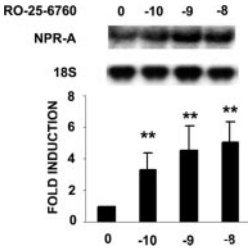
J Am Soc Nephrol 16: 279–283, 2005

This Month's Highlights

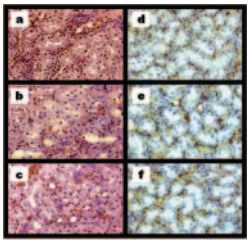
Basic Science



Cell Biology

1,25 Dihydroxyvitamin D Amplifies Type A Natriuretic Peptide Receptor Expression and Activity in Target Cells

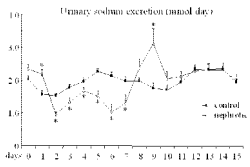
Kidneys and the Heart Working Together: Role of Vitamin D. Cardiovascular risk has recently garnered attention in the setting of chronic kidney disease (CKD), with vitamin D being a central element that by itself has beneficial effects on cardiovascular function. The article by Chen *et al.* (pages 329–339) in this issue of *JASN* describes a novel pathway for interaction between the active form of vitamin D (either endogenous or administered exogenously) that could potentially tie together some of the recent observations about the increasing risk of cardiovascular events, survival from acute myocardial infarction, and even all-cause mortality associated with more severe CKD. The natriuretic peptides are critically important for maintaining optimal volume status, and in the setting of advanced CKD, a relative insufficiency of 1,25 dihydroxyvitamin D as well as suboptimal renal responsiveness to atriopeptins could magnify the challenges of maintaining optimal volume status in these patients.



Basic Immunology and Pathology

Renal Ischemia/Reperfusion Injury: Functional Tissue Preservation by Anti–Activated β1 Integrin Therapy

ATN: If We Keep Those Ischemic Tubular Cells from Detaching, Will It Have a Protective Effect? Despite decades of research in readily available animal models and in man, acute renal failure, or ATN, remains a common clinical event that dominates the in-patient nephrology services at most institutions. We have learned that detachment of ischemic tubular cells leading to downstream obstruction of tubules is central to the pathophysiology of ATN and that cell-matrix interaction is dependent on attachment molecules such as integrins. In this study, Mampaso and colleagues (pages 374–382) administered a monoclonal antibody to an activation-dependent epitope on β1 integrin before inducing ischemic ATN in rats. The antibody produced remarkable morphologic and functional protection from ATN, apparently by preventing detachment of tubular cells from basement membranes, an effect also reproduced *in vitro*. While the molecular mechanism of the observed effect is somewhat unclear, the rather dramatic results reported in the study offer hope that an analogous approach may have eventual clinical application.

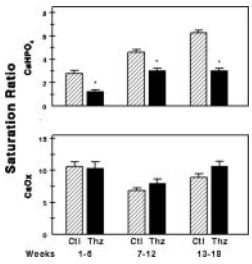


Pathophysiology of Renal Disease and Progression

Role of Uroguanylin, a Peptide with Natriuretic Activity, in Rats with Experimental Nephrotic Syndrome

Kidneys and the Gut Working Together: Role of the Guanylins. Guanylin and uroguanylin, like the atriopeptins, signal through receptors coupled to cyclic GMP generation. While the atriopeptins are released in response to baroreceptor stretch on the right side of the heart, the guanylins appear to be responsive to gastrointestinal

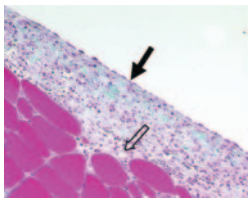
factors, including salt intake. In the article by Kikuchi *et al.* (pages 392–397) in this issue, and as highlighted in the editorial by Leonard Forte (pages 291–292), the release of uroguanylin in kidney circulation plays an important role in salt retention and natriuresis in an acute model of nephritic syndrome. Further work is needed to understand this intrarenal pathway and the specific effects of uroguanylin on electrolyte excretion. The possibility of therapeutic applications related to these pathways is an exciting prospect.



Basic Mineral Metabolism

Thiazides Reduce Brushite, but not Calcium Oxalate, Supersaturation, and Stone Formation in Genetic Hypercalciuric Stone–Forming Rats

Between a Rock and a Hard Place. Bushinsky and Asplin describe an unusual model of genetic hypercalciuria in this issue of *JASN* (pages 417–424). These rats form calcium phosphate (apatite) stones, which convert to calcium oxalate stones when their diet is supplemented with hydroxyproline (which is metabolized to oxalate). Chlorthaldone reduces urinary saturation of calcium hydrogen phosphate (brushite), even when the rats are placed on hydroxyproline and have increased urinary oxalate excretion. Calcium phosphate stones are distinctly unusual in humans, so these results may seem to be of limited utility. Recently, however, the thesis has been put forth at the initial nidus for calcium oxalate stone formation in humans is, in fact, calcium phosphate. These studies suggest that urinary calcium oxalate is not the best parameter to follow the response to therapy, and that the beneficial effect of thiazide diuretics in humans needs further exploration from a mechanistic point of view.

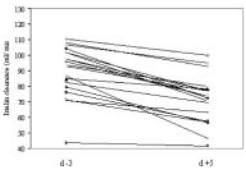


Basic Dialysis

Transient Overexpression of TGF-β1 Induces Epithelial Mesenchymal Transition in the Rodent Peritoneum

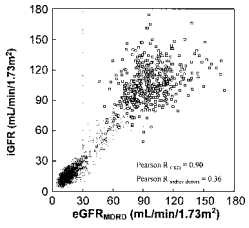
Getting a Molecular Grasp on Peritoneal Membrane Failure. A major limitation of long-term peritoneal dialysis is the gradual decline in peritoneal membrane efficiency due to progressive membrane sclerosis. Although several risk factors have been identified, such as episodes of peritonitis and use of acidic and hypertonic dialysate solutions, the cellular and molecular events that underlie peritoneal sclerosis are unclear. A potential role for TGF-β1 seems logical given its central role in all other fibrotic processes. In this issue of *JASN*, Margetts *et al.* (pages 425–436) study the consequences of transient intraperitoneal expression of TGF-β1 induced by gene transfer in rats. Peritoneal fibrosis was evident within four days. The central finding in this study was the transformation of normal peritoneal mesothelial cells into matrix-producing myofibroblasts. These transformed cells were thought to migrate across damaged basement membranes into the submesothelial layer in association with increased levels of MMP-2, a matrix-degrading metalloproteinase. The process of TGF-β1-induced epithelial-to-mesenchymal transition (EMT) explains at least one pathway by which intrinsic mesothelial cells become active participants in the process of peritoneal sclerosis. Equally notable, upon termination of TGF-β1 production, EMT and fibrosis appear to resolve. The present study provides further support for the hypothesis that TGF-β1 and its ability to recruit peritoneal membrane myofibroblasts via EMT are important in the pathogenesis of peritoneal membrane failure.

Clinical Nephrology



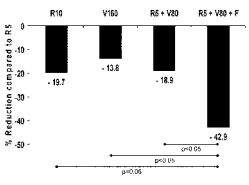
Nephroprotection by Theophylline in Patients with Cisplatin Chemotherapy: A Randomized, Single-Blinded, Placebo-Controlled Trial

Theophyllin Protects Against Cisplatin-Induced GFR Loss. Despite extensive research with often fascinating experimental results, disappointingly little has entered clinical practice and improved management of patients at risk to develop acute renal failure (ARF). Against this background, even small steps in this direction are welcome. The role of adenosine in the genesis of experimental ARF has been well documented, and theophylline antagonized adenosine-induced renal vasoconstriction in animal models of ARF as well as in patients exposed to radiocontrast. It remained undecided, however, whether this was true for other modalities of acute renal dysfunction and whether such benefit is also seen after rigorous hydration. In this issue, Benoehr *et al.* (pages 452–458) report on a trial that compared the effect of theophylline on GFR with that of placebo. Patients who were on a standard hydration scheme with essentially isotonic saline (but not bicarbonate, which recently was shown to provide superior renoprotection) received cisplatinum for different malignancies. Hydration alone did not prevent a decrease in GFR, but theophylline did. ARF did not occur in either arm of the study, but the intervention is potentially a step in this direction.



Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations in the Estimation of GFR in Health and in Chronic Kidney Disease

We Still Do not Know the Best Way to Measure Renal Function Clinically, but We Are Making Progress! It is now recognized that the measurement of serum creatinine is a misleading measure of kidney function and that identical values can reflect a wide range of GFR depending on the individual patient's age, gender, and race. Renal clearance methods like the creatinine clearance are logistically difficult to use in clinical settings and are subject to considerable measurement error. Estimating equations like the MDRD and Cockcroft-Gault equations multiply a serum creatinine value by a weighting factor derived from factors associated with 24-hr creatinine excretion (age and gender and race or weight). The result is a comparable estimate of renal clearance that allows any patient to be assigned to a common measure of kidney function. It is imperative that clinicians using decision support tools understand their origin and limitations as well as their applications. The report in this issue of *JASN* by Poggio *et al.* (pages 459–466) brings attention to several issues. First, laboratory calibration of serum creatinine measurement to the measurement used for derivation of the MDRD equation is an important determinant of accurate estimation of GFR; laboratories adopting GFR reporting based on this equation should address this issue. Second, for GFR <60 ml/min per 1.73 m^2 and for individuals with diabetic nephropathy, the MDRD equation was more accurate than the Cockcroft-Gault equation, while among healthy kidney donors the reverse was true. Third, these results remind us that any diagnostic test will misclassify some patients, and that the purpose of testing is to revise a prior diagnostic probability of the presence of CKD derived from a thorough patient assessment or, when the test abnormality is the first indication of kidney disease, to initiate a thorough evaluation of the patient.

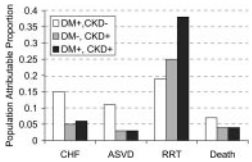


Diuretic and Enhanced Sodium Restriction Results in Improved Antiproteinuric Response to RAS Blocking Agents

In Patients Taking ACEI/ARB for Proteinuria, Don't Forget the Diuretic. In recent *post hoc* analyses of the Angiotensin Receptor Blocking trials, the reduction of urinary protein excretion foretells the overall beneficial response to therapy. Esnault *et al.* (pages 474–481) describe a nice crossover study with a relatively small number of patients that emphasizes the importance of optimal diuretic therapy in obtaining

reductions in urinary protein excretion during treatment with blockers of the renin-angiotensin system in patients with proteinuria. Dietary salt restriction to the US Recommended Allowance (2.4 g, which will be reflected by urinary sodium excretion of 100 mEq/day) is more difficult to achieve than optimal diuretic management. Superimposed prerenal azotemia can result if the patients are not followed closely. It is not clear in this study if furosemide was dosed twice a day, or if any additional efforts to achieve dietary salt restriction were successful, but these issues must be addressed in patients with proteinuria.

Epidemiology and Outcomes

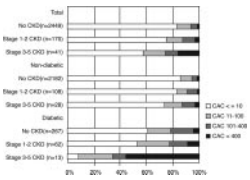


Chronic Kidney Disease and the Risk of Cardiovascular Disease, Renal Replacement, and Death in the United States Medicare Population, 1998–1999

More on the CKD–CVD Intersection: While CVD Risk Factors Predict Progression, Many Patients Die of CVD before Reaching ESRD. There is growing recognition that patients with chronic kidney disease are at increased risk of death and progression to ESRD. The report in this issue of *JASN* by Foley *et al.* (pages 489–495) at the US Renal Data System provides a detailed analysis of how CKD modifies risk of CVD and progressive CKD. Among individuals aged 65 years and older, Foley *et al.* noted strong graded increases in risk of atherosclerotic cardiovascular disease, heart failure, and death among individuals with diabetes or CKD and among individuals with both diagnoses. Of note, in each of the four groups of patients, the risk of death compared to that of progression to renal replacement therapy was 11 times greater among individuals with CKD and no history of diabetes, and six times greater for individuals with both CKD and diabetes. These observations emphasize two points. First, patients with CKD are at a much greater risk of progression to renal replacement therapy; and second, most CKD patients will die before they progress to ESRD, particularly from atherosclerotic vascular disease and congestive heart failure. Clinicians caring for CKD patients with cardiovascular disease and diabetes need to aggressively manage risk factors for adverse outcomes for the underlying disease, as well as those risk factors associated with progressive kidney disease.

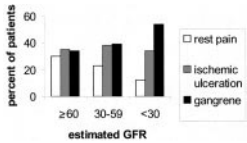
Incidence and Predictors of Myocardial Infarction after Kidney Transplantation

CVD Affects Transplant Patients Just Like It Does Patients with CKD in Native Kidneys, Maybe More So. Heart disease is a major cause of morbidity and mortality among posttransplant patients. The report by Lentine and her colleagues in this issue of *JASN* (pages 496–506) examines the risk of posttransplant myocardial infarction (MI) in a large retrospective cohort of recent kidney transplant recipients. Lentine *et al.* observed for MI at one and three years of 5.6% and 11.1%, respectively. Recipient characteristics associated with increased risk of posttransplant MI included older recipient age, diabetes mellitus, and a previous history of atherosclerotic heart disease. The risk of death following a posttransplant MI was increased by 89%. These observations raise several questions about the pretransplant management of patients on transplant waiting lists. Is there an association between medical management of cardiovascular risk factors, including dyslipidemia, glycemic control, and hypertension, and subsequent outcomes following transplantation? What is the association between pretransplant evaluation of cardiovascular risk and subsequent outcomes? Is the information about CVD risk incorporated into posttransplant care? What is the optimal management of posttransplant CVD risk? Clearly, additional observational studies and clinical trials are needed in this critical area of renal replacement therapy.



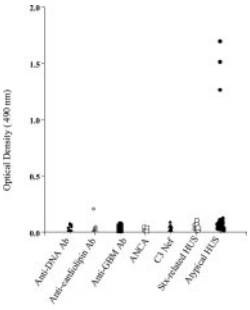
Association between Chronic Kidney Disease and Coronary Artery Calcification: The Dallas Heart Study

Coronary Calcification Is Increased and Predicts CVD in CKD As Well As in ESRD. The role of coronary artery calcification and arterial calcification as markers for increased risk of cardiovascular disease in both the general population and ESRD patients has been widely documented. In this issue of *JASN*, Kramer and her colleagues (pages 507–513) liken chronic kidney disease to the risk of coronary artery calcification in the general population. The authors note that arterial calcium scores were not associated with albuminuria and minor reductions in GFR (NKF stages 1 and 2), while more severe degrees of CKD were associated with substantially increased risk of high calcium scores. The study was conducted in a population-based cohort so the observations are unlikely to reflect selection bias. However, the cross-sectional nature of the study leaves the temporal relationship between impaired kidney function and increased arterial calcification unresolved. Of considerable interest, the observation that the degree of arterial calcium score at any CKD stage is greater in diabetic compared to non-diabetic patients.



Impact of Renal Insufficiency and Mortality in Advanced Lower Extremity Peripheral Arterial Disease

More Bad News—CKD Is More Common than We Thought in People Who Present Primarily with Peripheral Vascular Disease. It is not at all uncommon to encounter patients on dialysis rounds with single and double lower extremity amputations. The cause for amputations is typically diabetes with either arterial disease or peripheral neuropathy, or both, leading to rest pain, ischemic ulceration, or gangrene necessitating amputation. The article by O'Hare and her colleagues (pages 514–519) reminds us that CKD is also common in patients with peripheral vascular disease. O'Hare *et al.* observed that 38% of a cohort of nearly 6000 male veterans with peripheral vascular disease had stage 4 and 5 CKD and were at increased risk of death compared to patients with normal kidney function. Of particular interest is the observation that stage 5 CKD was associated with increased risk of ischemic ulceration and gangrene.



Clinical Immunology and Pathology

Anti–Factor H Auto-Antibodies Associated with Atypical Hemolytic Uremic Syndrome

An Autoimmune Mechanism for Atypical HUS. Diarrhea-negative hemolytic uremic syndrome (HUS) is a major clinical challenge as recurrent episodes are frequent and often lead to chronic kidney disease. Recurrent disease in renal allografts underscores the systemic nature of the disorder in some patients. It was first recognized 40 years ago that a subset of patients with both familial and sporadic HUS had low serum levels of the third component of complement (C3). It is now known that some of these patients express mutations in the gene that encodes factor H (HF1), a cofactor protein that regulates the rate of complement activation via the alternative pathway and the severity of complement-dependent (*e.g.*, endothelial) cell injury. What about the patients with two normal HF1 alleles but evidence of complement cascade activation associated with atypical HUS? Mutations in other complement-regulatory genes have been reported in some patients. In this issue of *JASN*, Dragon-Durey and colleagues (pages 555–563) report an autoimmune mechanism for acquired factor H–deficiency and atypical HUS. From a cohort of 48 children with non–shigatoxin-related HUS, three children were found to have a circulating antibody to factor H that blocked its activity. HF1 genotyping and factor H antigen levels were normal. It is notable that in additional to low serum C3 levels in two of the patients, anti-nuclear antibodies were detected in the three patients. Should these anti-factor H antibodies be shown to play a pathogenetic role, therapeutic implications are obvious.