Activation of the Tubulo-Glomerular Feedback by SGLT2 Inhibitors in Patients With Type 2 Diabetes and Advanced Chronic Kidney Disease: Toward the End of a Myth?

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Early after the onset of type 1 diabetes, patients exhibit a transient increase in glomerular filtration rate (GFR). This hyperfiltration is associated with hyperplasia of proximal convoluted tubules with increased expression of sodium–glucose cotransporter 2 (SGLT2), leading to increased proximal sodium reabsorption, decreased sodium delivery to the distal convoluted tubules, and inhibition of the tubulo-glomerular feedback, which induces afferent arteriole vasodilation and glomerular hyperfiltration. SGLT2 inhibitors (SGLT2i) decrease sodium reabsorption in proximal convoluted tubules and increase sodium delivery to the macula densa, thereby reactivating the tubulo-glomerular feedback. Hence, vasodilation of afferent arteriole is hindered, and intraglomerular pressure is decreased. However, reactivation of the tubulo-glomerular feedback is unlikely to occur in type 2 diabetes with more advanced chronic kidney disease (CKD) for several reasons:

First, in type 1 diabetes, SGLT2i significantly reduced GFR in patients with hyperfiltration (i.e., inulin-measured GFR $\geq$136 mL/min/1,73 m^2) during euglycemic as well as hyperglycemic clamps. This finding was associated with decreased plasma nitric oxide levels and effective renal plasma flow, and increased renal vascular resistance, suggesting reactivation of the tubulo-glomerular feedback. In congenital SGLT2 knockout with normal kidney function, the tubulo-glomerular feedback may be acutely stimulated by diuretics (1). However, patients with type 1 diabetes with true GFR $<$135 mL/min/1.73 m^2 did not exhibit this effect after 8-week administration of SGLT2i (2). This observation suggests that reactivation of the tubulo-glomerular feedback by SGLT2i only occurs at a stage of hyperfiltration. Therefore, in patients with type 2 diabetes, the more severe the CKD, the less likely that the tubule-glomerular feedback will be reactivated by SGLT2i.

Second, patients without diabetes do not have increased expression of SGLT2 in convoluted tubules and therefore cannot exhibit an inhibition of the tubulo-glomerular feedback. If tubulo-glomerular feedback was involved in the antiproteinuric effect of SGLT2i, this antiproteinuric effect should be stronger in patients with diabetes than in patients without diabetes. Actually, the nephroprotective effect of SGLT2i in patients without diabetes matches that of patients with diabetes.

Third, pathological studies in diabetic and hypertensive CKD show progressive intrarenal arterial stiffening with arteriosclerosis and arteriolar hyalinosis of the afferent arteriole that correlates with loss of autoregulation of the renal blood flow (3). This leads to progressive glomerular ischemia, hence, the opposite of hyperfiltration.

Fourth, along with SGLT2i, acetazolamide also increases the delivery of sodium to the distal segments of the tubules. However, tubulo-glomerular feedback reactivation by acetazolamide has never been described in patients with type 2 diabetes and GFR $<$60 mL/min/1.73 m^2.

Fifth, in one study investigators did analyze the renal hemodynamic effects of SGLT2i in patients with type 2 diabetes. Using gold standard GFR and plasma flow measures, the filtration fraction and renal vascular resistance were calculated. During both euglycemic and hyperglycemic clamps, SGLT2i did not increase renal vascular resistance, suggesting that the decreased filtration fraction was secondary to efferent arteriole vasodilation rather than afferent arteriole vasoconstriction (4).

Therefore, what could be the mechanism underlying SGLT2i-mediated decrease of intraglomerular pressure with acute loss of eGFR and subsequent albuminuria decrease in patients with type 2 diabetes with advanced CKD, on top of renin-angiotensin system (RAS) blockade?

Blockade of the RAS remains the cornerstone of proteinuria management and renal protection in patients with diabetes. However, volume overload inhibits RAS (due to renin inhibition) and

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decreases the efficacy of RAS blockers for hypertension and proteinuria. Diuretics decrease proteinuria when added to RAS blockers, even on top of salt restriction, and better than dual RAS blockade with ACE inhibitors and angiotensin receptor blockers (5). Diuretics were widely used in association with RAS blockers in renal studies. In fact, 84% of the patients with diabetes included in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study received both losartan and diuretics. SGLT2i act by inhibiting sodium-glucose cotransport in proximal convoluted tubules. SGLT2i increase natriuresis and rapidly decrease both body weight (mimicking thiazide-induced volume depletion) and blood pressure. When GFR falls below 60 mL/min/1.73 m^2, SGLT2i have a marginal effect on glycemia but still exert clinically significant antihypertensive activity, suggesting that a modest inhibition of sodium reabsorption in proximal convoluted tubules remains clinically significant in these patients.

In conclusion, SGLT2i may not act on tubulo-glomerular feedback and afferent glomerular arterioles in patients with type 2 diabetes and advanced CKD but, rather, more likely exert a synergistic effect with RAS blockers on efferent glomerular arterioles, most likely by controlling volume overload, just like they prevent congestion in heart failure. Beyond decreased intraglomerular pressure, the benefit of SGLT2 inhibitors is most likely explained by pleiotropic mechanisms, including blood pressure reduction as well as favorable effects on vascular function, reduction in tubular workload and hypoxia, and metabolic effects.

Duality of Interest. V.L.M.E. reports personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Janssen, personal fees from Bristol-Myers Squibb–Pfizer, personal fees from Novartis, personal fees from Bayer, and personal fees from Merck Sharp & Dohme, outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

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