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Adaptive Response as a Potential Key Link Between SGLT2 Inhibition and Renoprotection

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Growing attention has been focused on the benefits of sodium glucose cotransporter-2 (SGLT2) inhibitors, a novel class of oral hypoglycemic agents, in nephrology and diabetology. In *Kidney International Reports*, Liu *et al.*[1] reported an exploratory analysis of biomarkers affected by treatment with ertugliflozin, an SGLT2 inhibitor, using plasma samples from a proportion of participants in the VERTIS RENAL study, a multicenter, randomized, double-blind, placebo-controlled trial in which patients with type 2 diabetes and stage 3 chronic kidney disease were enrolled and followed up for 52 weeks.[2] A total of 231 patients were available for this exploratory analysis, and they had a median age of more than 65 years, a median hemoglobin A1c level of 8.0%, a median urinary albumin-to-creatinine ratio of 29.5 mg/g, and a median estimated glomerular filtration rate (eGFR) of 48 ml/min per 1.73 m^2. Of the potential biomarkers, they focused on KIM-1 and found that the KIM-1 level was significantly lower in the ertugliflozin group. Stratified analysis revealed that the change in KIM-1 level during the 52 weeks in these patients treated with ertugliflozin was almost identical irrespective of their baseline albumin-to-creatinine ratio or eGFR. It was also found that the baseline KIM-1 level was associated with the change in eGFR thereafter, and the change in the KIM-1 level was associated with the change in albumin-to-creatinine ratio,[1] suggesting a potential not only for evaluating KIM-1 in patients initiating treatment with an SGLT2 inhibitor but also for monitoring KIM-1 during the treatment.

KIM-1 is known as a tubular injury marker and is reported to be markedly induced by hypoxia in cultured human proximal tubular cells[3]; therefore, it may differ from other classical markers of tubular injury, including L-FABP and NGAL. In this study, L-FABP was not even evaluated and NGAL was not affected by treatment with ertugliflozin in contrast to KIM-1.[1] Interestingly, the discrepancy between KIM-1 and other tubular injury marker(s) was shared by another *post hoc* study that evaluated the effect of treatment with dapagliflozin, another SGLT2 inhibitor, for 6 weeks, on kidney injury markers in patients with type 2 diabetes comorbid with microalbuminuria or macroalbuminuria. In this study, KIM-1 was significantly reduced by treatment with dapagliflozin, whereas L-FABP and NGAL were not altered.[4] Taken together, it was suggested that hypoxia-induced tubular injury could be improved by treatment with these SGLT2 inhibitors. Moreover, evaluation of KIM-1 in addition to classical markers might provide insight even into the mechanism underlying tubular injury.

Hypoxia and subsequent tubular injury play a pivotal role in the development of kidney disease,[5] whereas SIRT1 and 5′ adenosine monophosphate-activated protein kinase (AMPK) expressed in tubular cells are known to be protective against tubular injury.[6] Both these molecules are activated not only by hypoxia but also by fasting and play pivotal roles in the adaptive response to deprivation of oxygen and nutrients by regulating mitochondrial homeostasis, antioxidant capacity, autophagy, angiogenesis, and gluconeogenesis. Nevertheless, activation of these molecules in tubular cells is known to be suppressed in obesity and diabetes, partly owing to intracellular accumulation of glucose and lipids, which is thought to be involved in the development of kidney disease.[6]

Our previous study is one of the earliest reports to reveal that inhibition of SGLTs, the targets of phlorizin which are localized in the

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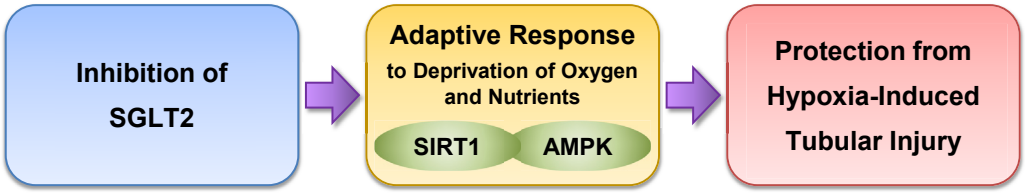

Figure 1. A potential mechanism of renoprotection by SGLT2 inhibitors *via* activation of the adaptive response by SIRT1 and AMPK. AMPK, 5′ adenosine monophosphate-activated protein kinase.

luminal membrane and responsible for inward efflux of glucose, activates SIRT1 through a reduction in reduced nicotinamide adenine dinucleotide-to-nicotinamide adenine dinucleotide^{+} ratio, thus enhancing gluconeogenesis; therefore, we propose that SGLTs could serve as glucose sensors in the proximal tubules of the kidney.[7] Together with reports published in the last couple of years, now it is thought that treatment with SGLT2 inhibitors activates not only SIRT1 but also AMPK, and the adaptive response by SIRT1 and AMPK could prevent progression of kidney disease.[6] Moreover, our report reveals that gluconeogenesis is suppressed by insulin signaling transmitted from the insulin receptor in the basolateral membrane of the proximal tubules.[7] Some of the other effects in the adaptive response, such as regulation of autophagy, is known to be also cancelled out by activation of Akt, the key downstream kinase of insulin signaling.[6]

Given these possible mechanisms, it is likely that treatment with ertugliflozin inhibited SGLT2 as a glucose sensor on the luminal side and blocked glucose reabsorption, which in turn induced the adaptive response. In addition, Akt-mediated suppression of the adaptive response was cancelled out indirectly by treatment with ertugliflozin *via* a reduction in serum insulin level leading to less robust activation of the insulin receptor on the opposite side of the proximal tubules. Consequently, SIRT1 and AMPK thus activated exerted their renoprotective effects to attenuate hypoxia-induced tubular injury (Figure 1), leading to the reduction in KIM-1 level in this exploratory analysis of the VERTIS RENAL study.[1]

Despite these findings, this study has several limitations. Above all, the study results need yet to be replicated in a larger scale in patients with different backgrounds, including those with severe proteinuria, those in an earlier stage of chronic kidney disease, and those with chronic renal failure in which the adaptive response failure might occur. It should be taken into account that the patients had a median albumin-to-creatinine ratio of less than 30 mg/g and a median eGFR of less than 50 ml/min per 1.73 m^2 in this study.[1] KIM-1 as a tubular injury marker should also be validated in patients with fair glycemic control, because the hemoglobin A1c level during follow-up was slightly below 8% in the control group of this study,[1] as in most clinical trials of type 2 diabetes.[8]

Moreover, blood pressure (BP) is another factor of importance contributing to the development of chronic kidney disease, but the effect of BP control on the KIM-1 level remains to be clarified. SGLT2 inhibitors are known to affect BP as well, and indeed, BP was significantly lower in the ertugliflozin group in the VERTIS RENAL study.[2] Most recently, we reported that eGFR decline was not associated with glycemic control but with BP control in patients with type 2 diabetes with baseline eGFR below 60 ml/min per 1.73 m^2, in a subanalysis of the J-DOIT3 study, a large-scale clinical trial to evaluate the effects of intensified multifactorial intervention on vascular complications.[9] Given that hypoxia is also induced by hypertensive kidney disease,[5] it is an issue of interest whether lowering of KIM-1 depends on improvement in glycemic control, improvement in BP control, or use of SGLT2 inhibitors itself.

Nevertheless, this study seems to represent a large step ahead revealing the potential of KIM-1 to be established as a novel marker of tubular injury, which is expected not only to predict eGFR decline thereafter but also to reflect the therapeutic effects of SGLT2 inhibitors. Moreover, on the basis of the available clinical data, the study provides us with insight into activation of the adaptive response to deprivation of oxygen and nutrients by SIRT1 and AMPK as a potential key mechanism accounting for protection of the kidney from hypoxia-induced tubular injury by treatment with SGLT2 inhibitors.

DISCLOSURE

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