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Longitudinal Changes in Circulating Ketone Body Levels in Patients With Acute Heart Failure: A Post Hoc Analysis of the EMPA-Response-AHF Trial

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ABSTRACT

Background: Ketone bodies are endogenous fuels produced by the liver under conditions of metabolic or neurohormonal stress. Circulating ketone bodies are increased in patients with chronic heart failure (HF), yet little is known about the effect of acute HF on ketosis. We tested the hypothesis that ketogenesis is increased in patients with acute decompensated HF.

Methods and results: This was a post hoc analysis of 79 patients with acute HF included in the EMPA-RESPONSE-AHF trial, which compared sodium-dependent glucose-cotransporter protein 2 inhibitor treatment with empagliflozin for 30 days with placebo in patients with acute HF [NCT03200860]. Plasma concentrations of ketone bodies acetone, β-hydroxybutyrate, and acetoacetate were measured at baseline and 5 different timepoints. Changes in ketone bodies over time were monitored using repeated measures analysis of variance. In the total cohort, median total ketone body concentration was 251 μmol/L (interquartile range, 178−377 μmol/L) at baseline, which gradually decreased to 202 μmol/L (interquartile range, 156−240 μmol/L) at day 30 ($P = .041$). Acetone decreased from 60 μmol/L (interquartile range, 34−94 μmol/L) at baseline to 30 μmol/L (interquartile range, 21−42 μmol/L) ($P < .001$), whereas β-hydroxybutyrate and acetoacetate remained stable over time. Higher acetone concentrations were correlated with higher N-terminal pro brain natriuretic peptide levels ($r = 0.234$; $P = .039$). Circulating ketone bodies did not differ between patients treated with empagliflozin or placebo throughout the study period. A higher acetone concentration at baseline was univariately associated with a greater risk of the composite end point, including in-hospital worsening HF, HF rehospitalizations, and all-cause mortality after 30 days. However, after adjustment for age and sex, acetone did not remain an independent predictor for the combined end point.

Conclusions: Circulating ketone body concentrations, and acetone in particular, were significantly higher during an episode of acute decompensated HF compared with after stabilization. Treatment with empagliflozin did not affect ketone body concentrations in patients with acute HF. (*J Cardiac Fail 2022;00:1−9*)

Key Words: Acute heart failure, ketone bodies, acetone, SGLT2 inhibitors, empagliflozin, NT-pro BNP.

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Heart failure (HF) is the leading cause of hospitalizations in individuals ages more than 60 years, and mortality rates are very high.[1] A central mechanism underlying HF is that cardiac uptake and use of fatty acids and carbohydrates is perturbed, leading to cardiac energy depletion.[2,3] Despite intense efforts, effective treatments to restore cardiac energy in HF remain limited.

Ketone bodies are endogenous fuels produced by the liver under conditions of metabolic or neurohormonal stress, a process called ketogenesis. Accordingly, circulating concentrations of ketone bodies are increased in patients with chronic HF, accompanied by an increase in the cardiac oxidation of these metabolites.[2,4,5] Studies in model organisms indicate that this increase in cardiac ketone oxidation is adaptive and that increasing ketone delivery to the heart can restore cardiac energy.[6,7] Surprisingly, relatively little is known about the mechanisms of HF-induced ketosis or changes in ketone concentrations in clinical HF. Ketone bodies are synthesized by the liver from free fatty acids through a process called ketogenesis. The two main ketone bodies, β-hydroxybutyrate and acetoacetate, are easily taken up by the heart and their oxidation occurs in a concentration-dependent manner.[8] The third ketone body, acetone, is a breakdown product of acetoacetate and is metabolically inert.[9,10] Acetone concentrations may, therefore, provide the best reflection of ketogenesis, because the levels of the other ketone bodies are also subject to changes in their metabolization rates.[11,12]

Although ketogenesis is primarily regulated by changes in the insulin-to-glucagon ratio, catecholamines and natriuretic peptides have also been shown to induce ketosis in an insulin-independent manner.[13] Furthermore, in animal models of HF,[14,15] and in patients at increased cardiovascular risk,[16,17] it has been shown that sodium-dependent glucose-cotransporter protein 2 (SGLT2) inhibitors induce ketosis through decreases in the insulin-to-glucagon ratio. Whether these drugs also induce ketosis in patients with HF is not well-described.

We hypothesized that ketogenesis is activated during an episode of acute decompensated HF and that circulating ketone body concentrations will, therefore, be higher during acute cardiac decompensation than after stabilization. We additionally hypothesized that SGLT2 inhibitors would further increase circulating ketone body concentrations in this setting. To test these hypotheses, we determined longitudinal changes in circulating ketone body concentrations over the course of 30 days in patients admitted for acute HF who were randomized to the SGLT2 inhibitor empagliflozin or placebo.

Methods

Study Design EMPA RESPONSE AHF Trial

This study is a post hoc analysis of the EMPA-RESPONSE-AHF trial (clinical trial registration number: NCT03200860), the design of which has been described in more detail elsewhere.[18] In brief, the EMPA-RESPONSE-AHF was a randomized, double-blind, placebo-controlled, multicenter pilot study in which patients with acute decompensated HF were randomized to empagliflozin or placebo treatment on top of standard of care within 24 hours after hospital admission and were treated for 30 days. The standard-of-care regimen was provided according to the applicable guidelines for treatment of acute HF. Clinical disease parameters, vital signs, demographic variables, medical history, medical therapy and laboratory assessments including N-terminal pro brain natriuretic peptide (NT-pro BNP), estimated glomerular filtration rate (eGFR), creatinine, and glucose were collected at baseline. The combined clinical end point included in-hospital worsening HF, rehospitalization for HF, and mortality after 30 and 60 days. The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice, and all participants provided written informed consent (METc 2017/411).

Study Population

The study included patients 18 years or older, who were hospitalized with acute HF, which was defined as presentation with typical signs and symptoms of congestion, increased NT-pro BNP levels, and treatment with loop diuretics at screening.[18] Patients with type 1 diabetes, with an eGFR of less than 30 mL/min/1.73 m^2 or a noncardiac cause of dyspnea were excluded. A detailed overview of the inclusion and exclusion criteria can be found in the original publication.[18] Patients were included and randomized to study treatment within 24 hours after initial presentation in the hospital.

Plasma Ketone Body Measurements

In the present study, 3 ketone bodies (acetone, β-hydroxybutyrate, and acetoacetate) were measured in nonfasting plasma samples, which were drawn at 6 timepoints during the treatment phase: at baseline, after 24 hours, after 48 hours, after 72 hours, after 96 hours, and after 30 days of treatment. Samples were collected in ethylenediamine tetra-acetic acid tubes, centrifuged and stored at -80° C within 2 hours of collection and thawed before analysis. Measurements were performed

using 400 MHz proton (1 H) nuclear magnetic resonance spectroscopy in the use of the Vantera Clinical Analyzer (LabCorp, Morrisville, NC).[19] The coefficients of variation ranged from 3.8% to 9.1% for acetone, 1.3%−9.3% for β-hydroxybutyrate, and 3.1%−7.7% for acetoacetate.[19]

Statistical Analyses

All statistical analyses were performed using the statistical package for social science (SPSS 23 for Windows+ SPSS Inc., Chicago, IL(. Baseline characteristics were presented as means ± standard deviations or medians (interquartile range [IQR]) for continuous variables or as percentages for categorical variables. Cross-sectional differences between tertiles of ketone body concentrations were evaluated using the Kruskal−Wallis test for nonparametric continuous variables, 1-way analysis of variance (ANOVA) for parametric continuous variables or the χ^2 test for categorical variables. The cohort was stratified in tertiles of baseline ketone body concentrations. Spearman's rho correlation coefficients were calculated 2 sided between ketone bodies and continuous clinical baseline parameters which were considered to be relevant based on clinical judgment. Changes in ketone body concentrations over time were determined using repeated measures ANOVA with within-patient analysis and the effect of empagliflozin on ketone body concentrations over time was determined using a repeated measures ANOVA with within- and between- patient comparisons. To explore relations between ketone body concentrations and clinical outcome, univariate and multivariate logistic regression analysis was performed using the backward likelihood ratio method. All baseline characteristics with a *P* of less than .01 or that were judged to be clinically relevant were included in the multivariate analysis. Impaired clinical outcome was defined as the composite of in-hospital worsening HF, rehospitalization for HF, and mortality after 30 days. Outcomes were reported as odds ratio with corresponding 95% confidence intervals. A *P* value of less than .05 was considered statistically significant for all analyses.

Results

Baseline Characteristics

A total of 79 patients randomized in the EMPA-RESPONSE-AHF between 2017 and 2019 were included in the analysis. Baseline characteristics were stratified for tertiles of TKB in Table 1. The median age among patients was 76 years (IQR 68−83), 34% were female, and the mean body weight was 85.1 ± 21.6 kg. In the total cohort, 47% of patients presented with HF de novo, median NT-pro BNP was 5236 pg/L (IQR 3416−8371 pg/L) and the median eGFR was 48 mL/min/1.73 m^2 (IQR 41−63 mL/min/1.73 m^2). The median baseline TKB concentrations were 251 μmol/L (IQR 178−377 μmol/L), compounded of acetone (60 μmol/L, IQR 23−93 μmol/L), β-hydroxybutyrate (126 μmol/L, IQR 91−179 μmol/L) and acetoacetate (60 μmol/L, IQR 40−92 μmol/L).

Demographic characteristics, New York Heart Association functional class, and vital clinical signs at baseline were similar among groups, although patients with higher baseline TKB concentrations tended to have higher heart rates (*P* = .050). Patients with higher baseline TKB concentrations had a higher left ventricular ejection fraction (LVEF) (*P* = .042), a higher prevalence of atrium fibrillation or flutter (*P* = .012), and higher NT-pro BNP concentrations (*P* = .036). Glucose, eGFR, and medical treatment did not differ between tertiles of TKB at the time of admission.

Longitudinal Changes in Circulating Ketone Body Concentrations

Longitudinal changes in circulating ketone body concentrations are depicted in Fig. 1 in relative changes from baseline values. TKB concentrations at baseline were 251 μmol/L (IQR 178-377 μmol/L), which gradually decreased to 202 μmol/L (IQR 156−240 μmol/L) at day 30 (*P* = .041). Similarly, acetone concentration was 60 μmol/L (IQR 34−94 μmol/L) at baseline and decreased to 30 μmol/L (IQR 21−42 μmol/L) at 30 days (*P* < .001). No significant changes in β-hydroxybutyrate or acetoacetate were observed over the time course of the study.

Associations Between Ketone Bodies and Clinical Parameters

Correlations between ketone bodies and continuous clinical parameters are depicted in supplementary Tables 1A−1D. Higher NT-pro BNP concentrations were significantly correlated with higher acetone levels (r = 0.234; *P* = .02) (Fig. 2). No significant correlations were found between NT-pro BNP and TKB, β-hydroxybutyrate, or acetoacetate. Furthermore, higher heart rate correlated with higher TKB (r = 0.237; *P* = .035) and with higher β-hydroxybutyrate concentrations (r = 0.243; *P* = .031). Other correlations were found between LVEF and both TKB (r = 0.361; *P* = .014) and β-hydroxybutyrate (r = .426; *P* = .003) at baseline.

Effect of Empagliflozin on Ketone Body Concentrations in Acute HF

Baseline total ketone body concentrations were similar between patients randomized to empagliflozin

Table 1. Baseline Characteristics Stratified by Tertiles of Total Ketone Body Concentration at Baseline

		Total Ketone Body Concentration at Baseline			
	Total ($N = 79$)	Tertile 1 ($n = 27$)	Tertile 2 ($n = 26$)	Tertile 3 ($n = 26$)	*P* Value
Baseline characteristics					
Female sex	26 (33)	10 (37)	11 (42)	5 (19)	.178
Age (years)	76 [68−83]	74 [61−81]	78 [72−84]	79 [70−84]	.429
Caucasian race	77 (97)	27 (100)	26 (92)	26 (100)	.124
Body weight (kg)	85.1 ± 21.6	82.8 ± 17.7	81.9 ± 24.5	90.6 ± 20.3	.281
Systolic BP (mm Hg)	124 ± 24	129 ±28	126 ± 23	118 ± 19	.247
Diastolic BP (mm Hg)	74 ± 15	75 ± 18	74 ± 15	73 ± 12	.932
Heart rate (bpm)	78 [67−93]	72 [61−86]	77 [67−94]	86 [73−103]	.050
Resp. rate (breaths/min)	20 [16−22]	20 [16−23]	20 [15−21]	19 [16−22]	.421
NYHA functional class III/IV	73 (95)	27 (100)	21 (88)	25 (96)	.124
Medical history					
LVEF; if known ($n = 46$)	36 [25−50]	25 [15−43]	35 [25−51]	50 [30−55]	**.042**
Heart failure de novo	37 (47)	11 (41)	15 (58)	11 (42)	.295
Ischemic etiology	22 (28)	5 (19)	8 (31)	9 (36)	.352
Atrial fibrillation/flutter	56 (71)	17 (63)	15 (58)	24 (92)	**.012**
Myocardial infarction	27 (34)	7 (26)	7 (27)	13 (50)	.115
Hypertension	49 (62)	18 (67)	16 (62)	15 (58)	.796
Type 2 DM	26 (33)	11 (41)	9 (35)	6 (23)	.382
COPD	21 (27)	9 (33)	4 (15)	8 (31)	.282
CVA	4 (5)	1 (4)	1 (4)	2 (8)	.757
Medical therapy					
ACEi	34 (44)	11 (42)	10 (38)	13 (50)	.694
ARB	15 (19)	9 (35)	3 (12)	3 (12)	.051
ARNI	3 (4)	0 (0)	1 (4)	2 (8)	.353
Beta-blocker	53 (68)	15 (58)	17 (65)	21 (81)	.192
MRA	36 (46)	14 (54)	12 (46)	10 (38)	.538
Loop diuretic	79 (100)	27 (100)	26 (100)	26 (100)	
ICD	12 (15)	5 (19)	3 (12)	4 (15)	.778
CRT	11 (14)	3 (11)	4 (15)	4 (15)	.873
Laboratory values					
NT-pro BNP (pg/mL)	5236 [3416−8371]	4559 [2924−5630]	6803[3810−11684]	5666 [3863−9393]	**.036**
eGFR (mL/min/1.73 m^2)	48 [41−63]	52 [41−63]	46 [41−62]	51 [42−73]	.838
Creatinine (μmol/L)	108 [86−139]	109 [86−136]	107 [85−143]	111 [85−142]	.986
Glucose (mmol/L)	7.7 ± 2.0	7.9 ± 2.0	7.8 ± 2.0	7.6 ± 1.9	.825
Ketone bodies					
TKB (μmol/L)	251 [178−377]	170 [152−181]	252 [222−266]	516 [376−691]	
Acetone (μmol/L)	60 [34−94]	31 [26−42]	59 [39−80]	114 [74−173]	
βhb (μmol/L)	126 [91−179]	86 [78−103]	123 [103−157]	229 [178−409]	
AcAc (μmol/L)	60 [40−92]	39 [33−54]	60 [45−73]	118 [91−197]	

AcAc, acetoacetate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin II receptor−neprilysin inhibitor; βhb, β-hydroxybutyrate; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, Cardiac resynchronization therapy; CVA, Cerebrovascular accident; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ICD, Implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, Mineralocorticoid receptor antagonist; NT-pro BNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; Resp., respiratory; TKB, total ketone bodies.

Data are shown as number (%), mean ± standard deviation, or median [interquartile range] and for tertiles of total ketone body concentration at baseline (tertile 1: ≤196 μmol/L; tertile 2: 197−321 μmol/L; tertile 3: ≥322 μmol/L).

and placebo treatment (252 μmol/L [IQR 161−457 μmol/L] vs 249 μmol/L [IQR 196-345 μmol/L], respectively). After randomization and over the course of treatment, no significant changes between treatment groups were found in circulating TKB (*P* value for ANOVA between groups = 0.389) or acetone concentration (*P* value for ANOVA between groups = 0.381) (Fig. 3).

Association Between Ketone Bodies and Clinical Outcome at 30 Days

In univariate logistic regression analyses, the baseline acetone concentration was associated with the incidence of the combined end point of in-hospital worsening of HF, all-cause mortality, and HF hospitalizations at 30 days after randomization (odds ratio 1.007 per μmol/L increase; 95% confidence interval 1.000−1.014, $P = .043$). Baseline concentrations of β-hydroxybutyrate, acetoacetate or TKB concentrations were not significantly associated with the combined end point. After adjustment for age and sex in a multivariate model, acetone did not remain an independent predictor for the combined end point.

Discussion

This study presents the first analysis of longitudinal changes in circulating ketone body concentrations in patients who were hospitalized for acute HF. We found that circulating TKB concentrations

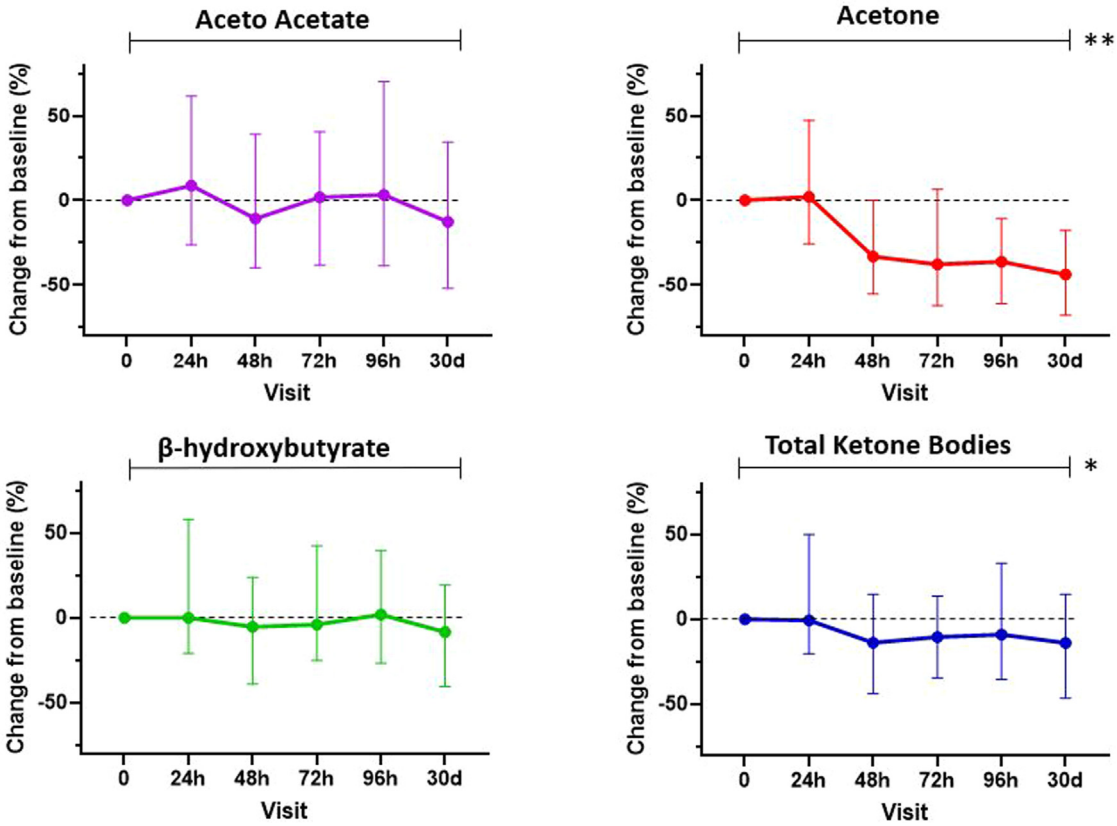

Fig. 1. Longitudinal changes in plasma ketone body concentrations in acute heart failure. Plasma ketone concentrations for the total cohort ($N = 79$), measured in μmol/L at 6 timepoints: baseline, after 24 hours, 48 hours, 72 hours, 96 hours, and 30 days. Data are displayed as median (interquartile range) relative delta change from baseline. Changes in concentration over time were measured using repeated measures analysis of variance. *$P < .05$; **$P < .001$.

were significantly higher during the initial stages of acute HF as compared with the concentrations after stabilization. A longitudinal analysis of all separate ketone bodies showed that the increase in circulating ketone body concentrations was primarily driven by acetone. Moreover, higher acetone concentrations at baseline were correlated with higher NT-pro BNP values. Surprisingly, treatment with the SGLT2 inhibitor empagliflozin did not influence circulating ketone body concentrations in acute HF. Furthermore, baseline acetone concentration was univariately associated with impaired clinical outcome after 30 days.

Enhanced knowledge on the mechanism of ketosis in HF could lead to better understanding of the mechanisms of current treatment options and could potentially lead to exploration of new therapies in the future.[20] Although chronic HF is associated with an increase in circulating ketone bodies compared with individuals without HF, data on the effect of

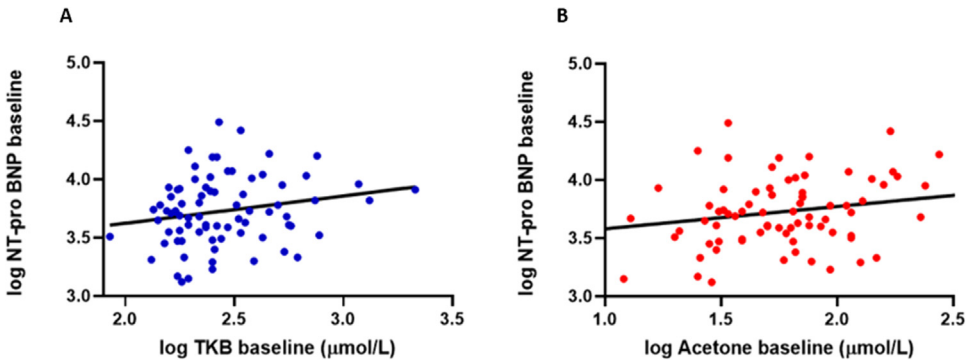

Fig. 2. Correlations between baseline ketone body concentrations and NT-pro BNP. Higher NT-pro BNP concentrations were correlated with higher acetone concentrations ($r = 0.234$; $P = .039$). Correlations between NT-pro BNP and total ketone bodies were nonsignificant ($r = 0.206$; $P = .070$). NT-pro BNP, N-terminal pro brain natriuretic peptide.

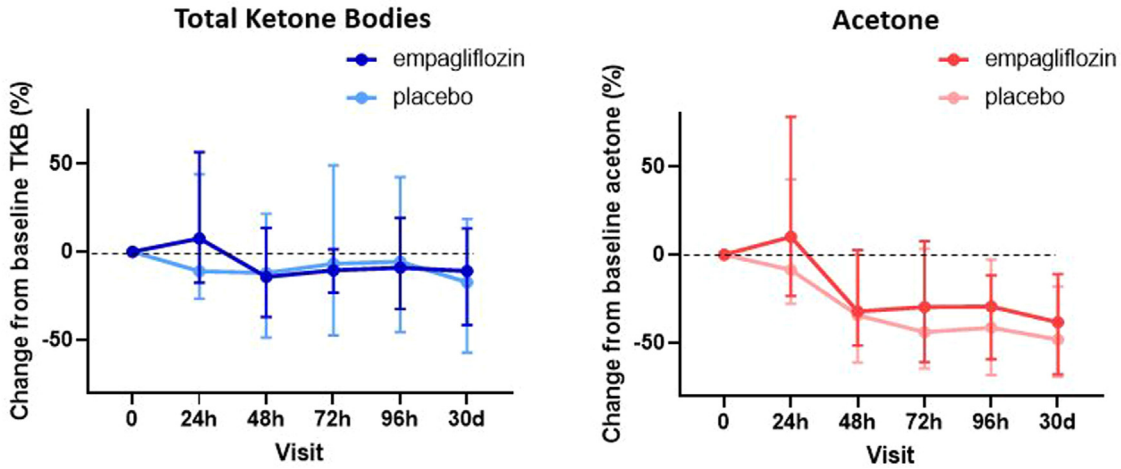

Fig. 3. Effect of empagliflozin on ketone body concentrations in acute heart failure. Plasma concentrations of ketone bodies were measured in μmol/L at 6 timepoints: baseline, 24 hours, 48 hours, 72 hours, 96 hours and 30 days. Data are displayed as median (in interquartile range) relative delta change from baseline. Changes in concentration over time were measured using repeated measures analysis of variance. TKB, total ketone bodies.

acute HF on ketosis are sparse.[2,4] In the healthy population, TKB concentrations remain at less than 100 μmol/L in the postprandial state.[4,21] However, absolute cut-off values for abnormal concentrations of ketone body concentrations have not been established, at least in part because ketone body concentrations are highly dependent on prandial status, diagnostic method, and assay. The limited number of studies that have measured circulating ketone body concentrations in patients with acute HF used a cross-sectional design, which does not inform on changes within an individual patient.[22,23] The only other article reporting longitudinal changes in ketone concentrations was performed using breath analysis assays, which is a suboptimal method lacking specificity.[23] Interestingly, these authors also reported increases in the concentration of the metabolically inert ketone body acetone, which also declined with the stabilization of HF.[23] Our study shows that both TKB and acetone concentrations are significantly elevated during an episode of acute decompensated HF compared with the stabilized situation. Furthermore, the ketone concentrations observed at 30 days after randomization were comparable with other studies in the chronic setting.[24,25]

The associations between circulating acetone concentrations and NT-pro BNP are in line with other studies and support the hypothesis that ketogenesis in HF could partly be driven by an increased hemodynamic load.[13,26] The rate of ketogenesis is, among other things, controlled by changes in the ratio between insulin and glucagon. Decrease in this ratio, which for example occur during fasting, promote lipolysis and the subsequent release of free fatty acids that are transformed into ketone bodies by the liver.[10,27] Moreover, catecholamines, natriuretic peptides and proinflammatory cytokines have also been shown to stimulate ketogenesis through multiple complementary mechanisms.[13] To this day, the mechanisms responsible for the increased ketogenesis in HF are not completely understood. Based on our findings that circulating ketone bodies are higher during an acute cardiac decompensation than after stabilization, it could be hypothesized that an increase in neurohormones and natriuretic peptides could influence ketone body concentrations in acute HF.[13] In line with this finding, we found a correlation between heart rate and higher levels of TKB and β-hydroxybutyrate. The association between higher total ketone bodies at baseline and higher LVEF corresponds with the results from previous experimental and clinical studies showing that an increase in ketone body concentrations was associated with an increase in the LVEF or cardiac output.[28,29] This finding is supported by the fact that this association is also existing for higher β-hydroxybutyrate, which is the ketone body that can be used by the heart, but not for the metabolically inactive acetone. However, whether there is a causal relationship between these variables cannot be concluded from this study.

Recently, SGLT2 inhibitors have emerged as novel treatment options for HF. The DAPA-HF and EMPEROR-Reduced trials showed that SGLT2 inhibition on top of standard of care led to a significant decrease in cardiovascular death or HF rehospitalizations in patients with chronic HF with reduced ejection fraction,[30,31] whereas EMPEROR-Preserved demonstrated this in patients with an LVEF of greater than 40% (HF with midrange ejection fraction and HF with preserved ejection fraction),[32] and SOLOIST and EMPULSE in diabetic and nondiabetic

patients with acutely decompensated HF.[33,34] Despite the consistency of this beneficial effect, the mechanisms underpinning the effects of SGLT2 inhibition remain incompletely understood. In nondiabetic animals with HF, treatment with SGLT2 inhibition increased both circulating ketone body levels and myocardial expression of multiple ketogenic enzymes.[14,15] In stable diabetic patients, there is robust evidence that SGLT2 inhibitors induce a longstanding, persistent increase in fasting ketone body levels.[17] However, it seems that the ketogenic effects of SGLT2 inhibitors are less evident in patients with normal glucose tolerance,[16] particularly when measured in nonfasting patients.[35] In the current study, treatment with empagliflozin on top of standard-of-care HF therapy did not lead to an increase in ketone body concentration in nonfasted patients. This finding is slightly contradictory to a recent study in which empagliflozin did increase fasting ketone concentrations in patients with chronic HF.[36] Whether the lack of ketogenesis observed in our study reflects the acute setting or the fasting state is currently unknown. More research is required to determine the true contribution of ketogenesis to the effects of SGLT2 inhibition in HF. It should be stressed, however, that the analysis of ketone body concentrations in a fed state is more representative. Furthermore, it can also be concluded from our data that treatment with SGLT2 inhibitors in the setting of acute HF did not increase the risk for diabetic ketoacidosis. These data also align with other recent reports which suggest that the risk of ketoacidosis in patients with HF treated with SGLT2 inhibitors is generally low.[37]

In this pilot study, a univariate association was found between acetone concentration and impaired clinical outcome after 30 days. This finding is in accordance with a different study in 130 patients with acute HF, which showed that acetone levels at time of hospitalization were associated with increased 3-month mortality rates.[22] It should be noted that both studies were not powered to detect a difference in clinical outcomes and that these results should be interpreted with caution. Nevertheless, ketone body concentrations have also been linked to adverse outcome in other clinical scenario's. Circulating ketone body levels were markedly increased in patients presenting with ST-elevation myocardial infarction and the degree of increase in ketone body levels was associated with the severity of cardiac dysfunction.[38] Furthermore, circulating ketone body levels predicted the incidence of new onset HF in a large, prospective cohort.[26] Together, these data conceivably indicate that ketogenesis is activated in patients with acute HF, suggesting that it may be a universal metabolic response to hemodynamic stress.

Limitations

The following limitations of this study should be noted. Previous elevations of ketone body concentrations after SGLT2 inhibition in both diabetic and nondiabetic patients have mostly been discovered under fasting conditions.[35] Nonfasting blood sampling could potentially mask the ketolytic effect of empagliflozin treatment to some extent. The fact that our analysis was performed in a fed state may, therefore, be interpreted as a limitation of our study. However, the fed state is more representative for the general hospitalized acute HF patient and fasting regimens are not recommended during the initiation of SGLT2 inhibitors.[39] We, therefore, consider the metabolic state of patients in this study to be a good reflection of the clinical syndrome of acute HF. Second, this cohort had a relatively small size and consisted of a mixed population of patients with HF with both preserved and reduced ejection fraction. Research on ketone body metabolism in larger and more homogenous cohorts of patients with acute HF could provide more insights into ketone body metabolism in acute HF. Nonetheless, this is the first study to provide a detailed longitudinal follow-up of all circulating ketone body levels in a population of patients with acute HF, making it unique in its kind. Previous reports in this setting employed breath analysis rather than quantitative biochemistry. Future studies are required to determine the mechanism responsible and to explore to which extent ketone bodies could serve as biomarkers for metabolic stress in acute HF.

Conclusions

Circulating ketone body concentrations, and acetone in particular, were significantly higher during an episode of acute decompensated HF compared with after stabilization. Empagliflozin did not affect ketone body concentrations in our study.

Lay Summary

Ketone bodies are endogenous metabolites that can fuel the heart and circulating ketone bodies are increased in patients with chronic heart failure (HF). Little is known about ketone body concentrations in the setting of acute HF. We performed longitudinal analysis of ketone body concentrations in the EMPA-response-AHF which randomized patients with acute HF to empagliflozin or placebo. A significant rise and fall in circulating ketone bodies was discovered in patients with acute decompensated HF. Treatment with empagliflozin did not affect ketone body concentrations in this setting. These data suggest that ketone body metabolism is activated during episodes of acute HF.

Three brief bullet points about how our work applies to patients:

- Circulating ketone bodies are increased in patients with chronic HF, yet little is known about the effect of acute HF on ketosis.
- Circulating ketone body concentrations, and acetone in particular, were significantly higher during an episode of acute decompensated HF compared with after stabilization.
- Improved understanding of ketone body metabolism in HF could provide mechanistic insights into the pathophysiology of HF and lead to novel treatments.

Proposed tweet

In this first longitudinal analysis of ketone body metabolism in patients with acute HF, circulating ketone bodies were significantly higher during decompensation than after stabilization. This suggests that ketone body metabolism is activated during episodes of acute HF.

Disclosures

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Supplementary materials

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