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Drug-induced osmotic nephropathy: Add SGLT2- inhibitors to the list?

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Medications are a common cause of kidney disease and can induce injury through a variety of mechanisms (1). The tubulointerstitium is the most common compartment involved in drug-induced kidney disease (DIKD). Drug-induced toxic acute tubular injury is most common, while acute tubulointerstitial nephritis from idiosyncratic drug reactions and crystalline nephropathy from precipitation of medications within the tubules also cause DIKD (1). A less common but none-the-less notable cause of DIKD is osmotic nephropathy (1,2). A number of medications (Table 1) have been described to cause this lesion including infusion of “hyperosmotic” medications such as carbohydrate-stabilized intravenous immune globulin (IVIg), hydroxyethyl starch, dextran, mannitol, and contrast medium (1-3). This lesion has also been described in rats exposed to intravenous glucose where significant amounts of glucose is noted in the urine (4). The recent description of 5 cases of biopsy-proven osmotic nephropathy with the SGLT2-inhibitors fits this experimental observation and will be discussed along with other medications (5-7).

Osmotic nephropathy was first described in 1906 by Lamy et al, (8) and subsequently rediscovered in the 1930s when sucrose infusions were used to combat cerebral and generalized edema (9). It is a histopathologic diagnosis characterized as swollen renal tubular epithelial cells filled with cytoplasmic vacuoles (Figure 1A) (2,10). In contrast to vacuolization of cells due to ischemic injury, osmotic nephropathy cells don’t have apical blebbing or nuclear dropout. Electron microscopy demonstrates cytoplasmic vacuoles that are lysosomes that can be small and appear empty or large with amorphous electron-dense material (2,10). Osmotic nephropathy occurs in the setting of intravenous administration of an offending agent that undergoes glomerular filtration followed by pinocytosis when the substance encounters the apical membrane of proximal tubular epithelial cells (1,2). Following pinocytosis, the offending agent found in the pinocytic vacuoles fuse with each other as well as the lysosomes where they accumulate and become engorged and distended (Figure 1B). Importantly, the vacuoles and cellular swelling do not occur due to an “osmotic” effect of the intracellular drugs to draw water into the tubular cells, making the term a misnomer that has persisted (1,2). Rather, it is the pinocytosis and lysosomal accumulation of drug that ultimately promotes intracytoplasmic vacuolization and proximal tubular cell swelling (1,2). Not uncommonly, swollen tubules are seen next to normal-appearing tubules. The severity of vacuolization and cell swelling is dose dependent. For example, depending on the severity of drug exposure, vacuolization of the tubular cells may be mild and focal with minimal swelling or produce a diffuse “clear cell” appearance with
marked swelling and basal displacement of nuclei (1,2,10). The straight segment (S2 and S3) of the proximal tubule is primarily involved, although the convoluted segment cells may contain vacuoles in severe cases while the distal and collecting tubules are spared (2).

Risk factors for development of osmotic nephropathy and kidney injury are related to both the drug and health of the kidney. The dose of offending drug is critical as larger doses and longer duration of exposure increased risk for this lesion (1,2,10). Other factors contribute to the severity and duration of tubular cell vacuolization and swelling. The digestibility of the drug importantly influences vacuolar retention; poorly digestible substances will remain longer within lysosomes and accumulate within the cells (1,2,10). Underlying chronic kidney disease or acute tubular injury (ischemic or toxic) also impacts on the severity of osmotic nephropathy (and kidney dysfunction) by impairing lysosomal digestion (1,2,10). In fact, persistent lysosomal alterations are an early sign of cell damage and may be associated with irreversible cell damage. Other risk factors, which likely reflect reduced kidney function, include diabetes mellitus and older age.

The histological presence of osmotic nephropathy does not always equate to proximal tubular dysfunction, and may in fact, occur in the absence of clinically overt AKI (1,2,10). However, severe and diffuse tubular involvement is often associated with urinalysis abnormalities (tubular proteinuria, swollen tubular cells with numerous vacuoles alone and within casts) and/or AKI (2,10). AKI and oliguria that develops from osmotic nephropathy is primarily due to tubular cell dysfunction with perhaps only a small contribution from tubular obstruction occurring from massively swollen cells, which occlude tubular lumens (2,10). Since both the duration of drug exposure and patient and drug-related risk factors for osmotic nephropathy are known, preventive measures can be instituted (1,2). These include primarily using alternative agents, reducing dose and duration of exposure, minimizing reduced kidney perfusion from volume depletion, and avoiding concurrent nephrotoxin exposure. In fact, the removal of sucrose as a stabilizer from most IVIg preparations has largely eliminated osmotic nephropathy as a complication. When AKI does develop, it usually resolves rather quickly on its own. However, some patients, especially those with the aforementioned risk factors, may require kidney replacement therapy. Most patients will recover kidney function with discontinuation of the offending agent.

**Medications most commonly associated with osmotic nephropathy**
Osmotic nephropathy is generally associated with the infusion of hyperosmotic or hyperoncotic agents. Some of the most common culprits are as follows. First, IVIg preparations, are the most frequently described agents to cause osmotic nephropathy (2-4,10). The different IVIg preparations contain different stabilizing substances (sucrose, glucose, maltose, sorbitol, glycine and albumin) to reduce immunoglobulin aggregation, but may precipitate osmotic nephropathy. The vast majority of cases are from IVIg containing sucrose, although rare cases have been described in IVIg containing other stabilizers (2). Second, radiocontrast-associated AKI may also be a form of osmotic nephropathy despite it being mentioned much less frequently as a mechanism of contrast-associated kidney injury compared to ischemia, oxidative stress and direct toxicity (2,11,12). Yet, kidney biopsy specimens from patients exposed to contrast frequently show classical osmotic nephropathy. The significance of these lesions in causing AKI is unclear (2,12). Third, intravenous mannitol has also been implicated in osmotic nephropathy. Its infusion into rabbits, cats, dogs and humans have described a dose-related osmotic nephropathy lesion (13). Finally, two volume expanders that were widely utilized in the past, low-molecular dextran and hydroxyethyl starch (HES), have also been associated with dose-related osmotic nephropathy in animals and humans (3,14-16). The small dextran polymers found in the dextrans, and starch fragments found in the large molecular weight/high substitution ratio HES preparations, are freely filtered and undergo pinocytosis by proximal tubular cells resulting in classic osmotic lesions. As with the other hyperosmolar agents, underlying risk factors increased development of AKI.

**SGLT2-inhibitors**

The SGLT2-inhibitors have revolutionized the treatment of CKD in both patients with diabetes and those with other forms of CKD (17). The addition of this class of medications to state of the art care has significantly reduced the progression of CKD. While these drugs have multiple beneficial effects, there are a few case reports of AKI and numerous reports in the FDA Adverse Events Reporting System (FAERS) of AKI associated with these drugs (18). While most of these cases are likely due to decreased glomerular capillary pressure, some may be due to the development of an osmotic nephropathy. Case reports of biopsy-proven osmotic nephropathy with the SGLT2-inhibitors have been published (5-7). The 5 patients in these reports ranged in age from 41 to 66 years, all had diabetes mellitus and hypertension, and had mild to moderately advanced CKD with eGFRs (ml/min/176m2) of
Three patients were on dapagliflozin, 1 on canagliflozin and 1 patient on empagliflozin (overdose of 50 mg). Serum creatinine on presentation ranged from 1.1mg/dL to 10.7mg/dL (mean 4.6mg/dL) while significant urine glucose was noted in all patients. Kidney biopsy in all patients revealed findings consistent with osmotic nephropathy with vacuolization and cell swelling limited to the proximal tubules. With supportive care and SGLT2-inhibitor discontinuation, all patient recovered kidney function back to baseline except for one patient left with higher stage CKD. Despite the novelty of these findings, it is humbling to note that in 1935, Homer Smith (19) described these lesions in dogs treated concomitantly with phlorizin and either sucrose or an equivalent amount of glucose (100 cc of 50%). Not surprisingly the sucrose caused a more severe lesion.

Why would this lesion develop with these drugs, which are clearly different than the hyperosmotic agents previously described? A possible explanation lies with experimental and clinical settings where the proximal tubules are exposed to significant amounts of filtered glucose. Glucose infusions have been associated with osmotic nephropathy in experimental studies and in humans exposed to 10% glucose solutions (2-4). Autopsy specimens of kidneys from diabetic patients suffering from severe hyperglycemia and DKA revealed proximal tubular cells packed with intracytoplasmic vacuoles—the Armanni-Ebstein lesion (6,20). The genesis of this lesion is not definitively known but is thought to result from severe hyperglycemia causing excessive amounts of urinary glucose, which then undergoes tubular cell pinocytosis. The large volume of pinocytosed glucose overwhelms the cell’s ability to metabolize the glucose load. Along the same line, the SGLT2-inhibitors may cause this lesion through their effect to block proximal tubular glucose transport in the S1 segment and send a large amount of glucose to the S3 segment. The S3 segment is also most prominently involved with the other drugs associated with osmotic nephropathy. In one case of SGLT2-inhibitor associated osmotic nephropathy, the lysosomal vacuoles had amorphous debris on electron microscopy as described with the other agents (6).

In conclusion, osmotic nephropathy is an under-recognized cause of drug-induced kidney injury. While many of the drugs associated with this lesion are no longer used (dextran, sucrose-containing IVIg) or used less commonly (mannitol, HES) in current times, contrast and the SGLT2-inhibitors are widely employed. The small number of cases of osmotic nephropathy described with the SGLT2-inhibitors may reflect that the lesion is either uncommon or is being missed (most AKI cases are not biopsied). A reasonable approach to
assess for this lesion would be to undertake a kidney biopsy in patients with SGLT2-inhibitor associated AKI that does not recover to baseline within 5-7 days.

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**Author Contributions**

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**Table 1. Medications associated with osmotic nephropathy.**

| Medication                                |
|-------------------------------------------|
| IVIg (sucrose) infusion                   |
| Contrast infusion                         |
| Hydroxyethyl starch infusion              |
| Mannitol infusion                         |
| Dextran infusion                          |
| Glucose infusion                          |
| Maltose infusion                          |
| SGLT2-inhibitors                          |

Abbreviations: IVIg, intravenous immune globulin;
Figure Legend

Figure 1. Osmotic nephropathy. A) Light microscopy focusing on the renal tubules demonstrates vacuolization and swelling of proximal tubular cells in a patient exposed to hydroxyethyl starch. This finding is characteristic of osmotic nephropathy. B) Apical membrane handling of various agents by proximal tubular cells increases cellular uptake of this potentially nephrotoxic drug. Drugs such as IVIg (stabilizers sucrose>glucose>maltose), hydroxyethyl starch, dextran, mannitol and contrast are filtered at the glomerulus, undergo apical cell membrane pinocytosis and enter the cell where they are translocated into lysosomes. These substances accumulate within lysosomes, which promote cellular swelling, occlusion of tubular lumens, and eventual lysosomal rupture resulting in tubular cell injury.
Figure 1B

Proximal Tubule

Apical

Basolateral

mitochondrion

nucleus

ATPase

K+

Na+

lysosome