Sodium glucose transporter 2 inhibition, euglycemic ketosis and bone mineral loss: Refining clinical practices

Sir,

The authors read with the great interest about the recent publication by Kalra *et al.* highlighting the occurrence of ketosis in a subset of patients receiving the sodium glucose transporter 2 (SGLT2) inhibitors for managing diabetes.[1] Additional literature in this regard is now available with European Medicines Agency and now reporting as many as 101 cases of diabetic ketoacidosis in patients receiving SGLT2 inhibitors (SGLT2i) for managing the type-2 diabetes mellitus (T2DM).[2] The use of the term "euglycemic ketoacidosis" has been proposed, as a majority of these patients had either normal or moderately raised blood glucose levels.[2] SGLT2 expression has been documented on pancreatic alpha cells, and its inhibition by SGLT2i is believed to increase the expression of preproglucagon gene, explaining the increased glucagon levels in these patients.[3] This increased glucagon not only leads to increased hepatic glucose output, blunting the efficacy of the drug but also leads to increased circulating glucagon/insulin ratio.[4] Increased glucagon/insulin ratio, especially in the setting of insulinopenia (sudden stoppage of insulin, uncontrolled diabetes with significant glucotoxicity, type-1 diabetes, catabolic state, severe malnutrition, starvation, metabolically decompensated state) leads to increased lipolysis and ketogenesis, which occurs in the setting normal to mildly increased blood glucose, a result of increased renal glycosuria due to SGLT2i. In addition, SGLT2i may also decrease urinary ketones excretion by enhancing the reabsorption of acetoacetate, as has been observed with phlorizin, thus further aggravating the process.[5]

Another important but less well highlighted issue with the use of SGLT2i is perhaps the adverse impact on bone health. Use of dapagiflozin in patients with moderate renal impairment over 104 weeks was associated with fractures in 7.74% patients (13/168), in contrast to none in the placebo group.[6] Pooled analysis of data from 8 clinical trials on the use of canagliflozin in managing diabetes (mean duration 68 weeks), revealed a 30% increased risk of fractures.[7] A decrease in bone mineral density at spine and hip has been documented with the use of canagliflozin at 300 mg/day for 52 weeks.[8] It has been suggested that the decreased sodium (Na^+) transport in proximal convoluted tubule (PCT) secondary to SGLT2 inhibition, leads to increased intra-luminal Na^+, leading to increased activity of sodium phosphate co-transporter (in the PCT), resulting in increased renal phosphate resorption.[7] Increased serum phosphate is a potent stimulus for increased release of parathyroid hormone (PTH) from the parathyroid glands, leading to increased bone turnover and bone mineral loss. Increased PTH also leads to increased fibroblast growth factor (FGF)-23, which in turn inhibits the activity of the renal 1-alpha-hydroxylase enzyme, leading to decreased circulating levels of 1,25-dihydroxyvitamin-D. 1,25-dihydroxyvitamin-D has an important role in increasing calcium absorption from gut and bone formation. In fact, the increased serum phosphate, PTH, FGF23 along with decreased 1,25-dihydroxyvitamin-D have been documented in patients receiving SGLT2i.[7]

The glycemic efficacy and the unique insulin independent glucuretic mode of action of SGLTi were never in doubt.[9] However in view of recent literature, in order to maximize the glycemic benefits along with minimizing potential side effects, it may be advisable not to use SGLT2i in perioperative, ill, hospitalized patients, patients on low carbohydrate diet, not taking orally, patients with malnutrition, in a metabolically, decompensate state, and to minimize the risk of euglycemic ketoacidosis. Similarly use of SGLT2i in patients of T2DM on pioglitazone or with any coexistent cause of bone mineral loss (postmenopausal osteoporosis, diabetes associated bone fragility, secondary osteoporosis) may be avoided till further data is available from the clinical studies. These clinical scenarios are in addition to old age patients with T2DM (possibly >75 years age), patients with autonomic neuropathy, those on loop diuretics, where use of SGLTi may be restricted due to the increased risk of hypotensive crisis secondary to osmotic diuresis induced by SGLT2i. Similarly, it may not be advisable to use SGLT2i in patients with recurrent urinary tract infections, or patients with any structural abnormality in the urinary tract which *per se* predisposes to urinary infection. The ideal clinical scenario where SGLT2i would probably be of the greatest clinical benefit would be a young obese or overweight, insulin resistant T2DM patient with metabolic syndrome.

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Conflicts of interest

There are no conflicts of interest.

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