Totally tubular, dude: rethinking DKD pathogenesis in the wake of SGLT2i data

Samuel Mon-Wei Yu¹ · Jeremy S. Leventhal² · Paolo Cravedi¹

Published online: 23 September 2020
© Italian Society of Nephrology 2020

Keywords Sodium glucose co-transporter 2 · Diabetic kidney disease · Proximal tubule · Tubuloglomerular feedback · Autophagy

Renoprotective effects of sodium-glucose co-transport 2 inhibitors (SGLT2i) represent a hallmark success after decades searching for novel diabetic kidney disease (DKD) treatments. In 2019, results from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) showed that SGLT2i treatment significantly reduced progression to end-stage kidney disease (ESKD), doubling of creatinine, as well as the incidence of several cardiovascular outcomes [1]. CREDENCE cemented SGLT2i as pillars, along with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), of pharmacological DKD therapy. Despite ever-growing use, controversy persists regarding how blocking one transporter produces such remarkable clinical improvements.

Dominant DKD pathogenesis theories revolve around podocyte injury, stemming from observations that early DKD manifestations include albuminuria. Most benefits of ACEi or ARB therapy are attributed to the correction of intraglomerular pressures and single nephron GFR (SNGFR). Glomerular filtration rate (GFR) is tightly controlled by two mechanisms: glomerular vascular tone (afferent and efferent arterioles) and urinary ion concentration (i.e., Cl^-). The *macula densa*, via Na-K-Cl co-transporter 2 (NKCC2), responds to increased Cl^- delivery with adenosine-mediated afferent arteriole vasoconstriction and decreased SNGFR. This phenomenon, known

as tubuloglomerular feedback (TG), helps maintain renal physiological homeostasis, and its dysregulation prominently mediates DKD. Hyperglycemia increases proximal Na^+/Cl^- reabsorption, decreasing concentrations sensed by *macula densa* cells and preventing appropriate SNGFR regulation. SGLT2i prevents this phenomenon, increases distal tubule Cl^- delivery, and, ostensibly, corrects TG/intraglomerular hemodynamics similarly to ACEi/ARB therapy. Many believe this mechanism predominantly explains clinical trial findings. However, by using measured GFR (mGFR) in type 2 DM patients on dapagliflozin, van Bommel et al. [2] demonstrated that dapagliflozin does *not* cause afferent arteriole constriction but, rather, post-glomerular vasodilatation. Whether these conflicting results represent a “class-effect” or differences among individual SGLT2i would require further studies to elucidate.

Aside from correcting TG feedback issues, how do SGLT2i protect from DKD progression? Growing evidence points to improved tubular homeostasis behind SGLT2i effects on DKD pathogenesis. SGLT2 is primarily expressed on brush borders of S1 proximal tubule segments, and its expression is increased by 40–80% with persistent glycosuria. Induced apical membrane SGLT2 expression maximizes glucose reabsorption, but also increases Na^+/K^+ -ATPase activity and oxygen consumption—causing hypoxia and tubular injury. Blocking SGLT2 may thereby improve proximal tubule oxygenation. Secondly, hyperglycemia itself also triggers tubular growth in response to various stimuli during the early hyperplastic to late hypertrophic phase, reflected by the enlarged size of kidneys commonly seen in diabetic patients (comprehensive review in [3]). After empagliflozin treatment in Akita mice, however, kidney growth was only partially attenuated, suggesting that tubular growth is regulated by not only luminal glucose delivery but also by other mechanisms. For instance, forms of familial renal

✉ Paolo Cravedi
paolo.cravedi@mssm.edu

¹ Department of Medicine, Translational Transplant Research Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA

² Division of Nephrology, White Plains Hospital, White Plains, NY, USA

hyperglycosuria where SGLT2 is missing do not develop progressive renal disease [4]. Lastly, a notion that increasing tubular senescence in both human and murine models of DKD might lead to maladaptive repair in chronic hyperglycemia milieu, but whether SGLT2i would modify the aging process requires further studies.

In a recent review [5], Packer suggests that restoration of autophagy represents an additional mechanism contributing to the renoprotective effects of SGLT2i. Autophagy, an intracellular catabolic process, maintains energy resources during nutritional deprivation by selectively sequestering and degrading organelles. This intricate process is predominantly regulated by two ubiquitously expressed proteins, mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). The mTOR complex 1 (mTOR1), a major sensor of intracellular amino acid, promotes protein synthesis (anabolism) and inhibits autophagy. Conversely, energy stress and an increased AMP/ATP ratio enhance AMPK activity as well as autophagy. AMPK-triggered autophagy regenerates the necessary nutrients from damaged/excess organelles. Increasing evidence indicates intact autophagy is necessary to slow DKD. For instance, podocyte-specific deletion of *Atg5*, a crucial autophagy protein, accelerated podocyte loss in murine models of both type 1 and 2 DM. Given its glycosuric effects, SGLT2i remarkably alters cellular metabolism in proximal tubules and, possibly, podocytes [6], toward a nutritional deprivation state, and thereby activates the AMPK pathway. Moreover, recent data support that SGLT2i augment ketolysis and inhibit mTORC1—an effect that ostensibly increases autophagy [7].

Another important modulator of autophagy and glucose homeostasis is sirtuin-1 (SIRT1). SIRT1 downregulation occurs during DKD in both proximal tubules and podocytes, likely due to increased insulin resistance, and has been implicated in diminished autophagy and mitochondrial injuries. An indirect effect of tubular SIRT1 expression on podocytes was revealed by Hasegawa et al. [8], who used genetically modified murine models and demonstrated that overexpression of SIRT1 mitigated albuminuria in DKD (*db/db*) mice. By contrast, deleting SIRT1 in proximal tubules exacerbated glomerular dysfunction from increased expression of claudin-1, a protein resulting in aberrant tight junction by interacting with podocin and nephrin. Similar to AMPK, SGLT2i may upregulate SIRT1 expression in proximal tubules due to glucose wasting, and therefore stabilize slit diaphragm between podocytes in addition to enhanced autophagy influx in proximal tubules.

Proximal tubules are the main focus of putative SGLT2i effects, but evidence suggests that other areas are targeted. For instance, Cassis et al. [9] reported an upregulation of podocyte SGLT2 expression in a murine model of protein-overloaded proteinuria induced by bovine serum albumin (BSA), and treatment with SGLT2i dapagliflozin

significantly improved albuminuria via restoration of cytoskeletal remodeling in the podocytes. More recently, abnormal tubular cell glucose metabolism has been implicated in acute kidney injury (AKI)-associated mortality, further highlighting the pivotal role of glucose homeostasis particularly in tubules. In conclusion, the extraordinary clinical success of SGLT2i, while improving outcomes of DKD, paved the way for a better understanding of DKD pathophysiology, possibly leading to the identification of new therapeutic targets for this and other progressive kidney diseases.

Compliance with ethical standards

Conflict of interest All authors listed here declare that they have no conflicts of interests.

Ethical approval The article does not contain any studies involving human participants or animals.

References

1. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW, Investigators CT (2019) Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. *N Engl J Med* 380(24):2295–2306. <https://doi.org/10.1056/NEJMoa1811744>
2. van Bommel EJM, Muskiet MHA, van Baar MJB, Tonneijck L, Smits MM, Emanuel AL, Bozovic A, Danser AHJ, Geurts F, Hoorn EJ, Touw DJ, Larsen EL, Poulsen HE, Kramer MHH, Nieuwdorp M, Joles JA, van Raalte DH (2020) The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int* 97(1):202–212. <https://doi.org/10.1016/j.kint.2019.09.013>
3. Vallon V, Thomson SC (2020) The tubular hypothesis of nephron filtration and diabetic kidney disease. *Nat Rev Nephrol* 16(6):317–336. <https://doi.org/10.1038/s41581-020-0256-y>
4. Santer R, Calado J (2010) Familial renal glucosuria and SGLT2: from a mendelian trait to a therapeutic target. *Clin J Am Soc Nephrol* 5(1):133–141. <https://doi.org/10.2215/CJN.04010609>
5. Packer M (2020) Role of impaired nutrient and oxygen deprivation signaling and deficient autophagic flux in diabetic ckd development: implications for understanding the effects of sodium-glucose cotransporter 2-inhibitors. *J Am Soc Nephrol JASN* 31(5):907–919. <https://doi.org/10.1681/ASN.2020010010>
6. Korbut AI, Taskaeva IS, Bgatova NP, Muraleva NA, Orlov NB, Dashkin MV, Khotskina AS, Zavyalov EL, Konenkov VI, Klein T, Klimontov VV (2020) SGLT2 inhibitor empagliflozin and dpp4 inhibitor linagliptin reactivate glomerular autophagy in *db/db* mice, a model of type 2 diabetes. *Int J Mol Sci*. <https://doi.org/10.3390/ijms21082987>

7. Tomita I, Kume S, Sugahara S, Osawa N, Yamahara K, Yasuda-Yamahara M, Takeda N, Chin-Kanasaki M, Kaneko T, Mayoux E, Mark M, Yanagita M, Ogita H, Araki SI, Maegawa H (2020) SGLT2 inhibition mediates protection from diabetic kidney disease by promoting ketone body-induced mTORC1 inhibition. *Cell Metab*. <https://doi.org/10.1016/j.cmet.2020.06.020>
8. Hasegawa K, Wakino S, Simic P, Sakamaki Y, Minakuchi H, Fujimura K, Hosoya K, Komatsu M, Kaneko Y, Kanda T, Kubota E, Tokuyama H, Hayashi K, Guarente L, Itoh H (2013) Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes. *Nat Med* 19(11):1496–1504. <https://doi.org/10.1038/nm.3363>
9. Cassis P, Locatelli M, Cerullo D, Corna D, Buelli S, Zanchi C, Villa S, Morigi M, Remuzzi G, Benigni A, Zoja C (2018) SGLT2 inhibitor dapagliflozin limits podocyte damage in proteinuric non-diabetic nephropathy. *JCI Insight*. <https://doi.org/10.1172/jci.insight.98720>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.