The nature and expense of spaceflight experiments placed understandable limitations on the study. The experimental design did not determine the relative contributions of various spaceflight exposures to the observed phenotype (cosmic radiation versus microgravity versus physical stresses). Only male mice were selected for travel, and findings could be very different in female mice. The 2-day delay between return from space and tissue collection may have altered some findings. Because of the need for immediate tissue collection, urine was not obtained, meaning that the authors were unable to verify whether lipid excretion was altered. Vitamin D levels and blood pressure were also not measurable.

In ideal circumstances, follow-up studies would focus on confirming the predicted changes in lipid metabolism and excretion based on the gene expression analyses. More detailed information on vitamin D levels, renin-angiotensin-aldosterone system activation, and blood pressure would be invaluable, and examination of changes in glomerular filtration and kidney salt and water handling are needed because of conflicting data in previous studies.[9] Finally, as there are many pharmacologic Nrf2 enhancers available, it would be interesting to determine if administration of these enhancers before and during spaceflight can affect muscle health and lipid excretion.

Renewed interest in space travel may increase opportunities for animal studies. For the scientific community, the challenge now is to continue to innovate and execute more complex experiments within the extensive constraints of spaceflight. The MHU-3 study is one small (but very significant) step leading to a giant leap forward in our understanding of the effects of spaceflight on mammalian physiology.

DISCLOSURE

The author declared no competing interests.

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SGLT2 inhibition in chronic kidney disease: a preventive strategy against acute kidney injury at the same time?

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Sodium-glucose co-transporter 2 (SGLT2) inhibitors are known to slow down progression of chronic kidney disease. However, theoretical concerns still exist that SGLT2 inhibitors could increase the risk of acute kidney injury. Heerspink *et al.* revealed that dapagliflozin, an SGLT2 inhibitor, reduced the risk of abrupt declines in kidney function during the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial. Their findings may serve to reassure clinicians prescribing SGLT2 inhibitors to patients with chronic kidney disease.

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see clinical trial on page 174

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are now regarded as not only glucose-lowering agents, but also novel therapeutic agents against heart failure and chronic kidney disease (CKD) progression, due to the results of several large randomized controlled trials [1,2] Initiation of SGLT2 inhibitors sometimes induces a moderate transient decrease in estimated glomerular filtration rate (eGFR), probably due to amelioration of glomerular hyperfiltration via tubuloglomerular feedback.[3,4] This initial dip in eGFR is independent of the benefits from SGLT2 inhibition and is now

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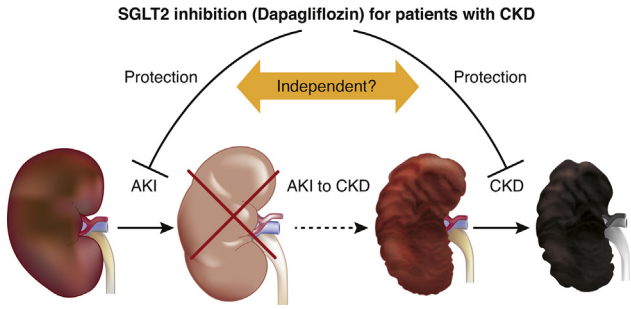

Figure 1 | Impact of sodium-glucose co-transporter 2 (SGLT2) inhibition for patients with chronic kidney disease (CKD). Dapagliflozin, an SGLT2 inhibitor, reduced the risk of abrupt declines in kidney function (almost the same events as those that occur in acute kidney injury [AKI]) in patients with CKD. Although the causal mediation analysis in this issue suggests that the protection against CKD is independent of the protection against abrupt declines in kidney function, further studies with a long-term observation period are needed to make a solid conclusion.

considered reversible, but some clinicians are still concerned that patients taking SGLT2 inhibitors are susceptible to kidney damage induced by sepsis, hypovolemia, or nephrotoxic substances. This concern is mostly derived from the fact that a similar dip in eGFR is observed in patients at the initiation of renin–angiotensin system inhibitors, the use of which occasionally precipitates acute kidney injury (AKI). However, meta-analysis of several cardiovascular outcome trials suggests that SGLT2 inhibitors reduce AKI in patients with type 2 diabetes.[5] The network meta-analysis of cardiovascular and kidney outcome trials also showed that SGLT2 inhibitors have a lower risk of AKI, compared with dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists.[6] However, these meta-analyses have limitations in that most participants were patients with diabetes, and AKI definition was inconsistent across studies. Even though accumulated real-world evidence also indicates that SGLT2 inhibitors are likely to reduce the occurrence of AKI in various populations,[7] the results have yet to reassure clinical nephrologists prescribing SGLT2 inhibitors to patients with CKD, owing to many residual confounding factors in these retrospective studies.

In this context, Heerspink *et al.* analyzed the impact of dapagliflozin on the pre-specified outcome of an abrupt decline in kidney function, defined as a doubling of serum-creatinine level between 2 subsequent study visits (not a change from the baseline serum-creatinine level) in the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.[8] The authors demonstrated that dapagliflozin, compared with placebo, was associated with a lower risk of an abrupt decline in kidney function in patients with CKD. The abrupt decline in kidney function occurred in 63 participants (2.9%) and 91 participants (4.2%) in the dapagliflozin and placebo groups, respectively (hazard ratio [HR], 0.68 [95% confidence interval {CI}, 0.49–0.94]; $P = 0.02$). The effects were consistent in patients with and without type 2 diabetes, patients with a baseline eGFR above or below 45 ml/min per 1.73 m^2, and patients with a urinary albumin-to-creatinine ratio above or below 1000 mg/g. Moreover, the effects were also similar in subgroups created *post hoc* of either baseline diuretic use or presence of heart failure at baseline. In contrast, the occurrence of AKI-related serious adverse events, which required hospitalization, led to prolongation of hospitalization or was associated with death, did not differ in the placebo (3.2%) versus dapagliflozin (2.5%) groups (HR, 0.77 [95% CI, 0.54–1.10; $P = 0.15$]).

Although these findings are reassuring for clinical nephrologists treating patients with CKD, some issues remain to be addressed to determine the exact impact of SGLT2 inhibitors on the occurrence of AKI and subsequent events.

First, the authors set the primary outcome as the doubling of serum-creatinine levels between 2 subsequent visits, which is different from AKI as defined by Kidney Disease: Improving Global Outcomes (KDIGO). As the median time interval between 2 visits was 100 days,[2,8] the authors could not have noted AKI events that occurred and then resolved within 3 months. Thus, future studies with shorter follow-up periods are needed to determine the net effects of SGLT2 inhibitors on the occurrence of AKI.

Second, the authors' causal mediation analysis showed that the benefits of dapagliflozin on hard kidney outcomes (end-stage kidney disease, kidney death, or all-cause mortality) could not be attributed at all to prevention of abrupt declines in kidney function, although they also showed that abrupt declines in kidney function had a strong association with hard kidney outcomes (HR for end-stage kidney disease or kidney death, 13.7 [95% CI, 9.7–19.3]; and HR for all-cause mortality, 9.3 [95% CI, 6.6–13.2]).[8] One possible explanation for this discrepancy is that the follow-up time in the DAPA-CKD trial was too short to demonstrate that a reduction in AKI occurrence by dapagliflozin translates into a subsequent reduced risk of hard kidney outcomes. Thus, further studies with a long-term observation period are needed to make a solid conclusion on this topic (Figure 1). However, the protection against CKD would be mostly derived from long-term effects of SGLT2 inhibition, including amelioration of glomerular hyperfiltration via tubuloglomerular feedback, rather than prevention of AKI.

Finally, the major question of whether SGLT2 inhibition can be an effective strategy to prevent AKI in high-risk patients, such as those undergoing cardiac surgery or nephrotoxic chemotherapy, remains unanswered. SGLT2 inhibitors would certainly reduce AKI events in patients with CKD, as well as in patients with type 2

diabetes, as shown in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) study. In the current study,[8] however, AKI-related serious adverse events were not significantly reduced with dapagliflozin treatment (HR, 0.77 [95% CI, 0.54–1.10; $P = 0.15$]), consistent with the analysis of patients with type 2 diabetes and CKD from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial (HR for AKI serious adverse events, 0.79 [95% CI, 0.52–1.19]).[5] These results suggest that SGLT2 inhibition cannot protect kidneys against severe injury, even if it is protective against mild kidney injury. Also, a possibility is that the protective effect of SGLT2 inhibition against AKI is dependent on pathogenesis of AKI (sepsis, hypovolemia, nephrotoxic substances, or ischemia/reperfusion), but most large clinical trials do not provide information on pathogenesis. Thus, we need to determine which type of AKI, in terms of severity and pathogenesis, is more responsive to the SGLT2 inhibition, to determine whether clinical application of SGLT2 inhibitors is an effective preventive strategy against AKI.

Another important question is whether even short-term treatment with SGLT2 inhibitors has a protective effect against AKI. A recent study targeting patients with coronavirus disease 2019 (COVID-19) has given us some insight into this question. In the Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) study,[9] either dapagliflozin or placebo was administered to patients with cardiometabolic risk factors, after the onset of COVID-19. This study design can allow us to observe whether short-term administration of SGLT2 inhibitors in high-risk patients has protective effects against AKI, beyond their effects in chronic conditions. Results showed that dapagliflozin treatment was well tolerated in patients with COVID-19. Notably, dapagliflozin treatment numerically reduced the occurrence of AKI (dapagliflozin group 3.4% vs. placebo group 5.5%), although the difference was not statistically significant, suggesting that even short-term SGLT2 inhibition in high-risk patients might provide some protection against AKI. Further studies targeting patients with acute disease conditions (undergoing sepsis, cardiac surgery, or nephrotoxic chemotherapy), which are likely to trigger AKI, are needed to determine the protective effect of short-term SGLT2 inhibition against AKI.

In conclusion, the pre-specified analysis of the DAPA-CKD trial has confirmed that dapagliflozin use, compared with placebo, was associated with a lower risk of an abrupt decline in kidney function in patients with CKD.[8] Although further studies are needed to determine the net effect of SGLT2 inhibitors on the occurrence of AKI and subsequent events, the results of this study should reassure clinical nephrologists treating patients with CKD.

DISCLOSURE

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