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EDITORIAL

Diabetes and the Kidney: Sweet Dreams

A spoonful of sugar makes the medicine go down.
—Robert B. Sherman, Richard M. Sherman; 1964

With apologies to Julie Andrews, a spoonful of sugar might be considered child abuse in this modern era of diabetes and obesity. As of 2015, more than 700 million adults worldwide have diabetes or impaired glucose tolerance, and about half of these are unaware of the diagnosis.[1] Almost certainly, the glut of type 2 diabetes has been fueled by the expanding obesity epidemic (pun intended). In the United States, the prevalence of obesity tripled from 13% in 1960 to 38% in 2014.[2] With respect to kidney disease, diabetes remains the most common cause of ESRD in the US, with an adjusted prevalence of nearly 800 per million people and rising.[3]

This parade of dreary statistics is enough to make even the most cheerful reader want to give up and eat a cookie. However, therapy for diabetes is rapidly evolving, and nephrologists and their patients have benefitted from many hypoglycemic medications. Metformin, one of the most effective and least expensive drugs, is now considered safe to prescribe in patients with CKD, with an estimated glomerular filtration rate (GFR) of at least 30 mL/min/1.73 m^2, without fear of lactic acidosis.[4,5] Liraglutide, a glucagon-like peptide 1 analog, decreases the risk of cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke, all of which are common hazards of CKD.[6]

However, no therapy in recent history has sparked as much excitement as the sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2, one of 12 members of the SGLT gene family, plays the dominant role in reclamation of glucose by the kidney.[7] Of the 180 g/d/1.73 m^2 glucose normally filtered through the glomerulus, 90% is reabsorbed by SGLT2 in a 1:1 ratio with sodium across the brush border epithelium of the S1 segment of the proximal tubule. The remaining 10% is reabsorbed by SGLT1 in later segments of the proximal tubule. In diabetes, hyperglycemia increases glucose filtration, and the proximal tubule undergoes hypertrophy in an attempt to reabsorb the massively increased filtered load of glucose. Because much more glucose is reabsorbed in the proximal tubule, and because glucose and sodium absorption are linked, much less sodium is delivered to the distal tubule. The macula densa interprets this low sodium (and chloride) delivery as low GFR and decreases tubuloglomerular feedback (TGF).[8,9] TGF is the mechanism by which the macula densa causes vasoconstriction of the afferent arteriole by releasing adenosine, 20-hydroxyeicosatetraenoic acid, and other signaling molecules. Inhibition of TGF allows the afferent arteriole to vasodilate. This vasodilation is maladaptive and causes glomerular hyperfiltration, which is thought to underlie the pathogenesis of diabetic kidney disease (DKD).[10] Accordingly, patients with early DKD demonstrate a "salt paradox," in which dietary sodium restriction actually increases GFR, often to more than 130 mL/min/1.73 m^2.[11]

SGLT2 inhibitors appear to disrupt this nefarious cascade. These agents were ostensibly developed to improve glycemic control by inducing glucosuria, but maybe more importantly, they seem to improve CV and kidney outcomes by inducing proximal tubule natriuresis.[12] Restoring sodium delivery to the macula densa should re-establish TGF and attenuate glomerular hyperfiltration. SGLT2 inhibitors act as advertised in animal models. In Akita diabetic mice, empagliflozin normalized GFR at 12 weeks, with decreased urine albumin excretion (UAE), glomerular size, and kidney weight.[13] SGLT2 inhibitors also deliver in clinical trials. In type 1 diabetics, empagliflozin 25 mg daily also decreased GFR, measured by inulin clearance, at 8 weeks (172 to 139 mL/min/1.73 m^2), but only in subjects with hyperfiltration. Those with normal glomerular filtration were unaffected.[10] Effective kidney plasma flow and kidney vascular resistance also normalized in hyperfiltering subjects. Parenthetically, afferent arteriolar vasodilation and hyperfiltration injury may cause other lesions, such as obesity-related glomerulopathy and some forms of focal segmental glomerulosclerosis. In a trial of obese, nondiabetic men with glomerular hyperfiltration,

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acetazolamide decreased GFR by 21% and increased kidney vascular resistance by 12%, whereas furosemide produced no change.[14] Acetazolamide and empagliflozin seem to temper glomerular hyperfiltration by the same mechanism: blocking a proximal tubule sodium transporter, boosting sodium delivery to the macula densa, and normalizing TGF and afferent arteriolar tone.

The icing on the cake was the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial, in which 7,020 type 2 diabetics were randomized to receive empagliflozin or placebo for about 3 years.[15] This study showed a 32-38% reduction in all-cause mortality, CV mortality, and hospitalization for heart failure. A separate analysis also revealed a 38-55% reduction in progression to macroalbuminuria (urine albumin-creatinine ratio $>$ 300 mg/g), decreased kidney function, and dialysis initiation.[16] The American Diabetes Association 2017 Standards of Medical Care considers the current evidence compelling enough to recommend empagliflozin for type 2 diabetics with CV disease to reduce the risk of CV death. Empagliflozin is the first diabetes medication to be approved by the Food and Drug Administration for this indication.[17,18]

Do the other SGLT2 inhibitors offer the same benefits as empagliflozin? All currently available SGLT2 inhibitors are congeners of phlorizin, a glucoside found in the root bark of fruit trees, which nonspecifically blocks a number of sugar transporters.[19] The more selective, orally bioavailable SGLT2 inhibitors, thus share a biochemical ancestor and provide similar glycemic control. Large clinical trials with canagliflozin and dapagliflozin are currently underway and will reveal whether the CV and renal values of empagliflozin can be generalized to the class of SGLT2 inhibitors.[20]

The next step in therapy, which will be a logical extension of this physiologic strategy, will be to combine SGLT2 inhibitors with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Dual blockade within the renin-angiotensin system (RAS) seems fruitless, as shown by trials such as Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, and Veterans Affairs Nephropathy in Diabetes.[21-23] Nonetheless, for more than 30 years, RAS blockers have been thought to confer kidney protection by decreasing efferent arteriolar vasoconstriction, thus decreasing glomerular capillary hydrostatic pressure.[24] On the other hand, SGLT inhibitors are thought to confer similar protection by decreasing afferent arteriolar vasodilation. Would dual blockade with a RAS inhibitor and an SGLT2 inhibitor achieve even lower glomerular capillary hydrostatic pressure and bestow synergistic benefits? This possibility is borne out in salt-sensitive, diabetic Dahl rats: combination therapy with luseogliflozin and lisinopril, compared to either agent alone, maximally reduced urine protein excretion, glomerular injury, and cortical and outer medullary fibrosis.[25] Only time, and careful clinical investigation, will tell whether these theoretical advantages will translate to improved patient care.

While this hemodynamic approach to DKD has made a quantum leap, a parallel, cellular approach has been percolating in relative obscurity with nearly as much promise. In the nucleus, genetic and epigenetic (ie, hyperglycemia-mediated) factors increase the risk of DKD at the transcriptional and translational levels.[26] In the cytoplasm, hyperglycemia causes a shift in glucose utilization from the glycolytic to the hexosamine and polyol pathways.[27] This alternative biochemistry, in turn, stimulates protein kinase C and poly(ADP-ribose) polymerase-1 and gives rise to advanced glycation end products, reactive oxygen species, and most recently appreciated, uric acid.[28] In the kidney, endothelial and mesangial cells are both affected by the diabetic milieu, but podocyte loss may be the most ominous result. Poly(ADP-ribose) polymerase-1 activation and reactive oxygen species generation lead to podocyte dedifferentiation, effacement, and apoptosis, and podocyte number is one of the best predictors of GFR, albuminuria, and glomerulosclerosis in DKD.[29]

This metabolic muddle offers many opportunities to intervene, some with currently approved medications. The activated vitamin D analog, paricalcitol, moderately decreased UAE (18-28%) in some trials of diabetics with albuminuria, although more robust clinical outcomes were not demonstrated.[30-32] Pentoxifylline, a tumor necrosis factor-α inhibitor, has been a second-line agent in the CKD armamentarium, but a recent trial of 169 type 2 diabetics with CKD showed improved estimated GFR and UAE at 2 years with this drug (differences of 4.3 mL/min/1.73 m^2 and 20.6%, respectively, favoring pentoxifylline).[33] Finally, the xanthine oxidase inhibitors, allopurinol and febuxostat, have attracted notice by consistently decreasing kidney and CV events (57-68%) in small trials of subjects with CKD, some of whom had diabetes; the Preventing Early Renal Function Loss in Diabetes trial of allopurinol in 490 type 1 diabetics with CKD, albuminuria, and hyperuricemia is currently under way.[34-36]

Novel agents are in earlier stages of development. The ill-fated bardoxolone methyl, a triterpenoid antioxidant and potent activator of Nrf2 (nuclear factor [erythroid-derived 2]-like 2), was abandoned due to a high rate of CV events in a phase 3 trial, but a bardoxolone derivative decreased atherosclerosis and glomerular and tubular injury in diabetic mice and may reopen this field of inquiry for clinical studies.[37,38] Nonselective endothelin receptor A and B (ET_A and ET_B) antagonists have also performed erratically, as ET_A blockade is beneficial (improved proteinuria and kidney function) but ET_B blockade is deleterious (sodium retention, peripheral edema, and congestive heart failure); selective ET_A inhibitors such as avosentan and sitaxsentan were similarly unsuccessful, but based on encouraging results from early studies (23-30% decreased risk of doubling of creatinine or ESRD at 3 years), the Study of Diabetic Nephropathy with Atrasentan trial is currently recruiting.[39] Finally, countless "blue skies" approaches in their therapeutic infancy include inhibiting inflammatory and fibrosis molecules, such as Janus kinase, protein

kinase C, tumor necrosis factor-α, transforming growth factor-β, and matrix metalloproteinases.[31]

These and countless other therapeutic approaches are only the beginning of a groundswell of basic and clinical scientific inquiry for treating DKD. Although the prevalence of obesity and diabetes has been growing for decades, and will almost assuredly continue to swell for decades to come, the incidence of ESRD attributed to diabetes has begun to plateau.[3] These divergent trend lines suggest that our existing therapy for DKD, including weight management with diet and exercise, glycemic and blood pressure control, and proteinuria reduction with RAS inhibitors and ancillary pharmaceuticals has already begun to pay dividends. A spoonful of sugar may help both the medicine and the kidney function go down, but there is cause for optimism. With the SGLT2 inhibitors and other novel therapeutics beginning to enjoy their day in the sun, we can hope that someday soon, all diabetic kidneys will dream sweet dreams.

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