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Editorial

Nutritional Status in Advanced Heart Failure and Heart Transplant Patients

Estado nutricional en insuficiencia cardiaca avanzada y receptores de trasplante cardiaco

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A close association between chronic illnesses and a deterioration in nutritional status, impaired quality of life, and an increased risk for morbidity and mortality has been long recognized.[1] Indeed, as early as in the third century BC, the Greek physician Hippocrates from Koos very neatly described the wasting syndrome associated with terminal disease: *'The flesh is consumed and becomes water, the abdomen fills with water, the feet and the legs swell, the shoulders, clavicles, chest and thighs melt away. This illness is fatal.'*[2] Approximately 50% of heart failure (HF) patients are thought to be malnourished, which may potentially aggravate HF symptoms.[3] Symptom progression carries a worse prognosis in terms of hospital admission[4] and higher risk of death during and after HF hospitalization.[5] The term malnutrition describes a nutritional problem or failure due to a combination of varying causes, many of them present in patients with HF, either as an epiphenomenon (ie, a reduction in food intake) or in the form of HF-related comorbidities[1] (eg, chronic kidney disease, hyperparathyroidism). The concept and even the name, malnutrition, itself implies that it can be cured by adequate nutrition.[1] Nutritional assessment may lead to recommendations for improving nutritional status in frail elderly patients.[2] However, nutritional assessment is often overlooked in patients with HF, and it has traditionally focused on sodium and fluid reduction. Traditional parameters of malnutrition (low body mass index [BMI] and hypoalbuminemia) are not reliable indicators of the nutritional status in HF patients: blood volume changes can significantly affect BMI and serum albumin concentration can be affected by conditions inherent to HF, such as chronic inflammation, fluid overload, hepatic congestion, and renal losses.

An overview of recent published guidelines demonstrates that HF research and attention has mainly focused on pharmacological improvements, new devices and certain comorbidities (sleep apnea, atrial fibrillation, iron deficiency), but nutritional status and/or management approaches are still lacking. This applies to advanced HF patients in general and, in particular, heart transplant recipients.

The recent International Society for Heart and Lung Transplantation listing criteria for heart transplantation states that candidates should achieve a BMI < 30 kg/m or percent ideal body weight $< 140\%$ before listing for cardiac transplantation,[5] although data to support these recommendations are limited and often conflicting. Findings from an analysis of 19 593 orthotropic heart transplant recipients aged ≥ 18 years did not find any significant association between obesity grade I (BMI of 30-34.9) and higher morbidity and mortality. It seemed that underweight and obesity grade II/III recipients were the groups with significantly higher morbidity and mortality compared with other groups.[6] These results reflect the well-described 'obesity paradox' that links higher BMI with lower short- and long-term mortality in HF; conversely, HF patients with low BMI have poorer survival. In the 2016 ESC guidelines for HF, nutritional deficiencies (thiamine, L-carnitine, selenium, iron, phosphates, calcium, vitamin D) are listed as a cause of HF, and cachexia is defined as a comorbidity in terms of percentage of weight loss. No specific recommendation for routine nutritional assessment is provided, and little discussion on potential interventions is given.[7,8] Similarly, the 2009 focused update of the ACC/AHA guidelines for the diagnosis and management of HF in adults mention the lack of evidence for the routine use of nutritional supplements to prevent dysfunction of or injury to the heart.[9]

In their elegant study published in *Revista Española de Cardiología*, Barge-Caballero et al.[10] report the postoperative prognosis of 574 heart transplant recipients according to the preoperative nutritional status as assessed by the nutritional risk index (NRI). The selection of a cohort of individuals referred for heart transplant is very interesting, because it includes the 2 main conditions potentially threatening this population: *a)* Cardiac cachexia, appearing in situations of advanced HF and chronic systemic inflammatory response syndrome; vasoconstriction and stimulation of the sympathetic nervous system are compensatory mechanisms of HF, which influence the inadequate use of nutrients. *b)* A form of malnutrition secondary to complications of cardiac surgery or any major surgery in patients with heart disease.

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Previous attempts to address this problem used serum albumin and BMI as single tools, which might not adequately predict long-term outcomes in this setting. Although low serum albumin strongly predicted mortality across the spectrum of HF severity from ambulatory patients to left ventricular assist device and heart transplant recipients, it has been demonstrated that prognostic information is better derived from the rate of change of serum albumin over time,[11] as well as by multivariate dynamic risk modelling.[11] Detailed assessments including body fat, biomarkers, serum albumin, cholesterol, and other anthropometric and survey measures indicate that the HF obesity paradox is substantially modulated by nutritional status and that, in turn, BMI is not a good predictor of nutritional status in HF.[12] Therefore, the combination of 2 key components of nutritional status, easily available at admission, in the NRI formula is a practical and reproducible approach.

More than one third of the patients referred for heart transplantation in the cohort described by Barge- Caballero et al.[10] were at nutritional risk, and 27% of them fell into the moderate-severe categories of NRI ($<$ 97.5). Significant differences were found between NRI groups for both BMI and serum albumin. Interestingly, mean BMI across the 4 NRI categories was not reduced, highlighting that this measure alone is not adequate to assess nutritional status. Similarly to what has been commented on regarding albumin, changes in BMI over time could carry more accurate prognostic information than cross-sectional values. In addition, it seems that the effects of BMI variations depend critically on whether they are intentional or not. While intentional weight loss could positively affect cardiac structure, an unintended loss would not. In fact, an unintentional weight loss may be a surrogate for the loss of metabolic reserves and may trigger adverse clinical outcomes. It would have been of utmost interest if the authors had reported both the BMI variation over time (pre- and postheart transplant) and whether or not it was intentional. One would expect that, if there were obese patients within nutritional risk categories, they could be considered somewhat malnourished in terms of low serum albumin (and probably other concomitant deficiencies).[13] From a practical approach, this additional information could guide interventions directed at optimizing the preoperative status of patients listed for heart transplant.

Integrating serum albumin and BMI into a single parameter allowed the authors to stratify different risk categories showing a significant correlation with outcomes. There has been growing interest in building risk scores that could predict outcomes in acutely ill patients; unfortunately, risk adjustment methods specifically designed for this population are lacking. The most widely published intensive care unit scoring system, Acute Physiology and Chronic Health Evaluation II (APACHE II)[14] has little application in patients with heart disease, where factors predictive of outcome may be lost or overshadowed by data only validated in greatly differing illnesses. A new scoring system named APACHE-HF has recently been described. It compromises a combination of parameters, including mean blood pressure, pulse, sodium, potassium, creatinine, hematocrit, age, and Glasgow Coma Scale, and has proven to more effectively predict adverse midterm outcomes in patients with acute HF.[15]

The authors of the study do not report information on hematocrit, white cell count, hemoglobin, blood urea nitrogen, uric acid, sodium, potassium, trasferrin, prealbumin, C-reactive protein, folic acid, vitamin B_{12}, heart rate, total cholesterol, or N-terminal pro b-type natriuretic peptide, many of them yielding prognostic meaning and/or present in risk scoring systems.[15] In addition to general risk in the acutely ill setting, several screening tools have been designed to specifically assess the patient's nutritional risk, such as the Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), Malnutrition Universal Screening Tool (MUST) and Nutritional Risk Screening (NRS-2002).[16] The information provided by Bonilla-Palomas et al.,[17] with MNA showed a high prevalence of malnutrition and risk of malnutrition in patients hospitalized for HF. In this study, a close association between malnutrition and prealbuminemia underline the usefulness of this parameter as a biochemical marker of malnutrition in the cohort studied. The role of nutritional status in the prognosis for HF was also reported by Gastelurrutia et al.[12] in an outpatient context. The results of both studies indicate that properly nourished patients have a significantly higher cumulative survival rate than undernourished patients. NRS-2002 applied to HF patients was also found to be adequate to detect nutritional risk.[18] However, given the development of new biomarkers for diagnosis, prognosis and treatment of patients with HF, and the peculiarities of advanced stages and/or heart transplant settings, these scales need to be validated before they can be used as a tool for identifying undernourishment. If some of the above-mentioned variables were combined with NRI, it might be possible to develop a preoperative risk scoring tool for patients listed for heart transplant.

Decision-making for the management of patients waiting for heart transplant must ride on a careful assessment of the potential reversibility of adverse prognostic factors. They are usually refractory to optimal medical therapy, including ACE-inhibitors, B-blockers, and mineralocorticoid-receptor antagonists at their maximal tolerated doses. In addition to their potential impact on HF prognosis, some agents may have beneficial therapeutic actions in sarcopenic patients irrespective of HF. For instance, an extracardiac effect from ACE-inhibitors may be harnessed for the management of body wasting. Patients taking ACE-inhibitors had a lower likelihood of losing weight and a lower decline in muscle strength and walking speed than those who had used ACE-inhibitors intermittently or not at all. These findings were confined to observational studies, with no scientific support from interventional studies or meta-analyses.[19] Given these contrasting findings, specifically designed trials are needed to definitively establish whether ACE-inhibitors and ARBs may offer therapeutic gain in the treatment of sarcopenia and HF-related undernourishment. Like ACE-inhibitors, beta-blockers represent a fundamental pillar in the treatment of HF. Previous studies have also shown that carvedilol and bisoprolol reduce the risk of weight loss in patients with HF. However, improvements in body weight in these patients appeared to be primarily attributable to the inhibition of lipolysis and gains in fat mass, whereas no muscle-specific effects could be demonstrated.[20] It is interesting that a recent study has shown that the beta-blocker espindolol reduced weight loss and increased hand-grip strength in cancer cachexia patients.[21]

Barge-Caballero et al.,[10] did not describe the medications taken by the patients in their study. There could be differences in prescriptions that might have altered outcomes. Previous reports noted that HF medications were less frequently prescribed for malnourished patients than for other groups. The patient's overall subjective assessment could influence the cardiologist to choose a treatment which has adverse effects. Improvements in treatments with new drugs (ivabradine, sacubitril/valsartan) that have proven to be safe and effective must be borne in mind, and undertreatment based on subjective judgement is strongly discouraged.[5,7] On the other hand, the high prevalence of nutritional risk and worse postoperative outcomes in this patient group indicate that early identification of patients at nutritional risk and implementation of nutritional support are necessary to prevent malnutrition.[16,17]

We believe that this is an important study that: *a)* reinforces the importance of nutritional assessment in patients with HF; *b)* confirms the clinical usefulness of NRI as an alternative

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screening tool that could replace BMI and albumin; and *c)* demonstrates the prognostic implications of nutritional state in this setting.

Finally, nutritional interventions would be an easy, widely available and affordable opportunity to alter an adverse natural history in potential candidates showing low NRI. Whether nutritional support has effects on clinical outcomes in HF patients at nutritional risk remains, however, unknown.[22] Although some documents have tried to resume nutritional recommendations in cardiac patients,[23] there is a lack of robust clinical trials, with an appropriate design and focused on the subgroups concerned by the present study (HF, pretransplant, malnourished patients). The ongoing PICNIC study is a randomized, controlled clinical trial to assess whether a nutritional intervention in malnourished patients admitted to hospital for HF may provide benefit in terms of morbidity and mortality.[22] The results of the PICNIC study will show the impact on prognosis of a nutritional intervention in malnourished patients admitted to hospital for HF.[22]

CONFLICTS OF INTEREST

None declared.

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