 2003 to 2007. Changes in the rate of outpatient visits to a nephrologist were assessed, along with use of health care resources and drugs commonly used to treat CKD (eGFR less than 60 mL/min/1.73 m^2).

After implementation of eGFR reporting, the rate of initial outpatient visits to a nephrologist for patients with CKD increased by 17.5 visits per 10,000 CKD patients per month—a relative increase of 68 percent. Among patients without CKD, the rate of nephrologist visits was unchanged.

When CKD was defined as an eGFR of less than 30 mL/min/1.73 m^2, the rate increased by 134.4 visits per 10,000 patients per month. Most of the increase occurred in women, patients aged 46 to 65 years or 86 years and older, patients with hypertension and diabetes, and those with comorbidity.

The increase in physician visits was specific to nephrologists—there was no change in visits to internists or general practitioners. Use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers did not increase among patients with CKD and proteinuria, including those with diabetes.

Laboratory reporting of eGFR might enhance early recognition and treatment of eGFR. However, it also has the potential for unintended negative effects. Automated eGFR reporting has been widely implemented, despite a lack of evidence.

Reporting of eGFR has led to substantial increases in the rate of initial nephrology visits by patients with CKD in Alberta, particularly those with more severe kidney dysfunction. Further research is needed to determine the effects of eGFR reporting on patient outcomes and on health care costs [Hemmelgarn BR, et al. Nephrology visits and health care resource use before and after reporting estimated glomerular filtration rate. *JAMA* 2010; 303:1151–1158].

Index to Advertisers

Industry Spotlight

Cholesterol Drug Tied to Rhabdomyolysis

At high doses, the drug simvastatin (Merck, also known as Zocor), puts patients at risk of developing rhabdomyolysis, a severe breakdown of muscle that can result in acute kidney injury, dysfunction, and even death.

In mid-March, the Food and Drug Administation issued a warning message that patients taking the highest allowable dose of Zocor, 80 mg, had an increased risk for muscle injury. The FDA issued the news partly in response to findings from the trial Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

Known risk factors for developing rhabdomyolysis include age above 65 years old, low thyroid hormone levels (hypothyroidism), and poor kidney function.

According to the FDA, myopathy is a known side effect of all statin medications. In fact, Merck said warnings about myopathy have always been part of the drug information package. "The labeling for simvastatin has reflected information about potential muscle effects since approval," according to a Merck statement about the FDA announcement.

"Simvastatin, when used as a supplement to a healthy diet, can help reduce LDL cholesterol and reduce the risk of death from cardiovascular disease in patients at high risk of coronary events," said Michael Rosenblatt, MD, Merck's chief medical officer. "We support the FDA's recommendation that patients continue taking their medication as prescribed by their physicians, and that patients speak to their physician if they have symptoms or questions."

The company is working with regulatory agencies to update the drug's labeling as needed.

The FDA recommends that health care professionals:

- be aware of the potential increased risk of muscle injury with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
- review patients' medical history and medications to determine whether simvastatin is clinically appropriate for each patient.
- discuss with patients the benefits and risks, including the risk of myopathy and rhabdomyolysis, of simvastatin therapy.
- be aware of potential drug-drug interactions with simvastatin.
- report any adverse events associated with the use of simvastatin to FDA's MedWatch program. Visit www.fda.gov for more information.

Dialysis Company Owes U.S. $19.4 Million

In deciding a "whistleblower" case originally filed in St. Louis in 2005, a federal court in Nashville on March 23 awarded the United States $19,366,705, plus interest, says the U.S. Department of Justice. The U.S. District Court concluded that Renal Care Group, Renal Care Group Supply Company (RCGSC), and Fresenius Medical Care Holdings, which acquired Renal Care Group in 2005, "recklessly disregarded federal law when billing the Medicare program for home dialysis supplies and equipment from 1999 to 2005."

U.S. District Judge William J. Haynes, Jr., held that defendants disregarded the mandates of the applicable Medicare statutes and regulations. He said that Renal Care Group employees raised complaints and concerns about the operation and Medicare billing activity of the RCGSC.

According to *Nashville Business Journal*, in October 1998, the company's chief operating officer for the south central region protested a corporate request that "encouraged some dialysis patients to switch from primarily facility care to much more at-home care—in which they used fluids and a machine or catheter to provide their own treatment," because of higher federal reimbursement.

The court scrutinized Renal Care Group and RCGSC in light of the two tiers of payments that Medicare gives to dialysis companies. Companies that operate dialysis facilities are supposed to bill Medicare using "Method I," which applied to Renal Care Group. Companies that supply patients with dialysis at-home supplies but don't run dialysis facilities, like RCGSC, are paid under Medicare "Method II," which pays 30 percent more.

The court's order noted that Renal Care Group did not follow the advice of the company's lawyers when operating the supply company, and discussed an internal audit of the supply company that found that 100 percent of the company's files were missing information that Medicare required for billing the government program.

The court held that "reckless disregard is sufficient for liability" under the federal False Claims Act, and that specific intent to defraud was not a standard that had to be met.

Fresenius has appealed the District Court decision. "We disagree with the court's conclusion that payment by the government (Medicare program) of claims by Renal Care Group's Method II company constituted 'unjust enrichment,'" Fresenius spokeswoman Terry Morris said in a statement.

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