[14] Wettasinghe KT, Sirisena ND, Andraweera PH, Jayasekara RW, Dissanayake VHW. A case series of five Sri Lankan patients with ovotesticular disorder of sex development. Clin Pediatr Endocrinol 2012;21(4):69–73.
[15] Hong X, Ying Y, Xu X, Liu Y, Chen Z, Lan X, et al. A dispermic chimera was identified in a healthy man with mixed field agglutination reaction in ABO blood grouping and mosaic 46, XY/46, XX karyotype. Transfus Apher Sci 2013;48(2):223–8 [Available from: https://www.sciencedirect.com/science/article/pii/S1473050212002406].
[16] Sugawara N, Kimura Y, Araki Y. Successful second delivery outcome using refrozen thawed testicular sperm from an infertile male true hermaphrodite with a 46, XX/46, XY karyotype: case report. Hum Cell 2012;25(4):96–9.
[17] Laursen RJ, Alsbjerg B, Vogel I, Gravholt CH, Elbaek H, Lildballe DL, et al. Case of successful IVF treatment of an oligospermic male with 46,XX/46, XY chimerism. J Assist Reprod Genet 2018;35(7):1325–8.

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Treatment with sodium-glucose cotransporter-2 inhibitors in heart failure patients: The potential benefits of monitoring FGF-23 levels?

Les inhibiteurs du co-transporteur du sodium-glucose de type 2 pour le traitement de l'insuffisance cardiaque : l'apport éventuel de surveiller le FGF-23

The prevalence of heart failure (HF) is continuously increasing, reinforcing the need for innovative diagnostic and therapeutic tools [1,2]. Inhibitors of sodium–glucose cotransporter 2 (SGLT2i) were developed to lower blood glucose levels in patients with T2DM and their effect, independent of insulin secretion, is mediated through the promotion of urinary glucose excretion [3]. SGLT2i improve several clinical outcomes in diabetic patients [3,4]. SGLT2i are also recommended as treatment in HF patients because of their benefits on both cardiac and renal functions [5,6]. The EMPEROR-Reduced Trial showed that Empagliflozin reduced the risk and total number of inpatient and outpatient worsening HF events in patients with HF and a reduced ejection fraction [6]. A prespecified meta-analysis on two independent large-scale trials showed that the effects of empagliflozin and dapagliflozin on hospitalizations for HF were consistent and suggest that these agents also improve renal outcomes and reduce all-cause and cardiovascular [5].

Several mechanisms explain the beneficial effects of SGLT2i. Through the promotion of glycosuria, SGLT2i increase diuresis and natriuresis and can therefore optimize ventricular loading conditions, in addition to reducing afterload and improving vascular structure and function [1]. Furthermore, SGLT2i could have different cardioprotective metabolic effects on improve myocardial energetics [1,3]. It was shown that the SGLT2i empagliflozin exerts direct pleiotropic effects on the myocardium by reducing diastolic stiffness and hence diastolic function. In a nondiabetic porcine model, empagliflozin reduced adverse cardiac remodeling and heart failure [7].

Considering their benefits on clinical outcomes, the effects SGLT2i on biological and neurohormonal responses were evaluated in different studies. SGLT2 inhibitors influence glucose metabolism, cations exchanges, lipid metabolism, kidney function, renin-angiotensin-aldosterone system, as well as various mediators of inflammation and fibrosis [3,8]. The influence of SGLT2i on natriuretic peptides has also been reported. In comparison to placebo, SGLT2i significantly decreased the levels of A-type natriuretic peptides (ANP) and B-type natriuretic peptides (BNP) [9]. In a subgroup of diabetic patients with diatolic dysfunction, lower NT-proBNP concentrations were reported in a canagliflozin group compared with a glimepiride group [10]. In HF patients with preserved ejection fraction, an extent of BNP reductions at four weeks in canagliflozin group in comparison to standard therapy group [12]. However, in another study including uncomplicated and relatively healthy type 2 diabetes participants, BNP levels were not affected [11].

Testing and monitoring of circulating concentrations of another biomarker, fibroblast growth factor 23 (FGF-23), could be relevant when SGLT2i treatment is initiated for at least two reasons.

First, as a biomarker of risk of adverse cardiovascular events. FGF-23 is produced by osteocytes and is a potent phosphaturic hormone regulating bone and mineral metabolism [2]. FGF-23 increases phosphate excretion, decreases 1-α-hydroxylation of 25-hydroxyvitamin D, and decreases PTH secretion [2]. FGF-23 concentrations are increased in different cardiometabolic disorders such as prediabetes, in patients with HF and in patients with atrial fibrillation [2,13]. Interestingly, FGF-23 appears also as a strong biomarker of adverse cardiovascular events [2,13]. Furthermore, FGF-23 is a biomarker of fibrosis and prognosis in HF patients with preserved ejection fraction [14].

Secondly, as a biomarker of bone and mineral metabolism. An association of SGLT2i and the risk of fractures as well as abnormal bone turnover and architecture has been suggested [15,16]. Therefore, attention was given to impact of SGLT2i on ions and biomarkers related to calcium metabolism. SGLT2i induce small increases in serum concentrations of magnesium, potassium and phosphate in addition to increase of parathyroid hormone (PTH) and decrease of 1,25(OH) vitamin D [17]. This was not related to significant change of calcium levels. SGLT2i inhibit sodium and glucose cotransport, enhancing phosphate carriage via sodium-phosphate cotransport in proximal tubules [17]. The increase in serum phosphorus level associated with SLGT2 inhibition was reported to be associated with increased of FGF-23 level, as part of a compensatory reaction to maintain phosphate homeostasis [18]. A raise of about twenty percent of FGF-23 circulating concentration was observed following treatment with dapagliflozin and canagliflozin but has not been documented yet for empagliflozin [18,19]. Such an increase in FGF-23 circulating level might not be trivial, with potential impact on bone and mineral metabolism (Fig. 1).

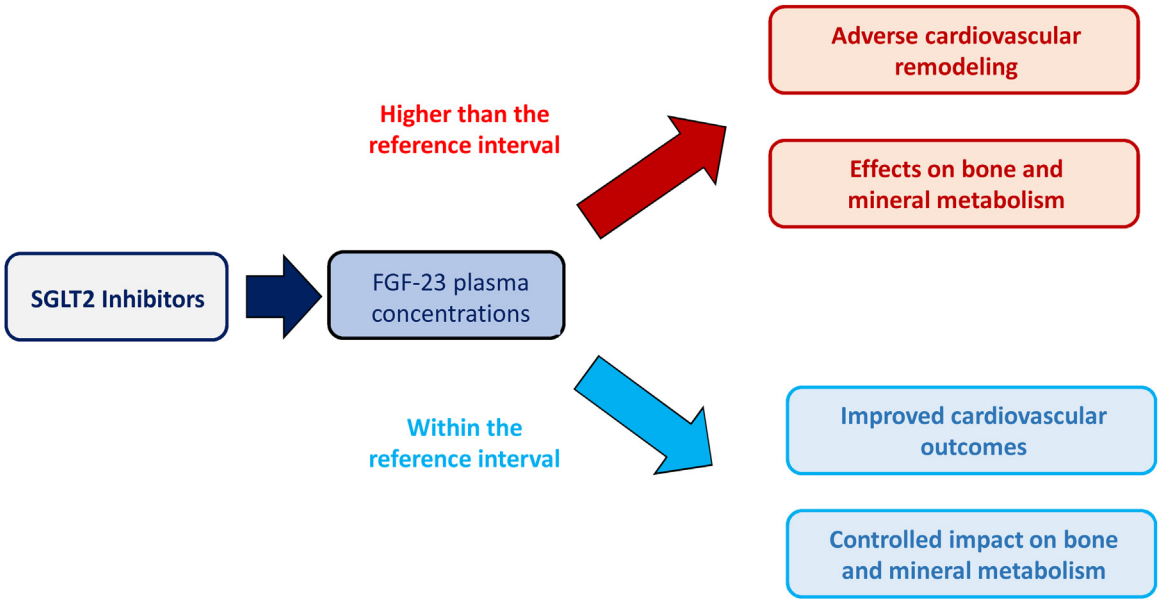

Fig. 1. The potential influence of sodium–glucose cotransporter 2 (SGLT2) inhibitors on bone and mineral metabolism and cardiovascular remodeling through stimulation of fibroblast growth factor 23 (FGF-23).

Conclusion

SGLT2 inhibitors have shown effective glucose-lowering effects associated with improved clinical outcomes in diabetic patients as well as in patients with heart failure. Because of its value as biomarker of bone and mineral metabolism and of adverse cardiovascular events, testing for FGF-23 could represent a powerful tool, in addition to standard of care biomarkers, to monitor the efficiency and safety of SGLT2i.

Ethical statement

The authors respect the code of conduct for ethical research and publishing.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Verma S, McMurray JJv. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia [Internet] 2018;61:2108–17 [cited 2019 Aug 24. Available from: http://link.springer.com/10.1007/s00125-018-4670-7].
[2] Fauconnier C, Roy T, Gillerot G, Roy C, Pouleur A-C, Gruson D. FGF23: clinical usefulness and analytical evolution. Clin Biochem [Internet] 2019;66:1–12 [cited 2019 Aug 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30853324].
[3] Verma S, McMurray JJv, Cherney DZI. The metabolodiuretic promise of sodium-dependent glucose cotransporter 2 inhibition: the search for the sweet spot in heart failure. JAMA Cardiol [Internet] 2017;2:939–40 [cited 2019 Aug 24. Available from: http://cardiology.jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2017.1891].
[4] Ingelfinger JR, Rosen CJ. Clinical credence – SGLT2 inhibitors, diabetes, and chronic kidney disease. N Engl J Med [Internet] 2019;380:2371–3 [cited 2019 Aug 24. Available from: http://www.nejm.org/doi/10.1056/NEJMe1904740].
[5] Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet [Internet] 2020;396(10254):819–29 [cited 2020 Aug 31. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620318249].
[6] Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced Trial. Circulation [Internet] 2021;143:326–36 [cited 2021 Aug 26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33081531].
[7] Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. J Am Coll Cardiol [Internet] 2019;73:1931–44 [cited 2019 Aug 24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109719336897].
[8] Heerspink HJL, Perco P, Mulder S, Leierer J, Hansen MK, Heinzel A, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia [Internet] 2019;62:1154–66 [cited 2019 Aug 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31001673].
[9] Feng X, Gu Q, Gao G, Yuan L, Li Q, Zhang Y. The plasma levels of atrial natriuretic peptide and brain natriuretic peptide in type 2 diabetes treated with sodium-glucose cotransporter-2 inhibitor. Ann Endocrinol [Internet] 2020;81:476–81 [cited 2021 Aug 26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32822653].
[10] Kusunose K, Imai T, Tanaka A, Dohi K, Shiina K, Yamada T, et al. Effects of canagliflozin on NT-proBNP stratified by left ventricular diastolic function in patients with type 2 diabetes and chronic heart failure: a sub analysis of the CANDLE trial. Cardiovasc Diabetol [Internet] 2021;20:186 [cited 2021 Sep 28. Available from: https://pubmed.ncbi.nlm.nih.gov/34521417/].
[11] Ueda T, Kasama S, Yamamoto M, Nakano T, Ueshima K, Morikawa Y, et al. Effect of the sodium-glucose cotransporter 2 inhibitor canagliflozin for heart failure with preserved ejection fraction in patients with type 2 diabetes. Circ Rep [Internet] 2021;3:440–8 [cited 2021 Sep 28. Available from: https://pubmed.ncbi.nlm.nih.gov/34414333/].
[12] Ang L, Kidwell KM, Dillon B, Reiss J, Fang F, Leone V, et al. Dapagliflozin and measures of cardiovascular autonomic function in patients with type 2 diabetes (T2D). J Diabetes Complications [Internet] 2021;35 [cited 2021 Sep 28. Available from: https://pubmed.ncbi.nlm.nih.gov/34024686/].
[13] Gruson D, Lepoutre T, Ketelslegers J-M, Cumps J, Ahn SA, Rousseau MF. C-terminal FGF23 is a strong predictor of survival in systolic heart failure. Peptides 2012;37(2):258–62.
[14] Roy C, Lejeune S, Slimani A, de Meester C, Ahn As SA, Rousseau MF, et al. Fibroblast growth factor 23: a biomarker of fibrosis and prognosis in heart failure with preserved ejection fraction. ESC Heart Failure [Internet] 2020;7:2494–507 [cited 2021 Aug 26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32578967].
[15] Pelletier R, Ng K, Alkabbani W, Labib Y, Mourad N, Gamble JM. Adverse events associated with sodium-glucose cotransporter 2 inhibitors: an overview of quantitative systematic reviews. Ther Adv Drug Safety [Internet] 2021;12 [cited 2021 Sep 29. Available from: https://pubmed.ncbi.nlm.nih.gov/33552467/].
[16] Jackson K, Moseley KF. Diabetes and bone fragility: SGLT2 inhibitor use in the context of renal and cardiovascular benefits. Curr Osteoporosis Rep [Internet] 2020;18:439–48 [cited 2021 Sep 29. Available from: https://pubmed.ncbi.nlm.nih.gov/32710428/].
[17] Ye Y, Zhao C, Liang J, Yang Y, Yu M, Qu X. Effect of sodium-glucose cotransporter 2 inhibitors on bone metabolism and fracture risk. Front Pharmacol [Internet] 2019;9:1517 [cited 2019 Aug 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30670968].
[18] Blau JE, Bauman V, Conway EM, Piaggi P, Walter MF, Wright EC, et al. Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH

axis in healthy volunteers in a randomized crossover study. JCI Insight [Internet] 2018;3(8):e9912 [cited 2019 Aug 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29669938].
[19] de Jong MA, Petrykiv SI, Laverman GD, van Herwaarden AE, de Zeeuw D, Bakker SJL, et al. Effects of dapagliflozin on circulating markers of phosphate homeostasis. Clin J Am Soc Nephrol [Internet] 2019;14:66–73 [cited 2019 Aug 24. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.04530418].

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