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EDITORIAL COMMENT

Micronutrients for Chronic Heart Failure

End of the Road or Path to Enlightenment?*

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Patients and many physicians strongly believe in the positive effects of combined multiple micronutrient supplementation for the prevention and treatment of cardiovascular disease. This belief extends to patients with chronic heart failure (CHF), more than 60% of whom take some form of over-the-counter micronutrient supplementation (1).

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The theoretical benefits of various micronutrients (2,3) have yet to be supported by large-scale clinical trials (4,5). The evidence base for most agents, and particularly combinations of micronutrients, is therefore limited to small-scale studies with surrogate endpoints (6,7). In this issue of *JACC: Heart Failure*, McKeag et al. (8) describe the neutral effects of 12 months of supplementation with a cocktail of micronutrients on left ventricular (LV) function, as measured by 3-dimensional echocardiography or magnetic resonance imaging, quality of life, 6-min walk distance, and markers of immune activation in the largest published population of ambulatory patients with CHF. This is the only study so far to use food diaries and blood concentrations of micronutrients to determine intake, biochemical deficiency, and the response on blood levels of supplementation. Their data reinforce the discrepancy between the basic science data, which suggests that there are potential benefits of various agents, and the results of clinical studies and should stimulate a review of the methodology employed in clinical studies that must be taken into account for future work if we are ever to clarify conclusively the benefit or otherwise of multiple (or individual) micronutrient supplementations in patients with CHF.

Future studies must choose their endpoints and follow-up time carefully (9). McKeag et al. (8) chose change in LV function at 1 year as their primary endpoint. This traditional measure of response relates poorly to symptoms (10), and change in left ventricular ejection fraction (LVEF) relates poorly to change in prognosis (11). The authors discuss that their population had mild symptoms, had mild LV systolic dysfunction, and were relatively young, whereas previous (positive) studies of micronutrient supplementation in which LV function was the primary endpoint enrolled older patients with more severe LV systolic dysfunction and were completed prior to the widespread use of cardiac resynchronization therapy (6). It is possible, therefore, that the patients in the present study, of whom 30% had cardiac resynchronization therapy and >95% were on a beta-blocker and an angiotensin-converting enzyme inhibitor, had reached a ceiling of LV function beyond which further improvement is unlikely. In the current era of combination medical and device therapy, study design must appreciate the possibility of a ceiling effect and target enrollment to a population with the potential to improve or at higher risk of events (12,13). Equally, recognizing that a lack of *improvement* in a variable does not equate to a lack of *response*, future studies must also be powered to take into account the influence of an intervention on the rate of deterioration of a chosen variable rather than its ability to improve it (9).

Ultimately, if we are to establish whether micronutrients, either individually or in combination, help patients with CHF, future studies should be large enough to detect a reduction in mortality and hospitalization rates. Only then can we expect micronutrient supplementation to feature prominently in guidelines. Accepting that funding for studies of nutritional interventions of this size is difficult to obtain without supportive pilot data, the choice of endpoints for proposals becomes even more crucial and should be limited to those features of the disease relevant to patients while also collecting mechanistic information. Although McKeag et al. (8) collected 6-min walk test and quality of life data, their study was powered for LVEF. They were, therefore, underpowered to detect a benefit for either of their patient-orientated secondary endpoints (14). Without a positive change in symptoms, quality of life, or walk distance, an improvement (or lack of deterioration) in LVEF is of little relevance to patients and could be viewed skeptically by committees that are asked to consider funding larger outcome studies. The impact of this changed approach has yet to be appreciated. For example, although studies in CHF patients are currently investigating the effects of vitamin D on exercise tolerance, only one is powered for 6-min walk distance (15). Using peak exercise capacity, for example, might be less relevant to most patients with CHF who will never undertake peak exercise and in whom the sensitivity of a change in peak oxygen consumption as a marker of improved prognosis is limited.

Finally, we must choose our intervention carefully. Although attention has recently turned away from antioxidants (16) and toward thiamine and coenzyme Q10, due to

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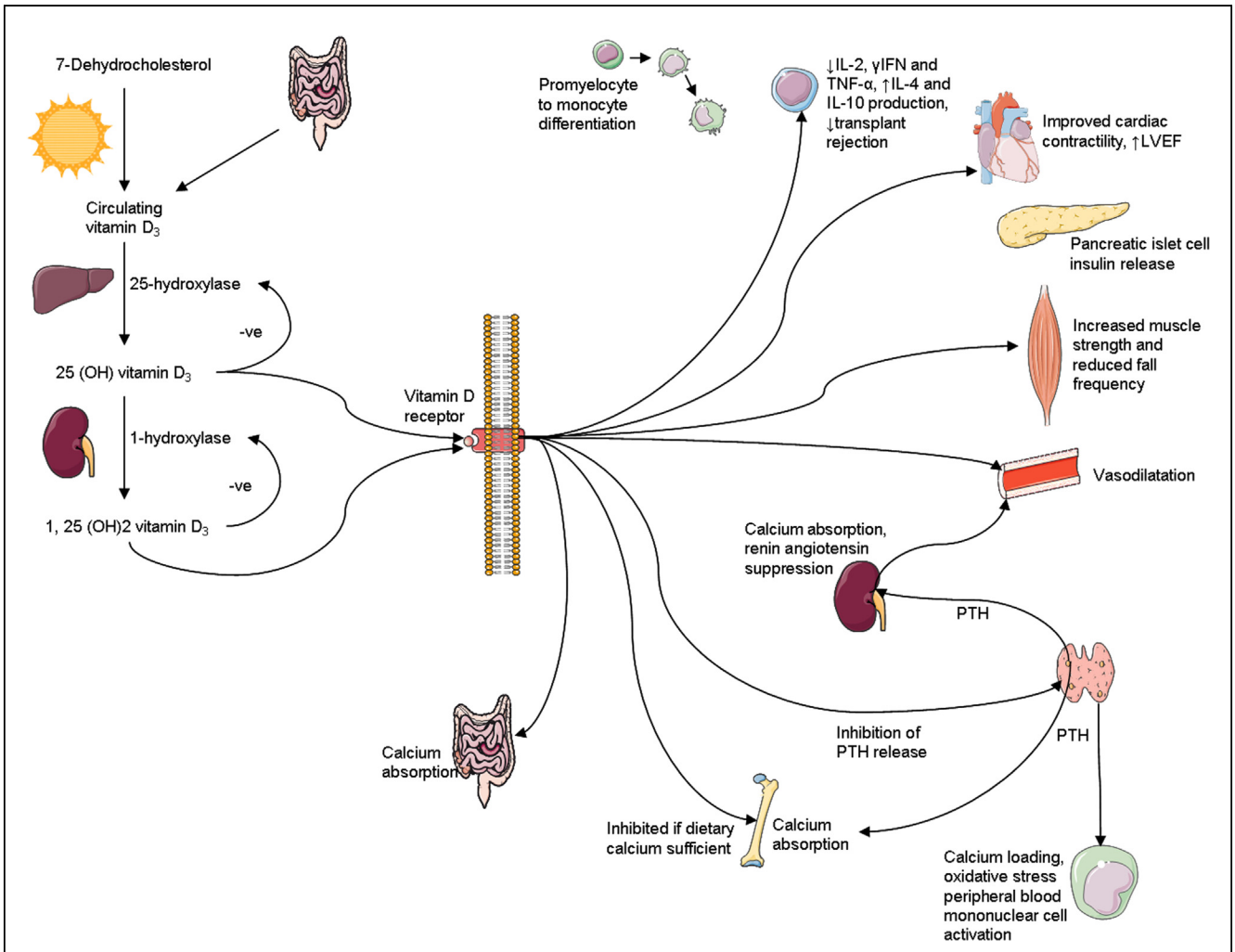

Figure 1 Schematic Illustration Summarizing the Known Pleiotropic Effects of Vitamin D of Potential Relevance in Chronic Heart Failure

IFN = interferon; IL = interleukin; LVEF = left ventricular ejection fraction; PTH = parathyroid hormone; TNF = tumor necrosis factor.

their respective effects on LVEF (17,18), much effort is also currently being given to vitamin D. Unlike most micronutrients, vitamin D deficiency is common, and low levels are associated with the risk of developing CHF (19,20), adverse outcomes (21–23), pathophysiology (24,25), and patient-orientated markers of severity (26,27). In addition, clear guidelines on vitamin D doses and duration of supplementation for clinical trials have been published (28). Thankfully, given its recognized widespread effects on the features of CHF (Fig. 1), previous work showing a lack of improvement in LVEF (29) or peak oxygen consumption (30) or with methodological problems (31,32) have not discouraged the initiation of clinical studies of vitamin D supplementation on patient-orientated outcomes in CHF, and 2 large studies powered for walk distance (15) and mortality are ongoing (33). If we are to move forward in the field, the design of future studies of other micronutrients must be similarly robust to demonstrate their safety and efficacy as therapeutic agents. The status quo of small, inconclusive studies is not sufficient, because we cannot assume that any supplement, however benign, will "do no harm" (34,35).

At present there are is no evidence that patients with CHF should take micronutrient supplements, but the data presented by McKeag et al. (8) do not signify the end of the road. Rather, a critical appraisal of their work takes us a little further along the path of enlightenment toward achieving an evidence base founded upon data from robust randomized, placebo-controlled trials of sufficient power that look at endpoints that matter to patients, from which we can draw conclusions when our patients ask our opinions about micronutrient supplementation.

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