Trace element equilibrium in acute heart failure and the effect of empagliflozin

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Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have shown to be potent therapeutic agents in heart failure (HF) irrespective of ejection fraction, improving cardiometabolic features and reducing risk of hospitalization for HF.[1] Favourable effects of SGLT2i on outcome have been explained by altering glucose metabolism, enhancing diuresis and stimulating erythropoiesis, and are presumed to arise (partly) through alterations in renal blood flow and glomerular filtration rate (GFR).[1,2] Yet, subsequent disruption in electrolyte equilibrium due to direct changes in filtrate composition is a frequently feared side-effect.[3] While clinical data have shown minimal or inconclusive impact on most plasma electrolytes, other than a slight increase in plasma magnesium concentration,[3] limited research has been performed in the acute phase of HF concerning the effect of SGLT2i on plasma trace elements. Trace elements are important for optimal cardiac function, but up to 50% of patients with HF present with single or multiple deficiencies, adversely and independently affecting prognosis.[4] Therefore, we aimed to elucidate the effect of empagliflozin on plasma calcium (Ca), copper (Cu), iron (Fe), selenium (Se) and zinc (Zn) levels in patients with acute HF.

We included 79 patients (≥18 years old) from the randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated HF (EMPA-RESPONSE-AHF). Patients were hospitalized for acute HF and within 24 h after admission randomized 1:1 to empagliflozin 10 mg/day (n = 40) or placebo (n = 39) for a treatment duration of 30 days. Plasma samples were collected at baseline, during the first 96 h of hospitalization, and after 30 days of treatment.[1] The EMPA-RESPONSE-AHF trial was approved by the ethics committee and conducted in accordance with the Declaration of Helsinki. The trial was registered with ClinicalTrials.gov (NCT03200860).[1] All patients provided written informed consent.

Simultaneous quantitative analysis of five trace elements (Ca, Cu, Fe, Se and Zn) in EDTA plasma was performed by total reflection X-ray fluorescence (TXRF; S4 T-STAR, Bruker Nano GmbH, Berlin, Germany). Baseline characteristics were stratified by treatment arm and included basic demographics (i.e. age/sex) as well as trace element measurements. Continuous data were reported as mean (standard deviation) for normal data and median (25th–75th percentile) for non-normal data, and categorical variables were reported as frequencies or percentages. *T*-tests for normally distributed data and Mann–Whitney Wilcoxon test for non-normally distributed data were used. The effect of empagliflozin on change in trace element concentration from baseline was determined with repeated measures linear mixed-effect (LME) models, which account for individual variability by estimating random individual effects. A p-value <0.05 was considered statistically significant. All tests and analyses were performed using STATA SE 17.0 (StataCorp LP, College Station, TX, USA).

Patient characteristics at baseline have been reported elsewhere.[1] Mean age was 74.4 (68.0–83.0) years and 33% of patients were female. At baseline, median estimated GFR was 47.6 (41.1–63.5) ml/min/1.73 m^2 and plasma osmolality was 304.8 (301.5–308.9) mOsm/kg, which were similar between the empagliflozin and placebo group (48.2 vs. 47.6, p = 0.76 and 304.8 vs. 305.1, respectively; p = 0.69), indicating no initial differences in GFR (*Table 1*). Absolute levels of all trace elements were reported at baseline, 96 h and 30 days of treatment (*Table 1*) and change in concentration from baseline was depicted graphically and determined by LME models (*Figure 1*). Analogous to 96 h of treatment, at 30 days no significant differences were observed between the empagliflozin and placebo treated patients in change from baseline for plasma concentrations of Ca (−0.60 mg/L vs. −3.46 mg/L; p = 0.17), Cu (−182.8 µg/L vs. −232.3 µg/L; p = 0.39), Fe (+249.0 µg/L vs. +352.9 µg/L; p = 0.30), Se (−3.0 µg/L vs. +1.72 µg/L; p = 0.06), or Zn (+48.3 µg/L vs. +23.5 µg/L; p = 0.51). Even though empagliflozin did not affect plasma trace elements, deficiency was observed for Se (<70 µg/L) in 84% of patients, Fe (<726 µg/L) in 39% of patients, and Zn (<700 µg/L for females and <740 µg/L for males) in 10% of patients.

In a well-characterized patient population with acute HF, empagliflozin did not change plasma levels of Ca, Cu, Fe, Se or Zn as compared with placebo. This is in concordance with earlier findings from DAPA-HF regarding unchanged plasma Fe in patients with chronic HF with reduced ejection fraction.[2] The trace elements measured in the present study need tight regulation and participate in numerous physiological functions, with evidence stating efficient reabsorption of Fe, Zn and Cu across vast segments of the nephron.[5] However, empagliflozin may also generally perform better than conventional diuretics concerning homeostasis of certain trace elements.[6,7] Treatment with loop diuretics – widely used in HF – and acetazolamide – a carbonic anhydrase inhibitor targeting the proximal tubule, similar to SGLT2i – was suggested to increase urinal calcium excretion,[7] although its effect on plasma Ca as well as other trace elements remains controversial. The effect of combined diuretics and SGLT2i use on trace element concentration, as well as the potential interplay between SGLT2i and commonly prescribed (non-) cardiovascular medications known to affect absorption and bioavailability of certain micronutrients (i.e. acid-suppressing drugs, antibiotics, statins), is yet to be assessed.[8]

In this post-hoc analysis of the EMPA-RESPONSE-AHF trial, we investigated the effect of empagliflozin on a wide array of plasma trace element concentrations. While pharmacodynamic properties may differ between medicines in the SGLT2i class, our results suggest safe trace element equilibrium with use of empagliflozin. The small sample size and absence of 24 h urinary measurements to determine 'functional' excretion of trace elements are limitations in this study. Nonetheless, based on the prevalent micronutrient deficiencies, we argue that nutritional repletion strategies in patients with HF may still be warranted.[4] To conclude, treatment with empagliflozin did not change

Table 1 Baseline characteristics and trace element measurements from EMPA-RESPONSE-AHF

Factor	Total cohort (n = 79)	Empagliflozin (n = 40)	Placebo (n = 39)	p-value
Demographics				
Age (years)	74.4 (68.0–83.0)	78.5 (72.5–83.0)	73.0 (61.0–83.0)	0.14
Female sex	26 (32.9%)	16 (40%)	10 (26%)	0.17
Weight at baseline (kg)	81.6 (73.0–93.8)	80.6 (73.8–97.0)	82.1 (73.0–93.6)	0.53
Systolic blood pressure (mmHg)	124.4 (23.7)	127.5 (22.2)	121.3 (25.1)	0.25
NYHA class III/IV	73 (92.4%)	35 (92%)	38 (97%)	0.57
Laboratory at baseline				
eGFR (ml/min/1.73 m^2)	47.6 (41.1–63.5)	48.2 (41.4–61.8)	47.6 (41.0–65.2)	0.76
Plasma osmolality (mOsm/kg)	304.8 (301.5–308.9)	304.8 (301.5–308.9)	305.1 (301.9–311.8)	0.69
Ca concentration (mg/L)	99.2 (6.6)			
Baseline		100.3 (6.1)	101.2 (6.7)	
96 h		97.9 (6.9)	97.1 (6.4)	
30 days		100.1 (7.3)	98.3 (5.3)	
Cu concentration (μg/L)	1425.6 (273.2)			
Baseline		1512.9 (275.6)	1526.2 (315.9)	
96 h		1418.0 (260.5)	1422.9 (266.3)	
30 days		1323.9 (234.7)	1330.0 (215.8)	
Fe concentration (μg/L)	778.2 (599.0–1042.8)			
Baseline		688.8 (478.3–851.9)	702.5 (572.4–822.0)	
96 h		831.4 (581.2–1188.8)	775.0 (608.4–923.8)	
30 days		882.2 (622.6–1148.2)	998.6 (817.5–1300.5)	
Se concentration (μg/L)	58.2 (13.2)			
Baseline		61.0 (11.7)	55.9 (13.5)	
96 h		60.3 (13.2)	54.3 (12.4)	
30 days		58.4 (13.5)	59.4 (14.6)	
Zn concentration (μg/L)	852.5 (764.7–961.9)			
Baseline		870.4 (793.6–991.4)	877.4 (749.0–952.6)	
96 h		873.8 (732.6–970.0)	793.8 (721.6–866.8)	
30 days		892.6 (807.2–1043.4)	824.0 (780.6–956.4)	

Ca, calcium; Cu, copper; eGFR, estimated glomerular filtration rate; Fe, iron; NYHA, New York Heart Association; Se, selenium; Zn, zinc.

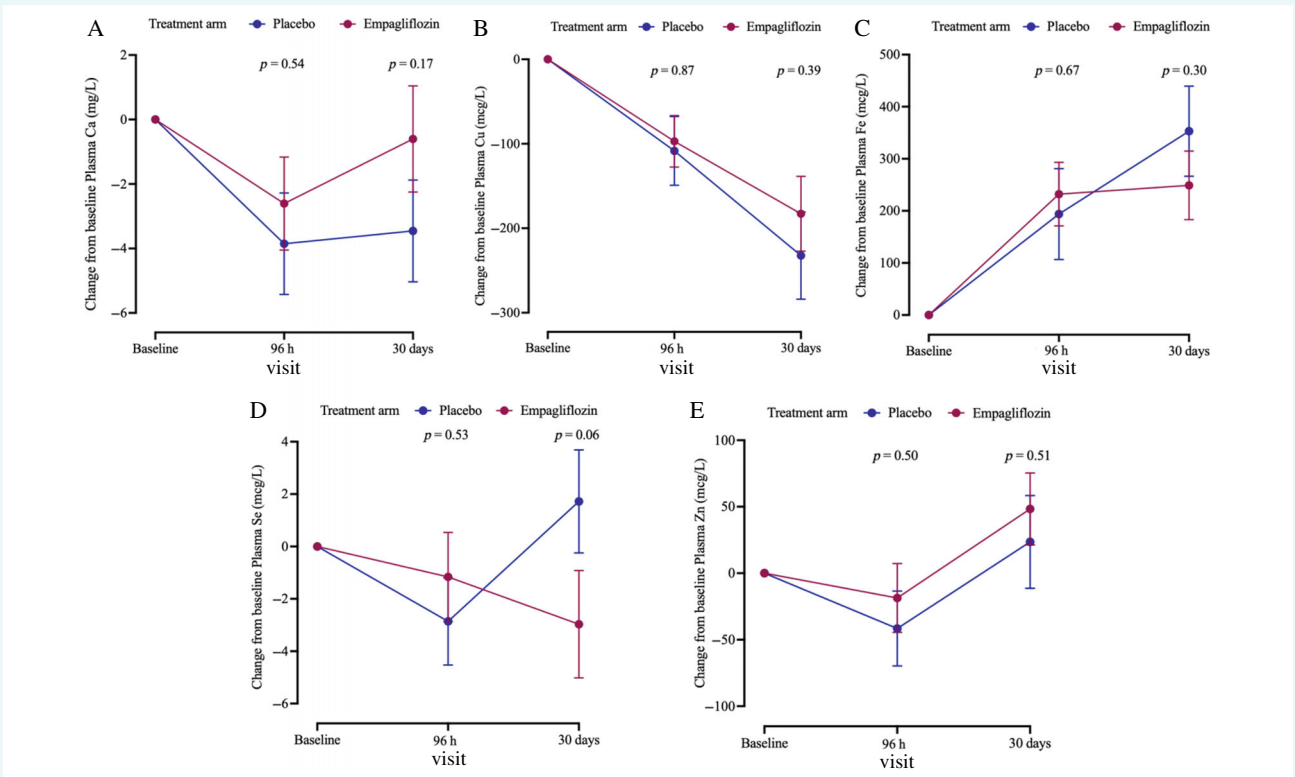

Figure 1 Depicting the change from baseline for (*A*) calcium (Ca), (*B*) copper (Cu), (*C*) iron (Fe), (*D*) selenium (Se) and (*E*) zinc (Zn) for both intervention groups. Change from baseline was used as outcome in a linear mixed-effects model. Mean values are shown by the dots, the bars represent the standard error. A p-value for interaction between each time point and treatment is shown.

plasma trace element levels in patients with acute HF.

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