JACC: HEART FAILURE VOL. ■, NO. ■, 2020

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Nutrition, Heart Failure, and Quality of Life

Beyond Dietary Sodium*

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Despite significant advancements in the past decades in the understanding of and targeted treatments for heart failure (HF), it remains a deadly disease with a high risk of hospitalizations and reduced cardiorespiratory fitness, ultimately leading to reduced quality of life (QoL). Notably, patients admitted to the hospital for acute decompensated HF present with minimal therapeutic options. Lifestyle interventions, such as diet, have shown promising data in improving HF-related outcomes; however, very little is known about their role in decompensated patients admitted for acute HF.

Dietary sodium restriction is perhaps the most commonly implemented nonpharmacologic strategy for patients with HF, particularly in those admitted for acute decompensated HF. However, the evidence is both limited and controversial, such that current American College of Cardiology Foundation/American Heart Association HF guidelines do not provide strong recommendations for such an approach. The theoretical principle behind sodium restriction is that excess dietary sodium promotes fluid retention and thereby exacerbates HF. To the contrary, sodium restriction in HF has been associated with neutral or even worse prognosis compared with less stringent goals (1). The latter has been hypothesized to occur through multiple mechanisms: excess contraction of intravascular volume, renal hypoperfusion, and reduced cardiac output. Such effects can ultimately promote the activation of the renin-angiotensin-aldosterone system, which is associated with unfavorable outcomes in HF.

In addition, adherence to sodium restriction remains challenging, even when meals are provided as part of a clinical trial. Sodium reduction is associated with: 1) increased perceived thirst, particularly when paired with fluid restriction; and 2) unintended reduction of dietary calories, and macro- and micronutrients may be, at least in part, attributable to a perceived decreased palatability of food secondary to sodium restriction.

The effects of sodium restriction on QoL and clinical outcomes remain to be elucidated. Fortunately, SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure; NCT02012179), an ongoing multicenter dietitian-led randomized controlled trial, is currently investigating whether a sodium restriction to <1,500 mg/day improves these parameters in ambulatory patients with HF. Of note, similar trials in acute decompensated HF are lacking.

Importantly, patients with HF often present with poor nutritional status that can profoundly affect the progression of the disease and its related prognosis, including excess adiposity (i.e., obesity); reduced lean mass strength, amount, and functionality (i.e., sarcopenia); a combination of both (i.e., sarcopenic obesity); or unintentional significant weight loss

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Heart Failure author instructions page.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2020.04.006

TABLE 1 Clinical Studies Investigating the Effects of Diet in Heart Failure

Study	Trial Type	EF (%)	N	Dietary Intervention	Outcomes
Sodium restriction					
Colín Ramírez et al. (Supplemental Ref. 1)	Randomized controlled trial	40 ± 15.6 (intervention) 42.3 ± 15.5 (control)	65	2,000- to 2,400-mg/day sodium vs. control for 6 months	Increase in physical activity and QoL assessed by a sum of KCCQ and MLHFQ scores and improvement in NYHA functional class in intervention group vs. control.
Paterna et al. (Supplemental Ref. 2)	Randomized trial	<35	232	2,760-mg/day vs. 1,840-mg/day sodium in recently decompensated patients (30 days post-discharge)	2,760-mg/day sodium group had lower readmissions at 180 days (primary endpoint) and combined readmission and mortality at 90 days.
Aliti et al. (Supplemental Ref. 3)	Randomized, single-blind controlled trial	26.0 ± 8.7	75	Inpatient, admitted for decompensated HF 800-mg/day sodium restriction vs. control until seventh day of hospitalization or discharge	No differences in 3-day change in weight and clinical congestion score in intervention vs. control (primary endpoint) and 30-day readmissions in intervention vs. control.
Philipson et al. (Supplemental Ref. 4)	Multicenter, randomized controlled trial	34 ± 11 (intervention) 37 ± 15 (control)	97	2,000- to 3,000-mg/day sodium restriction vs. control for 12 weeks	The intervention group demonstrated signs of clinical improvement vs. control (composite primary outcome), driven mostly by improvement in NYHA functional class and edema.
Colin Ramirez et al. (Supplemental Ref. 5)	Open-label, randomized controlled pilot trial	42.0 (25.0–50.5)	38	1,500-mg/day (low) vs. 2,300-mg/day (moderate, control) sodium restriction for 6 months	BNP decreased from baseline in the low-sodium group alone, but there were no significant differences between groups; KCCQ clinical score increased in both groups with no difference between groups.
Dietary patterns					
Hummel et al. (Supplemental Ref. 6)	Open-label pilot trial	69 ± 6	13	21 days of home delivered DASH/sodium restricted diet (1,150-mg/day sodium)	DASH diet lowered clinic and 24-h ambulatory blood pressure and BNP. Cardiac systolic and diastolic function, 6MWT, and NYHA functional class were improved.
Rifai et al. (Supplemental Ref. 7)	Randomized controlled trial	41 ± 13 (intervention) 40 ± 15 (control)	48	3 months of DASH diet intervention vs. control	Endothelial function was not better in the DASH group (primary endpoint), but QoL assessed by MLHFQ and 6MWT was improved vs. control.
Hummel et al. (Supplemental Ref. 8)	Multicenter, randomized single-blind controlled trial	39 ± 18	66	Home delivered DASH/sodium restricted diet (1,500-mg/day sodium) vs. control for 30 days post-hospital discharge for HF exacerbation	No significant difference between groups in change of KCCQ summary score (primary endpoint). There was a trend toward lower HF rehospitalization at 30 days in DASH vs. control.
Miró et al. (Supplemental Ref. 9)	Multicenter, prospective, observational study	51 ± 14	991	Adherence to a Mediterranean diet assessed by patient questionnaire in those seen in the emergency department for acute HF	After a mean follow up of 2.1 ± 1.3 yrs, adherence to the Mediterranean diet was not associated with a decrease in all-cause mortality (primary endpoint) but was associated with a decrease in rehospitalizations for HF.
Chrysohoou et al. (Supplemental Ref. 10)	Cross-sectional analysis	39 ± 20	372	Analysis of adherence to Mediterranean dietary pattern via food frequency questionnaire and MedDietScore	A Mediterranean dietary pattern was associated with improvements in filling pressure (via log E/A ratio).
Spaderna et al. (Supplemental Ref. 11)	Multicenter, prospective cohort study	21.5 (15.3–28.9)	318	Analysis of diet via food frequency questionnaire in candidates waitlisted for a heart transplant	After median follow-up of approximately a yr, high-sodium diets (correlated with higher fluid and saturated fat intake) were associated with high urgency of transplantation; intake of PUFA and monounsaturated fatty acid was associated with a decreased risk of deterioration/mortality.
Biddle et al. (Supplemental Ref. 12)	Prospective cohort study	33.9 ± 14.0	212	Analysis of average lycopene (a carotenoid found in red, orange, and yellow produce) intake via 4 days of food diaries	Greater intake of lycopene was associated with improvements in cardiac event-free survival (related cardiac death and time to first hospitalization for HF), independent of intake of sodium.

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resulting in both lean and fat mass tissues loss (i.e., cachexia). The nutritional causes and potential related targeted treatments of these abnormalities extend beyond sodium intake (**Table 1**) (2). Almost two decades ago, it was described that patients with HF present with a hypercatabolic state and an increased resting energy expenditure: using an indirect calorimetry, resting energy expenditure was increased by approximately 250 kcal/day compared with apparently healthy sedentary control subjects, therefore promoting a chronic negative energy balance and protein-calorie malnutrition (3). Furthermore, those with poor caloric intake tend to have worse intake of essential micronutrients (3). The

TABLE 1 Continued

Study	Trial Type	EF (%)	N	Dietary Intervention	Outcomes
Fatty acids					
GISSI-HF Investigators (Supplemental Ref. 13)	Multicenter, randomized, double-blind controlled trial	33.0 ± 8.5 (intervention) 33.2 ± 8.5 (placebo)	6975	N3 PUFA 1 g daily vs. placebo	After a median follow-up of 3.9 yrs, the N3 PUFA group demonstrated lower all-cause mortality, as well as the combined endpoint of lower all-cause mortality and hospital readmission (primary endpoint).
Nodari et al. (Supplemental Ref. 14)	Randomized, double-blind controlled trial	36 ± 7 (intervention) 37 ± 6 (placebo)	133	N3 PUFA 1 g daily vs. placebo for 12 months	Increase in EF in N3 PUFA vs. placebo (primary endpoint), as well as improvement in diastolic function, decrease in inflammatory biomarkers, and lower rate of HF admission.
Wu et al. (Supplemental Ref. 15)	Randomized, double-blind controlled trial	28 ± 1	31	Supplementation of L-alanyl-L-glutamine (8 g/day) and N3 PUFA (6.5 g/day) vs. placebo for 3 months	No change in peak VO_2, 6MWT, handgrip, or leg/arm skeletal muscle function in intervention vs. placebo (primary endpoints).
Colin-Ramirez et al. (Supplemental Ref. 16)	Cross-sectional analysis	45 (30-60)	118	Analysis of averaged 3-day baseline dietary fatty acid consumption for patients enrolled in a sodium restriction trial	As a percent of total kcal, increased PUFA and saturated fatty acids were associated with decreased and increased all-cause mortality, respectively.
Carbone et al. (Supplemental Ref. 17)	Cross-sectional analysis	60.4 (57.1-63.0)	23	Analysis of baseline 24-h dietary recall in patients enrolled in a trial for anti-inflammatory therapy	Dietary UFA were positively associated with peak VO_2, greater fat-free mass, and more favorable diastolic function.
Carbone et al. (Supplemental Ref. 18)	Single-arm pilot trial	58 ± 4	9	In patients with comorbid obesity, 12 weeks of daily supplementation with 1 serving of food rich in UFA. Preferred recommendations for intake were extra-virgin olive oil (54 g), canola oil (54 g), lightly salted mixed tree nuts (walnuts, hazelnuts, almonds, and pecans), or peanuts (28 g)	There was an increase in dietary UFA and plasma UFA (primary endpoints). An increase in exercise time and oxygen pulse, as well as a trend toward an increase in peak VO_2 was observed.
Lennie et al. (Supplemental Ref. 19)	Prospective cohort study	32 ± 14	42	Analysis of average fatty acid consumption via food diaries from 4 days	Saturated and trans fat intakes were associated with higher levels of TNF-α; omega-3 and PUFA intake were associated with lower sTNF-R1 and sTNF-R2 levels. Both sTNF-R1 and TNF-α were associated with decreased event-free survival (emergency department visit or hospitalizations for HF, as well as cardiac mortality).
Caloric restriction					
Evangelista et al. (Supplemental Ref. 20)	Randomized controlled trial	26 ± 7.3	14	12 weeks of a calorically restricted diet (500- to 800-kcal deficit), one group with high-protein (30% kcal), another group with standard protein (15% kcal) and a control diet without dietary changes	Greater weight loss, reduction in waist circumference, fat mass, and increase in 6MWT and peak VO_2 in the high-protein group vs. the other 2 groups.
Kitzman et al. (Supplemental Ref. 21)	Randomized controlled trial	61 ± 6	100	20 weeks of a 2 × 2 factorial study to assess the effects of exercise vs. diet 4 groups: exercise (supervised aerobic exercise 3× week), caloric restriction alone (400-kcal deficit), exercise and caloric restriction combined, and control	The independent effects of diet from baseline included increased peak Vo_2, but no effect on MLHFQ total score (primary endpoints). Exercise time, peak workload, 6MWT, reduction in weight, fat mass, inflammatory biomarkers, and total KCCQ score also improved with diet.

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initial thought was that HF leads to insufficient caloric intake by eliciting a hypercatabolic state, making the former more of a marker, rather than a mediator of the disease; however, this may not necessarily be the case. In fact, the direct effects of insufficient caloric intake on QoL and clinical outcomes in HF are largely unknown.

In this issue of *JACC: Heart Failure*, Bilgen et al. (4) provide crucial data, furthering our understanding of this question in patients admitted for an event of HF exacerbation (about one-third of whom presented with HF with preserved ejection fraction). They performed a post hoc analysis of the GOURMET-HF (Geriatric OUt-of-hospital Randomized MEal Trial in Heart Failure; NCT02148679), which previously found that a home-delivered DASH (Dietary Approaches to Stop Hypertension)-like meal program for 4 weeks started at time of discharge, was associated with favorable, yet exploratory, effects on clinical status and 30-day readmission rate. In the current analysis, the authors used the well-validated Block Food Frequency Questionnaire to retrospectively collect dietary information in 57 patients providing an average of the dietary intake for the year prior to the HF hospitalization event. The foods collected with the Block Food Frequency Questionnaire were then converted into calories, macronutrients, and micronutrients.

TABLE 1 Continued

Study	Trial Type	EF (%)	N	Dietary Intervention	Outcomes
Protein and amino acid supplementation					
Aquilani et al. (Supplemental Ref. 22)	Randomized, double-blind controlled study	34 ± 9 (intervention) 32 ± 6 (placebo)	95	30 days of mixed amino acid supplementation (4 g BID) vs. placebo	Peak Vo_2, workload and oxygen pulse improved in the intervention group but not placebo.
Rozentryt et al. (Supplemental Ref. 23)	Randomized, double-blind controlled pilot trial	25 ± 10 (intervention) 24 ± 5 (placebo)	29	In patients with clinically significant weight loss, 6 weeks of a high-calorie (600 kcal) high protein (20 g) oral nutrition supplement vs. placebo (12 kcal/day)	From baseline, intervention increased weight gain and overall MLHFQ score (primary endpoints), as well as 6MWT. Peak Vo_2 was not increased.
Pineda-Juárez et al. (Supplemental Ref. 24)	Randomized controlled trial	Not described	66	3 months of resistance training plus branch-chain amino acid supplement (10 g/day) vs. resistance training alone	There were no effects of branch chain amino acids on muscle strength or peak VO_2.
Lombardi et al. (Supplemental Ref. 25)	Open-label, randomized controlled trial	32.4 ± 6.3 (intervention) 32.4 ± 7.3 (control)	50	500-mg orodispersible L-carnosine vs. control for 6 months	In intervention vs. control, there was an increase in 6MWT, peak VO_2, workload, and QoL by visual analog score.
Oral micronutrient supplementation					
Witte et al. (Supplemental Ref. 26)	Randomized, double-blind controlled trial	26.1 ± 6.7	32	Daily multiple micronutrient supplement vs. placebo for 9 months	Increase in LVEF in the micronutrient group vs. placebo (primary endpoint), as well an increase in QoL scores assessed by questionnaire. 6MWT, NYHA functional class, and inflammatory biomarkers remained unchanged in both groups.
McKeag et al. (Supplemental Ref. 27)	Randomized, double-blind, controlled trial	38.3 ± 11.4 (intervention) 45.1 ± 9.0 (control)	74	Daily multiple micronutrient supplement vs. placebo for 12 months	No significant difference in EF between intervention and placebo (primary endpoint) or in MLHFQ questionnaire score, 6MWT, NT-proBNP, and inflammatory biomarkers.
Schoenenberger et al. (Supplemental Ref. 28)	Randomized, double blind control crossover trial	29.5 ± 2.5	9	28 days of treatments with 300-mg/day thiamine vs. placebo	Significant improvement in EF in thiamine group vs. placebo (primary endpoint); trend toward improvement in 6MWT.
Mortensen et al. (Supplemental Ref. 29)	Multicenter, randomized double-blind controlled trial	31 ± 10	420	2 yrs of treatment with 100-mg CoQ10 3× daily vs. placebo	Reduction in major adverse cardiac events in intervention vs. placebo (primary endpoint), as well as a reduction in rates of hospital stays for HF and in all-cause and cardiovascular mortality.
Hirai et al. (Supplemental Ref. 30)	Randomized, double-blind randomized crossover trial	32 ± 2	13	9 days of 70-ml beetroot juice BID that was concentrated vs. depleted in nitrates	No significant difference in time to exercise intolerance between nitrate and placebo (primary endpoint) or peak Vo_2.
Eggebeen et al. (Supplemental Ref. 31)	Randomized, double-blind, controlled trial	Included only ≥50%	20	1 week of nitrate concentrated vs. depleted beetroot juice	Increase in time to exhaustion during submaximal exercise at in intervention group (primary endpoint) but not after a single acute dose.
Coggan et al. (Supplemental Ref. 32)	Randomized, double-blind controlled crossover trial	34 ± 2	8	Patients ingested 140 ml of a beetroot juice that was nitrate concentrated (intervention) vs. depleted (control) and performed exercise testing 2 h after	There were no changes in ventilatory responses, but peak VO_2 improved after intervention vs. placebo (primary endpoints).
Boxer et al. (Supplemental Ref. 33)	Randomized, double-blind controlled trial	37.6 ± 13.9	64	6 months of weekly 50,000-IU vitamin D3 vs. placebo	There was no difference in changes in peak VO_2 in the intervention group vs. control (primary endpoint) nor in 6MWT.
Witte et al. (Supplemental Ref. 34)	Randomized, double-blind controlled trial	26.1 ± 10.68	229	100-μg vitamin D3 daily vs. placebo for 1 yr	Vitamin D3 did not increase 6MWD vs. placebo (primary outcome) but did increase EF and improve remodeling.
Zittermann et al. (Supplemental Ref. 35)	Randomized, double-blind controlled trial	28 (23-34) (intervention) 26 (24-35) (placebo)	892	4,000-IU vitamin D3 daily vs. placebo for 3 yrs	Vitamin D3 did not reduce all-cause mortality vs. placebo (primary endpoints); there was an increased implantation of mechanical circulatory support in the vitamin D3 group.
Schroten et al. (Supplemental Ref. 36)	Open-label, randomized controlled trial	35 ± 8	101	6 weeks of 2,000-IU vitamin D3 daily vs. control	Vitamin D3 decreased plasma renin activity (primary endpoint) and decreased plasma renin but did not change NT-proBNP.

Values are mean ± SD or median (interquartile range), unless otherwise indicated.

6MWD = 6-min walk distance; 6MWT = 6-min walk test; BID = twice a day; BNP = B-type natriuretic peptide; DASH = Dietary Approaches to Stop Hypertension; E/A = early filling velocity/atrial (late ventricular) filling velocity; EF = ejection fraction; HF = heart failure; IU = international units; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MedDiet Score = Mediterranean Diet Score; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PUFA = poly-unsaturated fatty acids; QoL = quality of life; TNF = tumor necrosis factor; UFA = unsaturated fatty acids; VO_2 = oxygen consumption.

Energy requirements were estimated using validated predictive equations; the authors defined individuals as having insufficient caloric intake when the actual caloric intake fell below 90% of the estimated total energy requirements. Finally, they investigated whether being classified as having inadequate caloric intake was associated with 12-week post-discharge changes in: 1) clinical status measured with the clinical summary score of the Kansas City Cardiomyopathy Questionnaire; and 2) all-cause hospital readmissions.

Similar to prior reports (3), more than 50% of patients admitted for HF reported a caloric intake <90% of estimated energy requirements. Surprisingly, individuals with insufficient caloric intake were more likely to be obese, although they also presented with a numerically greater number of comorbidities. Twelve weeks following discharge, patients with and without insufficient caloric intake experienced a significant improvement in clinical status measured with the Kansas City Cardiomyopathy Questionnaire clinical summary score; however, improvements were significantly smaller in those not meeting their estimated energy requirements. Even after adjustments for key nutritional risk screeners, inadequate caloric intake was associated with increases in both total length of rehospitalizations in days and number of patients with rehospitalizations: 124 days versus 18 days and 52% versus 17%, respectively. Importantly, individuals with insufficient caloric intake were also more likely to have reduced sodium, protein, and micronutrient intake; however, sodium intake did not predict changes in QoL and clinical outcomes. This finding raises the possibility of worse outcomes observed in patients consuming lower sodium intake in prior studies being potentially mediated by insufficient caloric intake (1). Thus, in clinical trials using dietary interventions (i.e., sodium restriction), investigators should aim for maintaining isocaloric participant diets (or at least preventing negative energy balance) throughout the trial to minimize the risk of confounders.

The results of this study, although limited by the small sample size and the exploratory nature of the analysis, complement a prior study published in the *JACC: Heart Failure* indicating that at time of admission in patients with acute HF, a greater adherence to a Mediterranean diet, a dietary pattern rich in unsaturated fatty acids and antioxidants, was associated with reduced risk of HF rehospitalization up to 1 year (5). Furthermore, in chronic stable HF, dietary interventions aimed at increasing unsaturated fatty acids consumption or improving adherence to the DASH diet, among others, have proven to be feasible and associated with favorable changes in exercise and functional capacity (2). Of note, both the Mediterranean diet and DASH diet are primarily composed of plant-based foods, suggesting that a prudent plant-based dietary pattern might be beneficial in HF.

In conclusion, Bilgen et al. (4) are commended for providing novel evidence, which will guide future randomized controlled trials investigating the effects of different caloric intake strategies in patients admitted for acute decompensated HF on clinical outcomes and QoL. Finally, dedicated trials investigating the distinction between patients with HF with reduced ejection fraction and HF with preserved ejection fraction separately and using indirect calorimetry for a more accurate estimate of energy requirements are encouraged to determine whether the effects discussed herein are efficacious in both forms of HF.

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REFERENCES

1. Doukky R, Avery E, Mangla A, et al. Impact of dietary sodium restriction on heart failure outcomes. J Am Coll Cardiol HF 2016;4:24–35.

2. Billingsley H, Rodriguez-Miguelez P, Del Buono MG, Abbate A, Lavie CJ, Carbone S. Lifestyle interventions with a focus on nutritional strategies to increase cardiorespiratory fitness in chronic obstructive pulmonary disease, heart failure, obesity, sarcopenia, and frailty. Nutrients 2019;11:2849.

3. Pasini E, Opasich C, Pastoris O, Aquilani R. Inadequate nutritional intake for daily life activity of clinically stable patients with chronic heart failure. Am J Cardiol 2004;93:41-3A.

4. Bilgen F, Chen P, Poggi A, et al. Insufficient calorie intake worsens post-discharge quality of life and increases readmission burden in heart failure. J Am Coll Cardiol HF 2020;8:XXX-XX.

5. Miro O, Estruch R, Martin-Sanchez FJ, et al. Adherence to mediterranean diet and all-cause mortality after an episode of acute heart failure: results of the MEDIT-AHF study. J Am Coll Cardiol HF 2018;6:52-62.

KEY WORDS diet, heart failure, nutrition, sodium

APPENDIX For an expanded references section, please see the online version of this paper.