Observations that early changes in renal hemodynamics beget later kidney damage was a seminal scientific discovery that ultimately led to development of the only class of agents, inhibitors of the renin-angiotensin system (ACE inhibitors and angiotensin receptor blockers), approved by regulatory agencies for the treatment of diabetic kidney disease (DKD) (1,2). The first drugs in this class were approved more than two decades ago, and the concept of glomerular hyperfiltration as a targetable mechanism for DKD goes back almost four decades. It is rather ironic that looking backward in this direction may move the field forward in the future. Despite tremendous efforts of the clinical and translational research community and enormous amounts of scientific evidence discovered about various disease mechanisms, no others have successfully translated to a new treatment for DKD. Processes like fibrosis and inflammation undoubtedly contribute in major ways to the pathogenesis of DKD, but many attempts to translate these mechanisms to therapeutic targets have not yet succeeded (3–7). This consequence is likely due to a number of issues in the design and conduct of clinical trials, lack of validated DKD biomarkers, and barriers in the regulatory and business domains (8).

Interest has resurged in renal hemodynamics because this DKD mechanism is targetable by strategies already in hand. In addition to the effects of renin-angiotensin system inhibition to decompress the glomerulus by releasing efferent arteriolar vasoconstriction, the sodium–glucose cotransporter 2 inhibitor class of oral hypoglycemic agents may reduce glomerular hyperfiltration by another mechanism. These agents increase distal tubular delivery of solute, specifically sodium chloride to the macula densa, and thereby reduce afferent arteriolar vasodilation via tubuloglomerular feedback (Fig. 1) (9). Recently, empagliflozin was shown to reduce estimated glomerular filtration rate (eGFR) in the short term and preserve it in the long term, the classic response of preventing progressive injury by ameliorating glomerular hyperfiltration and associated intraglomerular hypertension (10).

Hyperglycemia has long been known to promote glomerular hyperfiltration in patients with diabetes (11). Renal hemodynamics are also influenced by lifestyle factors including diet and body weight. For example, high-protein diets lead to elevated levels of circulating amino acids. Hyperglycemia interacts with amino acids to trigger glomerular hyperfiltration. When diabetes is poorly controlled, the kidney has increased sensitivity to amino acids with an augmented glomerular hyperfiltration response (12–14). In both type 1 and type 2 diabetes, these aberrant renal hemodynamics are corrected by intensive glycemic control. Weight loss after bariatric surgery has similarly been shown to reduce glomerular hyperfiltration and albuminuria, a hallmark of early DKD, in obese people with and without type 2 diabetes (15,16). The precise mechanisms that activate obesity-related glomerular hyperfiltration are uncertain, but reduction in GFR has been shown to correlate with decrease in glycemia, even within the subdiabetes range.

In this issue of Diabetes, Ruggenenti et al. (17) report that modest weight loss (approximately 5%) induced by 6 months of calorie restriction reduced GFR and improved insulin sensitivity in study participants with type 2 diabetes, abdominal obesity, and normal kidney function. Notably, only 27% of participants had overt glomerular hyperfiltration, defined as measured GFR (single injection iohexol method) of greater than 120 mL/min at baseline. Nevertheless, both those with and without glomerular hyperfiltration had reductions in GFR during the study. These data indicate that even those with “normal” GFR by reference standards may be hyperfiltering above their personal baseline.

Change in GFR correlated with reduction in numerous risk factors for DKD and cardiovascular disease, including blood pressure, blood glucose and glucose disposal rate, serum levels of hs-CRP and angiotensin II, and albuminuria. However, in multiple regression models, only blood pressure (mean arterial pressure as the covariate) remained
an independent predictor of GFR. The authors appropriately emphasize the importance of systemic blood pressure as a modulator of glomerular hyperfiltration. In other words, lower blood pressure predicted lower GFR within the normal range. However, these study participants had normal blood pressure and no clinical evidence of kidney disease. Whether patients at higher risk of progressive DKD, such as those with hypertension, albuminuria, or low GFR, would respond in a similarly favorable manner to weight loss induced by calorie restriction cannot be determined by the current study.

The mediators driving glomerular hyperfiltration in diabetes have not been clearly elucidated despite detailed physiological studies of putative metabolic and hormonal factors (12,14). However, previous studies have pointed to the importance of dietary protein and hyperglycemia as key stimulatory and permissive influences, respectively (12,13,15). In the study by Ruggenenti et al. (17), the lack of association between these and other covariates with GFR in an exploratory multiple variable analysis with limited power does not preclude their biological relevance. Moreover, a potentially important finding was that animal protein intake declined even though total protein intake did not change in the calorie-restricted group. Higher animal-based protein (amino acids) intake has been associated with higher blood pressure among individuals with cardiovascular disease and with loss of kidney function in women with chronic kidney disease (18,19). Similarly, significant improvement in insulin sensitivity, as measured by the gold standard of the hyperinsulinemic-euglycemic clamp, is a relevant benefit of weight loss (17).

Glucose disposal rate will covary with blood glucose, and including both parameters in a multiple variable model may obscure significant relationships of insulin and glucose metabolism to GFR.

The study by Ruggenenti et al. (17) is an important contribution that refocuses and advances understanding

---

Figure 1 — Glomerular structural and functional relationships as determinants of GFR. In the study by Ruggenenti et al. (17) of participants with type 2 diabetes and obesity, weight loss by calorie restriction lowered systemic blood pressure, blood glucose, and GFR. This may be interpreted as a decrease in glomerular hyperfiltration and, inferentially, intraglomerular hypertension by both decreasing transmitted blood pressure and modulating tubuloglomerular feedback. A: Normal glomerulus. The balance between vasodilation and vasoconstriction in the afferent (upstream) and efferent (downstream) arterioles determines intraglomerular pressure, a major regulator of GFR. Distal tubular delivery of solute, particularly sodium chloride, at the macula densa regulates afferent arteriolar tone via tubuloglomerular feedback. B: Glomerulus in diabetes. The afferent arteriole opens in response to vasoconstrictive factors such as hyperglycemia and high blood levels of amino acids. Because of a high filtered load of glucose, reabsorption of glucose and sodium chloride is increased in the proximal tubule. The afferent arteriole also dilates in response to decreased delivery of sodium chloride to the distal tubular macula densa via tubuloglomerular feedback. The efferent arteriole vasoconstricts in response to high local production of angiotensin II. Overall, the balance shifts to glomerular hyperfiltration as a result of high intraglomerular pressure from afferent arteriolar vasodilation and efferent vasoconstriction.
of renal hemodynamic mechanisms in the diabetic kidney. These sorts of studies are exceptional achievements because they require intensive effort, complex procedures, and resolute persistence to complete. The findings are visibly meaningful because a simple intervention available in most settings, balanced caloric restriction to accomplish modest weight loss, altered GFR in the direction of normality. If such changes are maintained over time, then the risk of development and progression of DKD might be reduced. As the authors properly note, large long-term studies are required to confirm this hypothesis. In the meantime, reducing glomerular hyperfiltration is another possible benefit of modest weight loss in obese patients with type 2 diabetes who do not yet have kidney disease. Small changes may reap big rewards.

Acknowledgments. Nancy Correll, of Providence Medical Research Center and Providence Health Care, provided outstanding editorial assistance with preparation of the figure and manuscript.

Funding. K.R.T. has been supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (R34DK094016, U01DK201502Z223, U01 DK085689, 1U54DK083912, 1UC4DK101198-01, SUM1DK100846-02), National Heart, Lung, and Blood Institute (R01HL070938, 1U01HL071556-01A1), National Center for Advancing Translational Sciences (ULTR000423), Patient-Centered Outcomes Research Institute (PI12001), and State of Washington (RFP 7).

Duality of Interest. K.R.T. has been a consultant on DKD therapeutics for Eli Lilly and Company, Boehringer Ingelheim, and NOXXON Pharma. No other potential conflicts of interest relevant to this article were reported.

References
1. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 1986;77:1925–1930
2. Anderson S, Rennke HG, Garcia DL, Brenner BM. Short and long term effects of antihypertensive therapy in the diabetic rat. Kidney Int 1989;36:526–536
3. Mathew A, Cunard R, Sharma K. Antibiotic treatment and other new strategies for improving renal outcomes. Contrib Nephrop 2011;170:217–227
4. Himmelfarb J, Tuttle KR. New therapies for diabetic kidney disease. N Engl J Med 2013;369:2549–2550
5. Alicic RZ, Tuttle KR. Novel therapies for diabetic kidney disease. Adv Chronic Kidney Dis 2014;21:121–133
6. Dieter BP, Alicic RZ, Meeker RL, Anderberg RJ, Cooney SK, Tuttle KR. Novel therapies for diabetic kidney disease: storied past and forward paths. Diabetes Spectr 2015;28:167–174
7. Pichler R, Afkarian M, Dieter BP, Tuttle KR. Immunity and inflammation in diabetic kidney disease: translating mechanisms to biomarkers and treatment targets. Am J Physiol Renal Physiol. 24 August 2016 [Epub ahead of print]. DOI: 10.1152/ajprenal.00314.2016
8. Linde PG, Archdeacon P, Breyer MD, et al. Overcoming barriers in kidney health-forging a platform for innovation. J Am Soc Nephrol 2016;27:1902–1910
9. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752–772
10. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
11. Wiseman MJ, Mangili R, Alberetto M, Keen H, Viberti G. Glomerular response mechanisms to glycomic changes in insulin-dependent diabetes. Kidney Int 1987;31:1012–1018
12. Tuttle KR, Bruton JL, Perusek MC, Lancaster J, Kopp DT, DeFronzo RA. Effect of strict glycemic control on renal hemodynamic response to amino acids and renal enlargement in insulin-dependent diabetes mellitus. N Engl J Med 1991;324:1626–1632
13. Tuttle KR, Bruton JL. Effect of insulin therapy on renal hemodynamic response to amino acids and renal hypertrophy in non-insulin-dependent diabetes. Kidney Int 1992;42:167–173
14. Tuttle KR, Puhlman ME, Cooney SK, Short RA. Effects of amino acids and gluconon renal hemodynamics in type 1 diabetes. Am J Physiol Renal Physiol 2002;282:F103–F112
15. Chagnac A, Weinstein T, Herman M, Hirsh J, Gaffer U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol 2003;14:1480–1486
16. Friedman AN, Wolfe B. Is bariatric surgery an effective treatment for type II diabetic kidney disease? Clin J Am Soc Nephrol 2016;11:528–535
17. Ruggenenti P, Abbate M, Ruggiero B, et al.; C.R.E.S.O. Study Group. Renal and systemic effects of calorie restriction in patients with type 2 diabetes with abdominal obesity: a randomized controlled trial. Diabetes 2017;66:75–86
18. Tuttle KR, Milton JE, Packard DP, Shuler LA, Short RA. Dietary amino acids and blood pressure: a cohort study of patients with cardiovascular disease. Am J Kidney Dis 2012;59:803–809
19. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 2003;138:460–467