Mitigation of the Adverse Consequences of Nutrient Excess on the Kidney: A Unified Hypothesis to Explain the Renoprotective Effects of Sodium-Glucose Cotransporter 2 Inhibitors

Milton Packer^{a, b}

^aBaylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA; ^bImperial College, London, UK

Keywords

Nephropathy · Autophagy · Diabetes · Sodium-glucose 2 transporters

Abstract

The 2 most common causes of chronic kidney disease worldwide (type 2 diabetes and obesity) are states of nutrient excess, suggesting that fuel overabundance leads to deleterious effects on the structure and function of the kidneys. Three pathophysiological pathways may potentially explain this linkage. First, both obesity and type 2 diabetes are characterized by glomerular hyperfiltration, which may result from increased proximal tubular reabsorption of sodium (due to enhanced glucose and sodium transport) coupled with activation of the renin-angiotensin system. Second, both obesity and type 2 diabetes are characterized by adipose tissue expansion and inflammation, followed by the augmented synthesis and release of lipid intermediates and proinflammatory adipocytokines that can have deleterious effects on the kidney. Third, states of nutrient excess cause a diminution in the activation of the energy sensors, sirtuin-1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK). The result is a suppression of autophagy, a lysosomal degradative pathway that is respon-

sible for the clearance of damaged organelles that are an important source of oxidative and endoplasmic reticulum stress and inflammation. Sodium-glucose cotransporter 2 (SGLT2) inhibitors induces a transcriptional paradigm that mimics fasting, which leads to the amelioration of glomerular hyperfiltration and adipose tissue inflammation as well as augmentation of AMPK/SIRT1 signaling and autophagy, thereby acting to mute organellar and cellular stress in the kidney. Therefore, SGLT2 inhibitors are positioned to antagonize all 3 pathways by which nutrient excess can lead to nephropathy.

© 2020 S. Karger AG, Basel

Obesity and type 2 diabetes represent 2 of the most common causes of chronic kidney disease worldwide. Marked weight loss or intensive glucose control can ameliorate the course of nephropathy and reduce the risk of end-stage renal disease. Interestingly, both obesity and diabetes represent states of nutrient excess, raising the possibility that caloric overabundance per se exerts deleterious effects on renal function. This paradigm has important implications for understanding the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors in preventing chronic kidney disease.

Fig. 1. Pathophysiological mechanisms by which nutrient excess may lead to renal injury and nephropathy. AMPK, adenosine monophosphate-activated protein kinase; NHE-3, sodium-hydrogen exchanger isoform 3; SIRT1, sirtuin-1; SGLT2, sodium-glucose cotransporter 2.

Mechanisms by Which States of Nutrient Excess May Cause Renal Injury

Three broad pathophysiological pathways could explain a linkage between nutrient excess and renal injury (Fig. 1).

Nutrient Excess in Obesity and Type 2 Diabetes Causes Glomerular Hyperfiltration

Both obesity and type 2 diabetes are characterized by increased renal plasma flow, filtration fraction, and glomerular filtration rate. Renal plasma flow increases to a lesser extent than glomerular filtration rate, implying the presence of renal vasodilation involving predominantly the glomerular afferent arteriole. Interestingly, both obesity and diabetes are accompanied by increased sodium and glucose reabsorption in the proximal renal tubule. The increased glucose absorption heightens the state of nutrient excess, whereas the enhanced sodium reabsorption contributes to the plasma volume expansion that supports an increased body mass. These proximal tubular events have been attributed to increased activity of the SGLT2 acting in concert with enhanced activity of sodium-hydrogen exchanger isoform 3 (NHE-3) [1]. As proximal renal tubular sodium transport is augmented, sodium delivery to the macula densa is diminished, leading (through tubuloglomerular feedback) to afferent arteriolar vasodilation. Additionally, both obesity and type 2 diabetes are accompanied by activation of the renin-angiotensin system [2], which not only promotes hypertension but acts preferentially to constrict the efferent arteriole. The combined effect of afferent arteriolar dilatation and efferent arteriolar constriction serves to increase glomerular filtration pressures, which (if sustained) can cause glomerular injury.

Nutrient Excess in Obesity and Type 2 Diabetes Causes Adipose Tissue Inflammation with Its Adverse Effects on the Kidney

Nutrient excess leads to an expansion of adipose tissue, whose hypertrophy is accompanied by transformation of its biology to a proinflammatory state. While brown adipose tissue combusts fatty acids and nourishes nearby tissues, white adipose tissue release fatty acids as well as proinflammatory adipocytokines, which can cause localized and systemic inflammation. Both obesity and diabetes are characterized by meaningful adipose tissue inflammation [3]. In both disorders, the infiltration of macrophages (with an altered polarization) into adipose tissue is accompanied by increased synthesis of proinflammatory cytokines (including leptin, tumor necrosis factor- α and interleukins 1 β and 6) and decreased production of adiponectin, thus leading to insulin resistance, particularly in patients with meaningful visceral adiposity.

Expansion of perirenal fat depots can cause a transmission of this inflammatory biology to the underlying renal parenchyma [4]. Additionally, both obesity and type 2 diabetes are accompanied by increased circulating levels of lipid intermediates (diacylglycerols and ceramides), which may promote renal insulin resistance and exert lipotoxic effects on the kidney [5]. Importantly, the adipose tissue inflammation in obesity and type 2 diabetes enhances the release of adipocytokines (e.g., leptin), which have been linked to renal inflammation and fibrosis. Leptin activates renal mesangial cells, promotes tubular inflammation, induces dysfunction of renal endothelial cells, and contributes to kidney fibrosis [5]. Leptin also potentiates activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, thereby promoting renal

tubular sodium reabsorption [5]. These actions may explain why circulating levels of leptin can predict the decline in glomerular filtration rate in the general population [6].

Nutrient Excess in Obesity and Type 2 Diabetes Suppresses Autophagy-Mediated Cellular Housekeeping in the Kidney

Nutrient excess suppresses autophagy, a lysosomally mediated degradative pathway that maintains cellular homeostasis by removing potentially dangerous constituents and recycling cellular components [7]. The primordial stimulus to autophagy is starvation, since the process aims to generate intracellular nutrients and ATP. However, increased autophagic flux serves the essential function of clearing the cytoplasm of damaged organelles and other injurious components, which are an important source of oxidative and endoplasmic reticulum stress. These cellular stresses can exert meaningful nephrotoxic effects.

Since autophagy is activated by starvation, autophagic flux is characteristically depressed in the states of nutrient excess (obesity and diabetes), especially in the kidney [8]. Impairment of autophagy has been implicated in the pathogenesis of both the glomerular and tubular lesions in diabetic nephropathy, particularly in the genesis of the podocyte injury that can lead to proteinuria and the derangements of proximal and distal tubular function that have been linked to advanced glycation end-products [9]. Two important stimuli to autophagy are the low-energy sensors, adenosine monophosphate-activated protein kinase (AMPK) and sirtuin-1 (SIRT1) [10]. AMPK discerns the balance between ATP and AMP in the cytosol, and SIRT1 is sensitive to levels of nicotinamide adenine dinucleotide and thus serves as a redox rheostat. Activation of AMPK and SIRT1 is essential to the ability of the kidney to minimize oxidative stress, a benefit that is likely to be mediated (in large part) by their action to promote autophagic flux. Yet, renal AMPK and SIRT1 activity is meaningfully diminished in both obesity and diabetes [10]; the reduction in low-energy sensor signaling can lead to the development of organellar dysfunction, cellular inflammation, and nephropathy.

Negation of Nutrient Excess Signaling by SGLT2 Inhibitors and Its Role in the Prevention of Nephropathy

SGLT2 inhibitors induce a biological state that mimics starvation, that is, these drugs trigger a fasting-like transcriptional paradigm [11]. Metabolically, SGLT2 inhibi-

tors increase the loss of calories in the urine, an effect that is accompanied by ketonemia, a marker of nutrient deprivation. The action of SGLT2 inhibitors to negate nutrient excess signaling in obesity and type 2 diabetes may ameliorate each of the potentially nephrotoxic mechanisms that are evoked by states of nutrient excess, that is, glomerular hyperfiltration, adipose tissue inflammation, and the suppression of autophagy-mediated cytoprotection.

SGLT2 Inhibitors Can Ameliorate the Glomerular Hyperfiltration That Is Seen in States of Nutrient Excess

SGLT2 inhibitors exert an immediate effect to antagonize the glomerular hyperfiltration that is seen in type 2 diabetes. Initiation of treatment with these drugs is accompanied by a rapid decline in glomerular filtration rate, which appears to be related to an intrarenal hemodynamic action of these drugs; the effect is rapidly reversed when exposure to these agents is discontinued, even after years of treatment [12]. Although the mechanism by which SGLT2 inhibitors act to decompress intraglomerular pressures is uncertain, it is noteworthy that SGLT2 inhibitors interfere with proximal tubular sodium reabsorption, and thus, enhance the delivery of sodium to the macula densa and promote tubuloglomerular feedback, thereby mitigating afferent arteriolar vasodilation [12]. According to the prevailing hypothesis, this action of SGLT2 inhibitors is linked to their glycosuric effect, that is, their action on the sodium-glucose cotransporter.

However, it is possible that SGLT2 inhibitors can interfere with proximal tubular sodium reabsorption in a manner that is independent of glycosuria. Most of the proximal tubular reabsorption of sodium in diabetes is mediated by increased activity of the NHE-3 [1], and SGLT2 and NHE-3 are colocalized and functionally intertwined in the early proximal tubule. Experimental knockout of NHE-3 depresses the expression of SGLT2 [13], and conversely, inhibition of SGLT2 interferes with the activity of NHE-3 [14]. A similar interplay between NHE-3 and the sodium-glucose cotransporter may also occur in the small intestinal epithelium, and an action to inhibit NHE-3 may explain the effect of acetazolamide to promote tubuloglomerular feedback in patients with obesity-related glomerular hyperfiltration [15]. Therefore, by interfering with the activity of proximal tubular NHE-3, SGLT2 inhibitors may be able to ameliorate glomerular hyperfiltration and reduce the progression of kidney disease in a manner that is independent of their actions on either glycemia or glycosuria.

Despite the appeal of this framework, it is important to note that the glycosuric and intrarenal hemodynamic effects of SGLT2 inhibitors are markedly attenuated when the glomerular filtration rate declines (e.g., <60 mL/min/1.73 m²). Yet, SGLT2 inhibitors exert meaningful renoprotective effects even in patients whose glomerular filtration rate is 20–60 mL/min/1.73 m² [16]. This observation suggests that the SGLT2 inhibitors to ameliorate glomerular hyperfiltration may be insufficient to explain the effect of these drugs to preserve renal function in large-scale trials. Such a finding is consistent with experimental studies showing that knock-out of SGLT2 attenuates glomerular hyperfiltration but does not prevent renal injury, inflammation, or fibrosis [17].

SGLT2 Inhibitors Subdue the Adipose Tissue Inflammation That Is Seen in Obesity and Type 2 Diabetes

SGLT2 inhibitors cause weight loss, which is in part related to caloric loss in the urine and in part related to increase energy expenditures. By promoting lipolysis and a shift to fatty acid oxidation, these drugs shrink the size of visceral fat depots, including those surrounding the kidneys. SGLT2 inhibitors promote browning in white adipose tissue, thus exerting a favorable effect to change the distribution of polarized macrophages, and consequently, they attenuate obesity-induced inflammation and insulin resistance [18]. SGLT2 inhibitors reduce the lipotoxic effects of diacylglycerols and ceramides, while minimizing the synthesis and release of proinflammatory adipocytokines, (especially leptin) and increasing the actions of adiponectin [19]. By virtue of all of these effects to subdue inflammation and promote a nourishing phenotype in adipose tissue, these drugs are positioned to act as physiological leptin antagonists. Such an action may explain their effects to promote renal sodium excretion and mitigate both glomerular and renal tubular dysfunction, inflammation and fibrosis in experimental obesity and diabetes.

SGLT2 Inhibitors Activate AMPK, Promote Autophagy, and Reduce Cellular Organellar Stress and Inflammation

By inducing a biological state that mimics starvation, SGLT2 inhibitors trigger a fasting-like transcriptional and metabolic paradigm, as evidenced by caloric loss in the urine and ketonemia. Essentially, SGLT2 inhibitors deceive cells into believing that they are nutrient-starved, and as a result, they activate low-energy sensors and

promote their ability to stimulate autophagy. Experimental studies have reported an effect of SGLT2 inhibitors to activate both SIRT1 and AMPK as well as cellular markers of autophagic flux [20–22], with the induction of SIRT1 signaling potentially representing a direct action [23]. Such an effect may explain why SGLT2 inhibitors ameliorate oxidative and endoplasmic reticulum stress, and this benefit is accompanied by the minimization of glomerular and tubular injury and inflammation as well as attenuation of the development of nephropathy [22]. Interestingly, in one trial, metformin (an established AMPK agonist with uncertain direct effects on SIRT1) attenuated the benefits of SGLT2 inhibition on the course of nephropathy (53% risk reduction in metformin users vs. 32% risk reduction in metformin nonusers, interaction $p = 0.01$), supporting a role for AMPK signaling in mediating part of the effects of SGLT2 inhibitors on the diabetic kidney [24]. Intriguingly, any increase in SIRT1 and AMPK signaling produced by SGLT2 inhibitors may also modulate proximal tubular sodium reabsorption and may directly enhance tubuloglomerular feedback [25]. This interplay effectively links changes in the activity of these low-energy sensors to the action of SGLT2 inhibitors to ameliorate glomerular hyperfiltration.

Synthesis and Conclusions

SGLT2 inhibitors induce a biological state that mimics starvation, that is, these drugs trigger a fasting-like transcriptional paradigm. This shift in the perceived balance of energy supply and demand is most readily apparent in the action of SGLT2 inhibitors to increase the loss of calories in the urine as well as to promote ketonemia, which is typically seen in states of nutrient deprivation. The ability of SGLT2 inhibitors to enhance nutrient deprivation signaling may be particularly important in mediating their effects to preserve renal function, which is typically compromised in states of nutrient excess. Both obesity and type 2 diabetes are characterized by glomerular hyperfiltration, adipose tissue inflammation, and the suppression of autophagy, which (individually or collectively) may act to cause renal injury. By mimicking a state of energy starvation, SGLT2 inhibitors can reduce intraglomerular pressures and minimize adipose tissue inflammation and the secondary release of potentially nephrotoxic mediators. Most interestingly, the action of SGLT2 inhibitors to activate SIRT1, AMPK, and autophagy may serve to clear injured organelles from glomerular and renal tubular cells, thus muting the cellular

stress and inflammatory response that is characteristic of obesity-related and diabetic nephropathy. Collectively, these effects may explain to the remarkable ability of SGLT2 inhibitors to preserve renal function in large-scale randomized controlled clinical trials.

Disclosure Statement

Dr. Milton Packer has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Boehringer Ingelheim, Cardiorientis, Daiichi Sankyo, Johnson and Johnson, NovoNordisk, Pfizer, Replensa, Sanofi, Synthetic Biologics and Theravance.

References

- Hallow KM, Gebremichael Y, Helmlinger G, Vallon V. Primary proximal tubule hyperreabsorption and impaired tubular transport counterregulation determine glomerular hyperfiltration in diabetes: a modeling analysis. *Am J Physiol Renal Physiol*. 2017 May;312(5):F819–35.
- Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res*. 2015 Mar;116(6):991–1006.
- Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. *Compr Physiol*. 2018 Dec;9(1):1–58.
- Ndisang JF, Jadhav A, Mishra M. The heme oxygenase system suppresses perirenal visceral adiposity, abates renal inflammation and ameliorates diabetic nephropathy in Zucker diabetic fatty rats. *PLoS One*. 2014 Jan;9(1):e87936.
- Packer M. Leptin-aldosterone-neprilysin axis: identification of its distinctive role in the pathogenesis of the three phenotypes of heart failure in people with obesity. *Circulation*. 2018 Apr;137(15):1614–31.
- Pedone C, Roshanravan B, Scarlata S, Patel KV, Ferrucci L, Incalzi RA. Longitudinal association between serum leptin concentration and glomerular filtration rate in humans. *PLoS One*. 2015 Feb;10(2):e0117828.
- Levine B, Packer M, Codogno P. Development of autophagy inducers in clinical medicine. *J Clin Invest*. 2015 Jan;125(1):14–24.
- Takahashi A, Takabatake Y, Kimura T, Maejima I, Namba T, Yamamoto T, et al. Autophagy inhibits the accumulation of advanced glycation end products by promoting lysosomal biogenesis and function in the kidney proximal tubules. *Diabetes*. 2017 May;66(5):1359–72.
- Lenoir O, Jasiek M, Hénique C, Guyonnet L, Hartleben B, Bork T, et al. Endothelial cell and podocyte autophagy synergistically protect from diabetes-induced glomerulosclerosis. *Autophagy*. 2015;11(7):1130–45.
- Kume S, Koya D, Uzu T, Maegawa H. Role of nutrient-sensing signals in the pathogenesis of diabetic nephropathy. *BioMed Res Int*. 2014;2014:315494.
- Osathanaphan S, Macchi C, Singhal G, Chimene-Weiss J, Sales V, Kozuka C, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -independent mechanisms. *JCI Insight*. 2019 Mar;4(5):123130.
- Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016 Jul;375(4):323–34.
- Pessoa TD, Campos LC, Carraro-Lacroix L, Girardi AC, Malnic G. Functional role of glucose metabolism, osmotic stress, and sodium-glucose cotransporter isoform-mediated transport on Na⁺/H⁺ exchanger isoform 3 activity in the renal proximal tubule. *J Am Soc Nephrol*. 2014 Sep;25(9):2028–39.
- Onishi A, Fu Y, Darshi M, Crespo-Masip M, Huang W, Song P, et al. Effect of renal tubule-specific knockdown of the Na⁺/H⁺ exchanger NHE3 in Akita diabetic mice. *Am J Physiol Renal Physiol*. 2019 Aug;317(2):F419–34.
- Zingerman B, Herman-Edelstein M, Erman A, Bar Sheshet Itach S, Ori Y, Rozen-Zvi B, et al. Effect of acetazolamide on obesity-induced glomerular hyperfiltration: a randomized controlled trial. *PLoS One*. 2015 Sep;10(9):e0137163.
- Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al; CREDESCENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019 Jun;380(24):2295–306.
- Vallon V, Rose M, Gerasimova M, Satriano J, Platt KA, Koepsell H, et al. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. *Am J Physiol Renal Physiol*. 2013 Jan;304(2):F156–67.
- Xu L, Nagata N, Nagashimada M, Zhuge F, Ni Y, Chen G, et al. SGLT2 inhibition by empagliflozin promotes fat utilization and browning and attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. *EBioMedicine*. 2017 Jun;20:137–49.
- Wu P, Wen W, Li J, Xu J, Zhao M, Chen H, et al. Systematic review and meta-analysis of randomized controlled trials on the effect of SGLT2 inhibitor on blood leptin and adiponectin level in patients with type 2 diabetes. *Horm Metab Res*. 2019 Aug;51(8):487–94.
- Umino H, Hasegawa K, Minakuchi H, Muraoka H, Kawaguchi T, Kanda T, et al. High basolateral glucose increases sodium-glucose cotransporter 2 and reduces sirtuin-1 in renal tubules through glucose transporter-2 detection. *Sci Rep*. 2018 May;8(1):6791.
- Inoue MK, Matsunaga Y, Nakatsu Y, Yamamoto T, Ueda K, Kushiya A, et al. Possible involvement of normalized Pin1 expression level and AMPK activation in the molecular mechanisms underlying renal protective effects of SGLT2 inhibitors in mice. *Diabetol Metab Syndr*. 2019 Jul;11(1):57.
- Aragón-Herrera A, Feijóo-Bandín S, Otero Santiago M, Barral L, Campos-Toimil M, Gil-Longo J, et al. Empagliflozin reduces the levels of CD36 and cardiotoxic lipids while improving autophagy in the hearts of Zucker diabetic fatty rats. *Biochem Pharmacol*. 2019 Dec;170:113677.
- Ying Y, Jiang C, Zhang M, Jin J, Ge S, Wang X. Phloretin protects against cardiac damage and remodeling via restoring SIRT1 and anti-inflammatory effects in the streptozotocin-induced diabetic mouse model. *Aging (Albany NY)*. 2019 May;11(9):2822–35.
- Inzucchi SE, Fitchett D, Jurišić-Eržen D, Woo V, Hantel S, Janista C, et al; EMPA-REG OUTCOME® Investigators. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? *Diabetes Obes Metab*. 2019, Epub ahead of print.
- Hasegawa K. Novel tubular-glomerular interplay in diabetic kidney disease mediated by sirtuin 1, nicotinamide mononucleotide, and nicotinamide adenine dinucleotide Oshima Award Address 2017. *Clin Exp Nephrol*. 2019 Aug;23(8):987–94.