EDITORIAL

# SGLT2 Inhibitors and Fracture Risk in Elderly Population

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Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are the latest class of anti-diabetic medication that inhibit the absorption of glucose from the proximal tubule of the kidney and hence cause therapeutic glycosuria. Four SGLT2i are currently commercially available ie. canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. SGLT2i reduce glycated hemoglobin and have shown favorable effects on body weight, blood pressure, lipid profile, arterial stiffness and endothelial function.[1]

The main adverse events include urinary tract and genital infections, as well as euglycemic diabetic ketoacidosis. Concerns have also been raised about their rare association with lower limb amputations, Fournier gangrene, risk of bone fractures, female breast cancer, male bladder cancer, orthostatic hypotension, and acute kidney injury. [1]

Since, Type 2 diabetes mellitus (T2DM) is associated with an increased fracture risk. It is debated presently that whether sodium-glucose cotransporter 2 (SGLT2) inhibitors influence fracture risk in T2DM particularly in the elderly patients or not.

The debate and concern was actually created by the finding that canagliflozin, a sodiumglucose co-transporter-2 (SGLT) inhibitor, increased the risk for fracture compared with placebo in the Canagliflozin Cardiovascular Assessment Study (CANVAS), a large randomized controlled trial (RCT). [2]

However, in a recent study SGLT2 inhibitors compared to glucagon-like peptide 1 (GLP-1) receptor agonists when used as add-on therapies to metformin suggested that SGLT2 inhibitors have no effect on fracture risk when compared to GLP-1 receptor agonists. [3]

Similarly, a retrospective cohort study suggested that SGLT-2 inhibitor use was not associated with increased osteoporotic fracture risk, irrespective of change in BMI. However, a high cumulative dose could be an important risk factor. [4]

Another nationwide Medicare cohort study indicated that SGLT-2 was not associated with an increased risk of fracture in older adults with T2DM compared with initiating a DPP-4i or GLP-1 receptor agonists, and results were consistent across all categories of frailty, age, and insulin use. [5]

In a recent meta-analysis of 30 randomized controlled trials patients with T2DM), the incidence of bone fractures did not differ between the groups receiving SGLT2 inhibitors and placebo.[6] When the effects of canagliflozin, dapagliflozin, and empagliflozin on fractures

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**Published Online First**: 10 Jan 2023

**Open Access at**: https://journal.jkscience.org



**Cite this article as:** Tandon VR, Mahajan A. SGLT2 inhibitors and Fracture Risk in Elderly Population. JK Science 2023;25(1):1-2

were analyzed separately, none was associated with increased risk for fracture. [6]

In another recent meta-analysis of 27 randomized controlled trials SGLT2 inhibitors did not show any increase in the risk of fracture compared with placebo. In groups at higher risk for fracture, including women and the elderly, no increase in the incidence of fracture was noted either. Moreover the effects of SGLT2 inhibitors on BMD did not show any change in the evaluated skeletal sites (lumbar spine, femoral neck, total hip, and distal forearm) . [7]

Therefore, available data are inconclusive to attribute any possibility of increased fracture risk to SGLT2 Inhibitors. However, advancing age, menopause and diabetes are themselves established risk factors for increased incidence of fracture. Although Sodium-glucose co-transporter 2 inhibitors have many benefits including tight glycaemic control as add on therapy and effective weight reduction, which is very relevant in advancing age population. However, till more safety data emerge from large clinical trials regarding fracture risk, they at present cannot be recommended as first line diabetic management for elderly population for long term mangement.

**Financial Support and Sponsorship**

Nil

**Conflicts of Interest**

There are no conflicts of interest.

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