Chronic kidney disease (CKD) is a growing major worldwide health problem. In the United States, ~14% of the population has CKD defined as an estimated glomerular filtration of <60 mL/min or an increased urine albumin/creatinine ratio of >30 mg/g. Decreasing estimated glomerular filtration or increasing urine albumin level is associated with development of many comorbid conditions, including highly significant increases in cardiovascular disease and a significant increase in mortality rates as compared with age-matched controls without CKD. A recent analysis led to the conclusion that possibly all of the excess mortality in people with type 2 diabetes mellitus (DM) as compared with the nondiabetic population is attributable to the development of CKD. Perhaps the impact of CKD is best illustrated by the epidemic rise in the end-stage renal disease (ESRD) population. In 1978, there were 41,421 people with ESRD (these numbers include all people on hemodialysis, on peritoneal dialysis, and who have received a transplant). In 2011, 612,966 people in the United States had ESRD (an ~15-fold increase in prevalence in 35 years). Considering that death rates for people on dialysis are ~20% per year and that there is a much better chance a CKD patient will die from cardiovascular disease than reach dialysis, there must be a very large number of people with CKD to produce the continued increase in prevalence in the ESRD population. There is also an enormous societal financial burden in that the cost of care for ESRD patients was nearly 30 billion dollars (~6% of the Medicare budget for ~0.2% of the population). And because this dollar amount does not take into account care the CKD (pre-ESRD) population, the financial costs are actually much higher for the care of all people with kidney disease. In addition, this is an epidemic of global proportions. Indeed India and China have the most people with DM and will eventually have very high numbers of CKD patients.

The 2 main causes of CKD are DM and hypertension. And of these, the rise in the CKD and ESRD population is mainly due to the epidemic increase in people with type 2 DM. Primary prevention of diabetic kidney disease is mainly achieved by controlling blood sugar and blood pressure. Secondary prevention (slowing progression) involves the same interventions plus the addition of a blocker of the renin-angiotensin-aldosterone system if the patient has increased urine albumin levels. Yet even with these treatments, the prevalence of CKD and ESRD attributable to DM continues to increase. Hence there are compelling needs to better understand the mechanisms responsible for diabetic kidney disease to develop more treatments.

Mechanisms that have been determined to play a role in the development and progression of diabetic kidney disease include increased levels of reactive oxygen species, activation of protein kinase Cβ, activation of transforming growth factor β, increased levels of advanced glycation end products, and others. To date, no intervention that targets 1 of these mechanisms has been shown to be effective. Perhaps a combination approach or targeting of mechanisms that links these processes will lead to better treatments. In addition to these mechanistic changes at the cellular level, another important mechanism involves glomerular hemodynamic alterations, the hyperfiltration hypothesis. It has been known for years from animal models of DM as well as from patients with DM that there is a phase at which the GFR rises. There are widely varying estimates for the prevalence of glomerular hyperfiltration (13% to 75% in type 1 DM patients and 0% to 40% in type 2 DM patients). The hypothesis is that hyperfiltration leads to death of glomeruli, which results in even higher individual filtration rates in the remaining glomeruli, which then cause loss of more glomeruli that results in decline in whole kidney GFR, ultimately ending in ESRD. This hypothesis led to the development of blockers of the renin-angiotensin-aldosterone system as angiotensin II is one of the major regulators of glomerular filtration by causing preferentially greater vasoconstriction of the efferent arteriole over the afferent arteriole. Inhibition of angiotensin II will cause a decrease in intraglomerular pressure and lead to a decrease in GFR. A recent analysis illustrated the importance of the initial decrease in GFR caused by angiotensin II inhibition, where it was observed that the greater the initial decline in GFR, the better the long-term outcome for kidney function.

Hence much research has focused on the mechanisms underlying glomerular hyperfiltration and the significance of glomerular hyperfiltration for long-term outcomes. Glomerular filtration is determined by a combination of the hydrostatic and oncotic pressure gradients across the glomerular capillary and the permeability of the capillary basement membrane. Blood enters the capillary via the afferent arteriole
and exits via the efferent arteriole. Smooth muscle–derived cells called mesangial cells hold the network of capillaries in the glomerulus together. Glomerular hyperfiltration can occur as a result of changes in afferent vascular tone or blood volume that allows higher flows to the glomerular capillaries, by mesangial relaxation that leads to greater surface area, and to efferent arteriole vasoconstriction that leads to higher glomerular hydrostatic pressures. The main sensors that regulate glomerular hemodynamics are the juxtaglomerular cells and the macula densa, which comprise the juxtaglomerular apparatus. The juxtaglomerular cells are specialized afferent arteriole cells that sense pressure. When the intra-arterial pressure decreases, renal is released which cleaves angiotensinogen to angiotensin I. Angiotensin-converting enzyme converts angiotensin I to angiotensin II, causing vasoconstriction of the efferent arteriole preferentially more than the afferent arteriole with a resultant rise in glomerular pressure. The other main regulator is a set of specialized cells in the distal convoluted tubule called the macula densa (which is located next to the glomerulus and the juxtaglomerular cells because of the looping architecture of the nephron) that sense sodium and chloride. Sodium and chloride delivery to the macula densa is determined by the amount filtered at the glomerulus and the amount reabsorbed in the proximal tubule and the loop of Henle. Sodium reabsorption in the proximal tubule occurs mainly by the sodium-hydrogen antiporter as well as by other proximal tubule sodium transporters including the sodium glucose cotransporter, a set of sodium amino acid cotransporters, and the sodium phosphate cotransporter. When there is a decrease in solute concentration at the macula densa that may occur as a result of decreased GFR or to increased uptake of sodium proximal to the macula densa, signals from the macula densa act on the afferent arteriole causing vasodilation and increased blood flow to the glomerulus. This process is called tubuloglomerular feedback (TGF).

Glomerular hyperfiltration can potentially occur by alterations in any of the factors controlling GFR. A role for TGF and the sodium glucose cotransporter (SGLT) in hyperfiltration has been shown in studies from animals using phlorizin, a nonspecific inhibitor of SGLT whereby phlorizin led to a decrease in glomerular hyperfiltration suggesting that TGF and SGLT, at least in part, play a role in glomerular hyperfiltration. Until now, no human studies have been done to assess the role of SGLT in TGF in diabetic kidney disease.

The interesting article by Cherney et al has addressed this issue by using one of the new class of drugs that inhibit SGLT2, empagliflozin. In the proximal tubule, ≈80% to 90% of the SGLT proteins are SGLT2. Thus, SGLT2 inhibitors will target most of the sodium glucose cotransport in the proximal tubule. This class of medications has been approved to treat patients with type 2 DM and a GFR of >45 mL/min to lower blood sugar by causing loss of glucose in the urine. The main side effects of these medications to date are the modest increases in urinary tract infections and vulvo-vaginal infections. Otherwise they appear to be safe in patients without CKD. Safety in patients with CKD has not yet been determined. The authors studied 40 people with type 1 diabetes (27 with glomerular hyperfiltration, GFR >135 mL/min; and 13 without hyperfiltration). They gave empagliflozin for 8 weeks and measured GFR before administering empagliflozin and after 8 weeks of SGLT2 inhibition under euglycemic and hyperglycemic clamp conditions. In the hyperfiltrating patients the estimated glomerular filtration rate decreased significantly, whereas the patients without hyperfiltration were unaffected. This result suggests that TGF plays a role in glomerular hyperfiltration and that SGLT2 inhibitors can decrease the hyperfiltration at least in the short term. Figure 1 from the Cherney et al article illustrates TGF. The authors also suggest that SGLT2 inhibitors may be an effective treatment for CKD. The pros and cons for this drug as a treatment for CKD can be stated as follows.

The arguments for using these medications in CKD patients are as follows: (1) they decrease glomerular hyperfiltration. The authors note that this effect is similar to the GFR-decreasing effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers albeit by a different mechanism; (2) they may help to protect the viability of proximal tubule cells by limiting uptake of glucose. Many studies suggest that tubular damage is very important in the pathogenesis of diabetic kidney disease. And a recent study suggests that SGLT2 inhibitors can protect cultured human proximal tubular cells; (3) these medications lower blood pressure on average up to 5 mm Hg; (4) they cause weight loss. Hence, SGLT2 inhibitors may protect kidney function by 4 mechanisms, lowering of glomerular hyperfiltration, by limiting hyperglycemic damage to proximal tubule cells, by lowering blood pressure, and by causing weight loss.

The arguments against using these medications in CKD patients are as follows: (1) It is not clear that hyperfiltration is clearly of mechanistic importance for the development of diabetic kidney disease or simply a marker of risk. There are a number of recent articles reviewing the evidence for and against glomerular hyperfiltration in diabetic kidney disease. It is not clear as to whether targeting glomerular hyperfiltration will help long-term outcomes. Angiotensin-converting enzyme I and ARB medications certainly lower GFR, but it is not known as to whether lowering GFR is the mechanism by which they work or only a marker of their efficacy. Angiotensin II has multiple other potentially deleterious actions (increasing inflammation, increasing reactive oxygen species, etc.). Hence the effect of inhibition of angiotensin II may be attributable primarily to inhibiting these other actions rather than altering glomerular filtration. (2) SGLT2 inhibitors will protect proximal tubule cells from the effects of high glucose but glomeruli and vasculature are still exposed to high glucose. Thus hyperglycemic damage may still be occurring at other sites in the kidney. (3) The distal nephron (loop of Henle, distal convoluted tubule, and collecting ducts) will be exposed to a constant flow of glucose. Under normal physiological conditions, these cells have no glucose in the luminal filtrate. Studies to date suggest that DM patients without CKD who are treated with these medications appear to be at low risk for kidney damage. But studies are limited as to the safety for patients with CKD. It is possible that long-term exposure to high glucose in the distal nephron of patients with CKD may be deleterious.

The article by Cherney et al has provided important insights into the possible role of TGF in humans with DM. SGLT2 inhibitors are a very interesting new class of drugs for the treatment.
of DM. Their utility in CKD patients remains to be determined. Careful studies and follow up will be needed to be sure these drugs are beneficial and do not cause harm to the CKD patient.

Disclosures
Dr Stanton has served on the Global Renal Advisory Board for Boehringer-Ingelheim.

References

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Sodium Glucose Transport 2 (SGLT2) Inhibition Decreases Glomerular Hyperfiltration: Is There a Role for SGLT2 Inhibitors in Diabetic Kidney Disease?

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