Potential Hypoxic Renal Injury in Patients With Diabetes on SGLT2 Inhibitors: Caution Regarding Concomitant Use of NSAIDs and Iodinated Contrast Media

DOI: 10.2337/dc16-2200

In their seminal work, Wanner et al. (1) found that the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin provided renal protection over 4 years of follow-up in patients with type 2 diabetes. Furthermore, the incidence of overt acute kidney injury (AKI) showed a trend in favor of the treatment group, especially beyond 18 months of randomization. However, a recent U.S. Food and Drug Administration Drug Safety Communication reports 101 cases of AKI in patients treated with SGLT2 inhibitors, some of whom required hospitalization and dialysis (2).

There might be a few explanations for this troubling news, other than mere chance and publication bias. While an initial reduction in glomerular filtration rate, related to transglomerular pressure reduction, is a reversible inherent factor of long-term renal protection, SGLT2 inhibition could potentially lead to significant renal impairment under specific conditions. One such condition suggested in the Drug Safety Communication is dehydration caused by osmotic diuresis and natriuresis, particularly among frail patients on diuretics. A second plausible possibility is intensification of renal parenchymal hypoxia and hypoxic kidney injury. The renal medulla is characterized by low ambient \( PO_2 \), reflecting limited local blood flow, hardly sufficient for the intense regional transport activity and oxygen consumption. Palm et al. (3) found that parenchymal oxygenation is further reduced in the diabetic kidney, reflecting additional alterations in renal microcirculation and enhanced tubular transport. We also reported (4) that hypoxia and the expression of hypoxia-inducible factors are intensified in the diabetic kidney and that experimental diabetes predisposes to medullary hypoxic tubular injury. The introduction of SGLT2 in the management of diabetes may further aggravate medullary hypoxia. In fact, O’Neill et al. (5) recently reported that SGLT inhibition in intact and diabetic rats intensifies medullary hypoxia, conceivably reflecting enhanced solute delivery to distal nephron segments, increasing medullary transport workload and oxygen consumption. Increases in erythropoietin and reticulocytosis following SGLT2 inhibition further suggest intensified hypoxia at the corticomedullary junction. SGLT2 inhibitor–mediated medullary hypoxia might be clinically important under circumstances where there is concomitant predisposition to medullary hypoxic injury, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or radiocontrast agents (4).

Tubular injury can currently be detected by urine biomarkers, such as neutrophil gelatinase–associated lipocalin or kidney injury molecule-1, preceding or even in the absence of overt renal functional impairment. Such biomarkers were not evaluated in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), nor were they systematically studied in the reported cases of SGLT2 inhibition–associated AKI. From this perspective, we believe that studies using urine biomarkers are required to assess the true occurrence of hypoxic tubular injury in patients on SGLT2 inhibitors with declining kidney function.

Thus, it is prudent to suggest that special care be taken regarding maintenance of the hydration status to reduce the risk of volume depletion in high-risk patients with diabetes on SGLT2 inhibitors. Furthermore, the possibility of SGLT2-induced hypoxic AKI should be thoroughly investigated and validated in humans. Meanwhile, with this possibility in mind, we propose avoidance of the concomitant administration of agents that lead
to iatrogenic hypoxic medullary injury: avoidance of NSAIDs in patients on SGLT2 inhibitors and cessation of SGLT2 inhibitors prior to radiocontrast studies.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors contributed equally to the generation of the hypotheses that formed the basis for this observation. S.N.H. wrote the manuscript with the participation and feedback of M.K., S.R., C.R., and Z.A. S.N.H. is the guarantor of this work and, as such had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis.

References