HHS Public Access

Author manuscript

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2016 June 09.

Published in final edited form as:

Lancet Diabetes Endocrinol. 2015 January ; 3(1): 8–10. doi:10.1016/S2213-8587(14)70227-X.

SGLT2-inhibitors Trigger Downstream Mechanisms That May Exert Adverse Effects Upon Bone

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SGLT2 inhibitors decrease plasma glucose concentrations by inhibiting proximal tubular reabsorption of glucose in the kidney.[1] The attractive efficacy profile of glucose-lowering plus weight loss must be balanced against possible side effects, including an increase in the incidence of treatment-emergent bone fractures observed in clinical studies. In a study of moderate renal impairment, 9.4% of patients treated with dapagliflozin (10 mg) experienced bone fractures while no fractures were observed in placebo-treated patients.[2] Furthermore, a ~30% increase in bone fractures was observed in canagliflozin-treated patients in eight pooled clinical trials with longer mean duration (68 weeks).[3] Although these data suggest the possibility that SGLT2 inhibitors might increase the risk of bone fractures, additional data will be required before drawing a firm conclusion.

SGLT2 inhibitors increase tubular reabsorption of phosphate, thereby increasing serum phosphate levels[3,4] (Fig. 1A). The body has evolved complex homeostatic mechanisms to regulate phosphate, and an increase in serum phosphate has the potential to exert an adverse impact upon bone (Fig. 1B). For example, phosphate administration increases PTH secretion.[6] Furthermore, SGLT2 inhibitors increase levels of both phosphate and PTH.[3,4] While canagliflozin caused a small increase in mean PTH (+7.9%), the standard deviation (SD) was relatively large (39.3%).[3] Thus, a substantial number of canagliflozin-treated patients might experience a >50% increase in PTH levels – a change that could be clinically significant. In addition, phosphate administration has been reported to increase FGF23 levels

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Contributors

All authors contributed to reviewing the published literature, drafting and revising the manuscript, reviewing it for intellectual content, designing a follow-up study to test the hypothesis, and have approved the final form of the manuscript.

Conflicts of interest

SIT was previously employed by and currently owns restricted stock in the Bristol-Myers Squibb Company. In addition, he is a paid consultant and adviser for the following companies: Aegerion Pharmaceuticals, Inc.; Ambrx, Inc.; Calibrium, LLC; Genkyotex, S.A.; Isis Pharmaceuticals, Inc.; Nimbus Discovery, LLC; Yabao Pharmaceutical Co., Ltd.; and Cadila Healthcare Limited. Neither JEB nor KIR have any conflicts of interest to report.

in healthy volunteers,[7] which would decrease 1,25-dihydroxyvitamin D levels. However, the mechanisms whereby phosphate regulates FGF23 remain controversial.[8] In *in vitro* studies, phosphate exerts a direct effect to increase FGF23 mRNA levels in primary human fetal bone cells.[9] In contrast, some evidence suggests phosphate decreases FGF23 expression by an indirect mechanism – possibly mediated by PTH.[8] In light of the controversy, it is critical to conduct clinical studies to assess the effect of SGLT2 inhibitors upon FGF23 levels.

Phosphate administration increases both PTH and FGF23, two hormones that exert opposing effects upon vitamin D metabolism[8] with PTH increasing and FGF23 decreasing 1,25-dihydroxyvitamin D levels. Accordingly, if SGLT2 inhibitors increase levels of both PTH and FGF23, one could not predict *a priori* the net impact upon 1,25-dihydroxyvitamin D. Nevertheless, available data suggest that SGLT2 inhibitors decrease mean 1,25-dihydroxyvitamin D levels.[3] Canagliflozin caused a small decrease in mean 1,25-dihydroxyvitamin D levels (−12%), but the SD was relatively large (42.4%).[3] Thus, a significant percentage of canagliflozin-treated patients could experience a clinically significant ~50% decrease in 1,25-dihydroxyvitamin D levels.

In contrast to clinical data suggesting an increase in PTH, supratherapeutical doses of dapagliflozin decreased PTH in rats.[10] An investigative toxicology study elucidated the mechanism.[10] Dapagliflozin is relatively selective for SGLT2, but high doses administered in toxicology experiments were sufficient to inhibit intestinal SGLT1, which led to glucose malabsorption. Colonic bacteria fermented the unabsorbed glucose, which acidified the intestinal contents. Acid pH increased solubility of calcium, promoted calcium absorption, suppressed PTH, and promoted ectopic calcification. These supratherapeutic doses of SGLT2 inhibitor are unlikely to be relevant to human pharmacology with approved doses of selective SGLT2 inhbitors.[10]

Sustained increases in PTH enhance bone resorption, and increase the risk of bone fractures. Similarly, increased levels of FGF23 have been associated with bone disease.[8] Finally, decreased levels of 1,25-dihydroxyvitamin D may decrease absorption of Ca^{+2} from the GI tract, and impair bone calcification. Consistent with these mechanisms, canagliflozin was observed to increase bone turnover as reflected by increases in levels of both collagen type 1 beta-carboxy-telopeptide levels and osteocalcin (biomarkers for bone resorption and bone formation, respectively). In addition, both DXA and quantitative CT detected a decrease in bone mineral density in the lumbar spine and total hip after 52 weeks of therapy with canagliflozin (300 mg).[3] In contrast, there was no statistically significant change in bone mineral density at the distal forearm and femoral neck. Additional data could place these observations into context – including a correlation of clinical outcomes (i.e., fractures) with changes in bone biomarkers and bone mineral density in individual patients.

The existence of numerous homeostatic mechanisms creates challenges in interpretation of studies of mechanisms whereby SGLT2 inhibitors could affect bone health. For example, an increase in serum phosphate is predicted to increase FGF23 and PTH – both of which promote phosphaturia. Because of this negative feedback, the maximum increase in mean serum phosphate may be transient and/or small in magnitude. Nevertheless, even small changes may significantly affect bone health over years of drug exposure. Finally, it is

important to recognize that most drug-treated patients do not experience bone fractures. Bone fractures may be most likely to occur in the subpopulation of "outlier" patients with above average changes in bone-related parameters. In short, mean data may not provide a full picture of the impact upon bone.

Patients with type 2 diabetes are especially susceptible to adverse effects of drugs upon bone because of coexisting bone diseases (including post-menopausal osteoporosis, renal osteodystrophy, and diabetes-associated bone fragility). As reported in the ADOPT trial, thiazolidinediones increase the risk of bone fractures.[11] After a one year lag, rosiglitazone-treated patients experienced an increase in bone fractures (hazard ratio, 1.6). Similarly, the fracture rate was not increased during the first year of treatment with canagliflozin, but patients experienced more fractures during the second year of therapy.[3] The median follow-up for rosiglitazone-treated patients was four years, suggesting that the average duration of the pooled canagliflozin studies (68 weeks) was likely too short to provide conclusive data on fracture risk. Fortunately, ongoing FDA-mandated cardiovascular outcome studies with SGLT2 inhibitors are of sufficient size and duration to assess the risk of bone fractures.

Several arguments have been advanced suggesting that the observed increase in fracture rate might be a "chance phenomenon".[2] For example, some fractures occur in the feet, hands, and patella, which were stated not to be associated with bone health.[2,3] At the time of the FDA's Dapagliflozin Advisory Committee, eight fractures had been observed among patients treated with dapagliflozin (10 mg) in the special study of patients with moderate renal impairment. These included one patient with a fractured patella and one with a foot fracture. It is impossible to draw firm conclusions based upon these two patients – either about the distribution of fractures among anatomical sites or whether the increased number of fractures will ultimately be confirmed as a toxicity associated with SGLT2 inhibitors.

In contrast to biomarker data suggesting canagliflozin increases bone turnover,[3] it has been reported that dapagliflozin does not affect mean bone mineral density or biomarkers of bone turnover in patients with normal to mildly impaired renal function.[3,4] These obervations raise the question of whether the bone effects might be a compound-specific rather than mechanism-based. However, the literature suggests that any differences among compounds may be the consequence of dose selection rather than an intrinsic difference between the two compounds. Whereas the 300 mg dose of canagliflozin delivers maximal inhibition of SGLT2,[3] the 10 mg dose of dapagliflozin delivers only sub-maximal inhibition.[12] Specifically, the 10 mg dose was reported to cause ~35 g/day of urinary glucose excretion – approximately 35% less than the urinary glucose excretion caused by maximally effective doses of dapagliflozin (50–100 mg).[4] Thus, canagliflozin (300 mg) might be more efficacious than dapagliflozin (10 mg) with respect to all mechanism-based pharmacology (both mechanism-based toxicity and glucose-lowering). It would require head-to-head trials to draw firm conclusions about comparative benefit:risk profiles of individual SGLT2 inhibitors.

In conclusion, SGLT2 inhibitors have been observed to increase the incidence of treatment-emergent bone fractures, and the risk of fractures appears to increase over time. We have hypothesized plausible pathophysiologic mechanisms with potential to mediate adverse

effects upon bone. Future mechanistic research may identify patients who are most vulnerable to develop drug-induced bone fractures (e.g., post-menopausal women), and may suggest therapeutic approaches to minimize the risk.

Acknowledgments

This work was supported by the Intramural Research Programs of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). We are grateful to Dr. Michael T. Collins and Dr. Marc L. Reitman for helpful scientific discussions.

Role of the Funding Source

KIR and JEB received salary support from NIDDK and NICHD, respectively. NIDDK reviewed and approved the manuscript for publication, but the views and opinions of the authors expressed in this manuscript do not necessarily state or reflect those of the U. S. Government.

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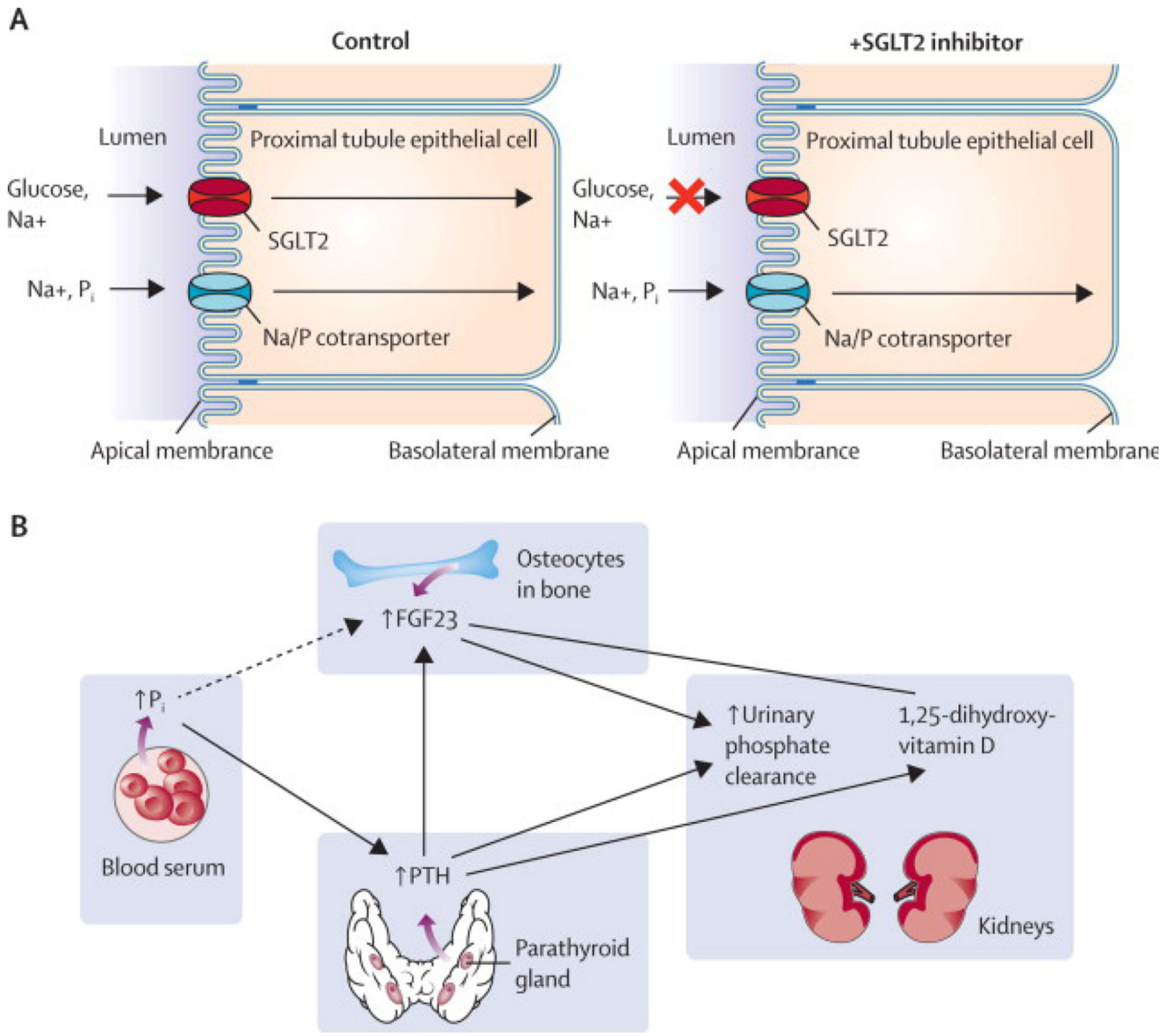

Figure 1. Proposed mechanisms whereby SGTL2 inhibitors exert adverse effects on bone

Panel A: Published data demonstrate that SGLT2 inhibitors increase serum phosphate levels,[3,4] probably by promoting renal tubular phosphate reabsorption.[5] Because of the action of SGLT2 inhibitors to decrease Na^+ transport, this increases the electrochemical gradient for Na^+, thereby driving increased co-transport of phosphate and Na^+. In human studies, phlorizin (a non-selective SGLT1/ SGLT2 inhibitor) decreased phosphate clearance by an average of ~80% during the first hour after phlorizin administration.[5] Furthermore, phlorizin promotes phosphate reabsorption in perfused proximal convoluted tubules. This is likely the mechanism of the observed SGLT2 inhibitor-induced increase in serum phosphate. *Panel B*: Increased levels of serum phosphate are predicted to increase secretion of PTH by the parathyroid gland.[6] Either directly or indirectly (e.g., mediated by effects of PTH), the increased serum phosphate has the potential to increase FGF23 secretion by osteocytes in

bone.[7–9] The effect of phosphate to promote PTH secretion is believed to be mediated, at least in part, by the effect of increased phosphate levels to decrease levels of free ionized Ca^{++}.[6] Both PTH and FGF23 promote phosphaturia by decreasing renal tubular reabsorption of phosphate.[8] In contrast, the two hormones exert opposite effects upon 1α-hydroxylation of 25-hydroxyvitamin D – with PTH increasing and FGF23 decreasing 1,25-dihydroxyvitamin D formation.[8]