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Review Article

Iron absorption, bone marrow fat and hematopoiesis in heart failure: Additional mechanisms of action for sodium-glucose co-transporter 2 inhibitors (SGLT2i)?

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) exert cardiorenal benefits, including reductions in the rate of hospitalization for heart failure (HF).[1] It has been suggested that the SGLT2i-induced decrease in HF events involves multifactorial mechanisms beyond glucose lowering. These include natriuresis and volume depletion, a metabolic shift towards ketone bodies (a "better fuel" for the myocardium), improved oxygen supply due to increased hematocrit, reduced glomerular pressure, altered Na^+/H^+ exchange in the kidneys and the heart, as well as reduced sarcoplasmic calcium that improves ventricular contractility.[1] However, the exact mechanisms remain unknown.

Iron deficiency (ID) negatively affects mitochondrial function and has been linked to HF development.[2] Furthermore, ID is common in HF patients, and it has been related to impaired quality of life, reduced exercise performance as well as increased rates of hospitalization and mortality, irrespective of the presence or absence of anemia.[3,4] Intravenous iron therapy is recommended in patients with HF and ID,[5] improving symptoms, exercise capacity, outcomes and quality of life, as well as reducing HF hospitalizations.[4,6,7]

ID in HF may result from impaired iron absorption due to intestinal interstitial edema.[8] SGLT2i may selectively decrease interstitial volume, while minimally affecting blood volume.[9,10] Whether these drugs also improve intestinal interstitial edema, and thus indirectly ID in HF patients, should be investigated. It should be noted that ID may impair glucose metabolism, thus predisposing to incident diabetes mellitus (DM).[11,12] ID has also been linked to worse glycemic control in both type 1 and 2 DM patients, as well as with the development of diabetic complications.[11] Therefore, preventing or treating ID and ID-related anemia can be beneficial, especially in DM patients.

Inflammation and overactivity of both the renin-angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS) may inhibit iron cellular uptake by blocking the transferrin receptor.[4] SGLT2i have been shown to reduce inflammation in cardiac and renal tissues.[13–15] Furthermore, the levels of high-sensitivity C-reactive protein (hsCRP), a reliable inflammatory marker in the circulation, were significantly decreased by empagliflozin, dapagliflozin, luseogliflozin and ipragliflozin.[16–19] No data exist for canagliflozin, ertugliflozin, sotagliflozin and tofogliflozin. Regarding SNS overactivity, luseogliflozin improved SNS circadian rhythm in rats,[20] whereas dapagliflozin significantly decreased noradrenaline expression in the heart and kidney of mice.[21] It has been suggested that SGLT2i can decrease SNS activity, thus explaining why these drugs can lower plasma volume and blood pressure without affecting heart rate.[22] Whether inhibition of inflammation and the SNS, induced by SGLT2i, may also enhance the function of transferrin receptor, and thus iron uptake, remains to be elucidated. Such an effect could improve ID in HF patients.

Serum ferritin is a reliable indicator of iron stores.[8] In the general population, a ferritin level of <30 μg/L reflects an absolute ID, whereas higher cut-off values (i.e. 100 μg/L) should be used in HF, since ferritin is an acute phase reactant and thus its levels are elevated in chronic inflammatory diseases (including HF).[8] Another type of ID is functional ID, characterized by low transferrin saturation (TSAT) that is calculated as the ratio of serum iron and total iron-binding capacity by transferrin (TIBC).[8] In HF, functional ID is defined as serum ferritin 100–300 μg/L in combination with a TSAT of <20%.[8]

A 24-week single-arm, nonrandomized, open-label study, showed that dapagliflozin 5 mg/day significantly improved serum ferritin concentrations in 16 type 2 diabetes mellitus (T2DM) patients with biopsy-proven nonalcoholic steatohepatitis (NASH).[23] Similarly, canagliflozin 100 mg/day significantly reduced serum ferritin levels at 3 and 6 months in 35 T2DM patients with nonalcoholic fatty liver disease (NAFLD) diagnosed by ultrasonography.[24] Ipragliflozin (50 mg/day) and luseogliflozin (2.5 mg/day), currently available only in Japan, were also reported to lower serum ferritin concentrations: ipragliflozin after 4 months in a case study[25] and luseogliflozin after 24 weeks in 40 T2DM patients with NAFLD (defined by ultrasonography) in a prospective, single-arm trial.[26] An ongoing randomized, double-blinded, placebo-controlled trial will measure plasma concentrations of transferrin, iron, TSAT and ferritin in 34 T2DM patients treated with empagliflozin or placebo.[27] There are no data for ertugliflozin, sotagliflozin and tofogliflozin. Therefore, there is some limited evidence that SGLT2i may lower ferritin levels and TSAT, but further research is needed.

Bone marrow (BM) adipose tissue has been recognized as an endocrine organ.[28] After subcutaneous and visceral adipose tissue, BM fat is the third largest fat depot.[29] BM adipocytes can negatively influence hematopoiesis through the secretion of adipocyte-derived factors and direct contact with cells.[29] Furthermore, fat and bone cells arise from the same progenitor within the bone marrow niche.[30] In this context, the expansion of BM adiposity has been reported as fatty degeneration of the red marrow.[28] Hypertensive HF is characterized by increased erythropoietic demand and reduced BM adipose tissue.[28]

There are no data on the effects of SGLT2i on BM fat. Of note, SGLT2 expression in BM is very low,[31,32] suggesting a minor role of SGLT2i within bone tissue.[33] However, dapagliflozin was shown to reduce macrophage infiltration and improve fat metabolism in mice bone marrow.[34] Furthermore, SGTL2i have been reported to increase

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hematopoiesis in BM.[35] Taking into consideration that a negative association exists between BM fat and hematopoiesis, it follows that when hematopoiesis increases, BM adiposity may decrease. SGLT2i may also reduce abnormal peri- and intra-organ fat (APIFat) deposition, and especially NAFLD and epicardial fat.[36–39] Whether BM fat accumulation is affected by SGLT2i should be investigated.

The prevalence of anemia in HF ranges from 30% in stable HF to 50% in hospitalized patients, irrespective of the presence of reduced or preserved ejection fraction.[40] Anemic HF patients are older, have more edema and requirement for diuretics, are more likely to have T2DM and chronic kidney disease, as well as more prone to lower exercise capacity, worse quality of life and functional status compared with non-anemic patients.[40] Overall, anemia is a marker of poor prognosis and HF severity.[41] Of note, elevations in hematocrit has also been observed during SGLT2i therapy, most likely due to their diuretic effect, as well as enhanced erythropoiesis.[42–45] Indeed, SGLT2i can increase erythropoietin and hematocrit.[46] This effect was initially regarded as a double-edged sword i.e. beneficial for the heart but at the same time potentially increasing the risk of ischemic stroke since higher hematocrit levels have been linked to a greater stroke incidence.[47] Of note, both decreased and elevated hematocrit concentrations have been associated with an increased risk of ischemic stroke.[48] The initial speculation on this issue was not confirmed in clinical trials and meta-analyses since there was no evidence that SGLT2i raise stroke risk.[49,50] However, an increased risk of lower-extremities amputation has been observed with canagliflozin use (but not with other SGLT2i), especially in patients with a history of amputation or peripheral vascular disease.[51] The exact mechanism for this drug-side effect remains unclear.

The results of ongoing clinical trials with dapagliflozin [Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF)[52] and empagliflozin [EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved)[53] and EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced)[54]] in HF patients without T2DM may provide more data on the mechanisms by which SGLT2i influence heart function.

In conclusion, SGLT2i may beneficially affect several pathways involved in HF development and progression. Further research is needed to elucidate the effects of these drugs on iron metabolism, BM and hematopoiesis.

Declaration of Competing Interest

NK has given talks, attended conferences and participated in trials sponsored by Amgen, Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Mylan, NovoNordisk, Sanofi, Servier and Vianex. DPM has given talks and attended conferences sponsored by Amgen, AstraZeneca and Libytec.

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