EDITORIAL

Nutrient Deficiencies in Heart Failure: A Micro Problem With Macro Effects?

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Dietary micronutrient deficiency is common in adults with heart failure (HF), with >20% having low intake of vitamin A, calcium, magnesium, selenium, and iodine and up to 75% having low intake of vitamin D.[1] Micronutrients are necessary cofactors for normal cardiac metabolism, and deficiencies have been implicated in the development and progression of HF.[2,3] There is increasing interest in nutrition among patients with HF, two thirds of whom report taking vitamins or supplements, despite limited evidence of impact on outcomes.[4,5] Acknowledging this disconnect, the National Heart, Lung, and Blood Institute and the National Institutes of Health Office of Dietary Supplements convened a Working Group in 2013 to address the impact of nutrition on HF, which recognized substantial knowledge gaps and a need to improve the quality of evidence.[6]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Lennie and colleagues present a multicenter prospective cohort study evaluating the impact of dietary micronutrient deficiencies on clinical outcomes in ambulatory patients with HF.[7] The study enrolled 274 patients recruited from 3 HF clinics affiliated with academic medical centers in Georgia, Indiana, and Kentucky, with 1-year follow-up. Patients were eligible if they had documented HF with either reduced or preserved ejection fraction with clinical stability for 3 months. Primary exclusion criteria included urgent listing for cardiac transplantation or presence of a left ventricular assist device, end-stage illness that would considerably shorten life expectancy, or conditions other than HF or diabetes mellitus that required dietary restrictions. Four-day food diaries were collected from 246 patients to estimate the intake of 17 micronutrients, including 11 vitamins and 6 minerals. Deficiencies were defined by the Institute of Medicine's Food and Nutrition Board recommendations,[8] and a summary score was created. Dichotomized micronutrient deficiency was the key independent variable in the analysis, with patients deficient in ≥7 micronutrients considered to have high micronutrient deficiency. The primary outcome of the study was survival free of all-cause hospitalization or death.

The median (range) number of deficiencies was 4 (0–14) micronutrients. Patients with high micronutrient deficiency were more likely to be younger, to be nonwhite, and to have more depressive symptoms measured using the Beck Depression Inventory II. Notably (for a study focused on malnutrition), the mean baseline body mass index was >30 kg/m^2 and was similar between the groups. Additional important characteristics of the diet differed between groups, including lower energy and sodium intake, albeit with higher sodium per 1000 kcal in the high micronutrient deficiency group. The primary outcome of all-cause hospitalization or death occurred in 44% (n=27) of the high micronutrient deficiency group versus 25% (n=47) of the low-deficiency group, driven primarily by hospitalizations. In the time-to-event analysis adjusting for race, comorbidity, body mass index, depression, estimated sodium intake, and HF severity, patients with high micronutrient deficiency had almost double the hazard of events compared with those without (hazard ratio [95% confidence interval], 1.92 [1.15–3.21]). This association remained after both the addition of NT-proBNP (N-terminal pro-B-type natriuretic peptide) to the model and in a sensitivity analysis adjusting for caloric intake. These findings in US patients with HF support and extend similar observations by these authors in a South Korean cohort.[9]

This study was well designed, with several key strengths. Self-reported dietary assessment methods are challenging to do well and are without an established gold standard for comparison. In this study, meticulous food diaries, including both weekends and weekdays, were collected by participants with rigorous in-person verification. Although challenging to replicate in larger studies, such "documented" food diaries are clearly superior to unverified food records.[10] Appropriate methods for determining micronutrient deficiency were used,

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including probability ratios when population-based data were available and reference standards when these were not. Attempts were made to adjust for other potential dietary mediators, such as sodium and energy intake. Finally, many patients were enrolled from multiple sites with detailed follow-up of clinical events, limiting potential bias.

However, important questions and opportunities remain. Participants were surveyed after 3 months on stable medical therapy without hospitalization. This strategy presumably reduces variability in dietary intake related to acute illness but excludes the patients most at risk. Depending on illness severity and the screening method, 15% to 90% of patients hospitalized for HF are undernourished. Malnutrition markedly increases the risk for hospital readmission and death.[11] Yet, little is known about how dietary intake changes over the course of HF or how such changes may affect outcomes. Ideally, future studies on this topic would repeat dietary assessments around the time of HF hospitalization and assess the overall burden of recurrent hospitalizations, institutionalization, and death.

Two other clinically relevant points are important to emphasize. First, diuretics, nearly ubiquitous in HF management, increase excretion of and contribute to deficiencies in water-soluble vitamins, such as thiamine.[12] Although the analysis adjusted for HF severity using the Seattle Heart Failure Model score, which includes diuretic prescription and dosing,[13] the dietary model likely underestimated the true severity of some micronutrient deficiencies in HF. Second, low body weight is an ominous prognostic sign in HF and is generally assumed to reflect cardiac cachexia, malnutrition, or both. It is striking that among patients with high micronutrient deficiency in the current study, 49% were obese and none were underweight. In a recent large cohort study, severe malnutrition appeared uncommon in obese patients with HF. However, the screening instruments used were based on body mass index and blood biomarkers, which also reflect inflammation.[14] As the authors suggest, a high index of suspicion and a more nuanced assessment are needed to characterize malnutrition in obese patients with HF, particularly in those with acute decompensation.

Current HF guidelines recognize that although nutrition is likely important, more data are needed to provide adequate dietary guidance.[15] Work centered on single micronutrient deficiency and supplementation in HF has produced mostly neutral results in clinical trials.[3] This fact, along with increasing controversy related to dietary sodium restriction,[16] has led to growing interest in overall dietary quality. In the Women's Health Initiative cohort, participants with HF who had greater adherence to the Dietary Approaches to Stop Hypertension eating pattern had slightly lower mortality over a median of 4 years, with a similar trend for Mediterranean diet adherence.[17] However, even the best observational studies can be limited by the logistical challenges and accuracy of nutrient measurement, and resulting associations between diet and outcomes can be affected by unmeasured confounders.[18]

A few small clinical trials have moved beyond dietary risk assessment in cohort studies and the supplementation of single micronutrients to directly assess the effects of nutritional support in HF. The PICNIC (Nutritional Intervention Program in Hospitalized Patients With Heart Failure Who Are Malnourished) study randomized 120 Spanish inpatients with HF at risk for nutritional complications to a multidisciplinary dietary intervention. The program involved tailored dietary recommendations delivered through monthly in-person nutrition-focused visits. With this intensive support, 27% of patients died or were hospitalized for HF over 12 months of follow-up, versus 61% in the usual care group.[19] The recently published GOURMET-HF (Geriatric Out-of-Hospital Randomized Meal Trial in Heart Failure) pilot study randomized 66 US patients with HF at hospital discharge to 4 weeks of home-delivered, low-sodium, Dietary Approaches to Stop Hypertension–compliant meals compared with usual care. Although the primary outcome of disease-specific quality of life did not differ between groups, secondary analyses showed a trend toward reduction in HF symptoms and 30-day readmissions in the group receiving meals.[20]

The study by Lennie and colleagues[7] provides another important link between micronutrient deficiencies and outcomes in patients with HF. The findings promote much-needed thinking beyond sodium restriction or individual nutrient supplementation toward maintaining overall dietary quality. The time is right to conduct larger clinical trials of comprehensive dietary support in HF, which hold strong potential to improve quality of life and outcomes in this vulnerable population.

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