Current Heart Failure Reports (2019) 16:189–200
https://doi.org/10.1007/s11897-019-00437-y

BIOMARKERS OF HEART FAILURE (J. GRODIN & W.H.W. TANG, SECTION EDITORS)

Anabolism to Catabolism: Serologic Clues to Nutritional Status in Heart Failure

Laura Murphy[1] · Alastair Gray[1] · Emer Joyce[1,2]

Published online: 12 October 2019

Abstract

Purpose of Review Malnutrition, sarcopenia, and cachexia are areas of increasing interest in the management of patients with heart failure (HF). This review aims to examine the serological markers useful in guiding the physician in identification of these patients.

Recent Findings Traditional nutritional biomarkers including albumin/prealbumin, iron, and vitamin D deficiencies predict poor prognosis in malnutrition and HF. Novel biomarkers including ghrelin, myostatin, C-terminal agrin fragment, and adiponectin have been identified as possible substrates and/or therapeutic targets in cardiac patients with sarcopenia and cachexia, though clinical trial data is limited to date.

Summary Increased focus on nutritional deficiency syndromes in heart failure has led to the use of established markers of malnutrition as well as the identification of novel biomarkers in the management of these patients, though to date, their usage has been confined to the academic domain and further research is required to establish their role in the clinical setting.

Keywords Malnutrition · Sarcopenia · Cachexia · Frailty · Heart failure

Introduction

Heart failure (HF) is increasing in prevalence and is currently estimated to affect 6.5 million Americans [1]. It places a significant burden on healthcare resources, with costs directly attributable to HF care estimated to reach $53billion by 2030 [2]. Despite promising advances in pharmacological and device management over the past decade, HF patients remain at significantly increased risk of morbidity and mortality [3]. Attention in recent years has thereby been increasingly directed at additional substrates that can positively impact HF outcomes outside of traditional myocardial and cardiovascular system models, including associated metabolic and wasting conditions. Involuntary loss of body weight (cachexia) and muscle wasting (sarcopenia) are more common in the HF population, particularly in more advanced disease states. Early identification and treatment of these wasting conditions may be associated with improved outcomes in this patient group, particularly those who may progress to advanced therapies including ventricular assist devices and cardiac transplantation.

In this article, we review both current diagnostic strategies available to identify HF patients with impaired nutritional status and contemporary therapeutic strategies to modify and potentially reverse some of these factors. We will also discuss potential therapeutic targets for these factors in future.

Heart Failure and Impaired Nutritional Status: Pathophysiological Links

Chronic HF and impaired nutritional status and muscle wasting share many common pathophysiological processes. The causes contributing to wasting in HF are multifactorial. Gut hypoperfusion and interstitial edema cause nausea and anorexia as well as malabsorption of nutrients. Neurohormonal activation with increased activity of the sympathetic nervous and renin-angiotensin-aldosterone systems leads to increased energy expenditure at baseline and thereby induces a catabolic state. A further imbalance between anabolic

✉ Emer Joyce
emerjoyce@mater.ie

[1] Department of Cardiology, Mater Misericoridiae University Hospital, Dublin, Ireland

[2] Heart Failure and Cardiac Transplantation, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland

and catabolic metabolism in these patients derives from reduced anabolic mediators including growth hormone (GH), insulin-like growth factor-1 (IGF-1), testosterone and ghrelin, as well as increased inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) with resulting increased oxidative stress [4]. An overview of the interlinking between these biomarkers and pathophysiological processes in malnutrition and HF is provided in Fig. 1.

HF patients are also more vulnerable to nutritional deficiencies due to the presence of multiple co-morbidities including hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation, chronic lung disease, chronic kidney disease, chronic liver disease, and anemia [5]. HF patients may also experience worsening nutritional status and wasting through evolving into a frailty phenotype, which is being increasingly recognized as prevalent in all HF groups and stages. There is no strict definition of how it should be assessed in HF, leading to significant variability in the stated prevalence of frailty, ranging from 21% in community dwelling adults up to 70% in patients hospitalized with acute decompensated HF (ADHF) [6, 7]. The most commonly used assessment method to define the presence of frailty is the Fried Phenotype, which identifies patients as frail based on deficits in three or more physical domains. Unintentional weight loss, or cachexia, is one of these domains, alongside self-reported exhaustion, low physical activity, slow walking speed, and low grip strength [8]. In summary, it is clear that HF pathophysiology is currently undergoing a paradigm shift. For so long, the therapeutic focus has been solely on the myocardium and cardiovascular system itself, but for further incremental improvements, HF clinicians are increasingly looking towards substrates such as metabolism and nutrition as current and future targets for new successful therapies. This includes assessing clinically relevant related phenotypes, including malnutrition, sarcopenia, and cachexia.

Assessment of Nutritional Status in Heart Failure

Malnutrition is defined as a low body mass index (BMI) (< 18.5 kg/m^2) or unintentional weight loss of > 10% habitual body weight cumulative or > 5% over 3 months in association with *either* a low BMI (< 20 kg/m^2 aged < 70 years, < 22 kg/m^2 aged > 70 years) *or* a low fat-free mass index (FFMI) (females: < 15 kg/m^2, males: < 17 kg/m^2) [9]. The assessment of malnutrition in HF patients is complicated by the fact that underlying loss of muscle mass and weight may be masked by edema so that in routine clinical assessments, the patients' weight may remain stable in the setting of congestion but they may in

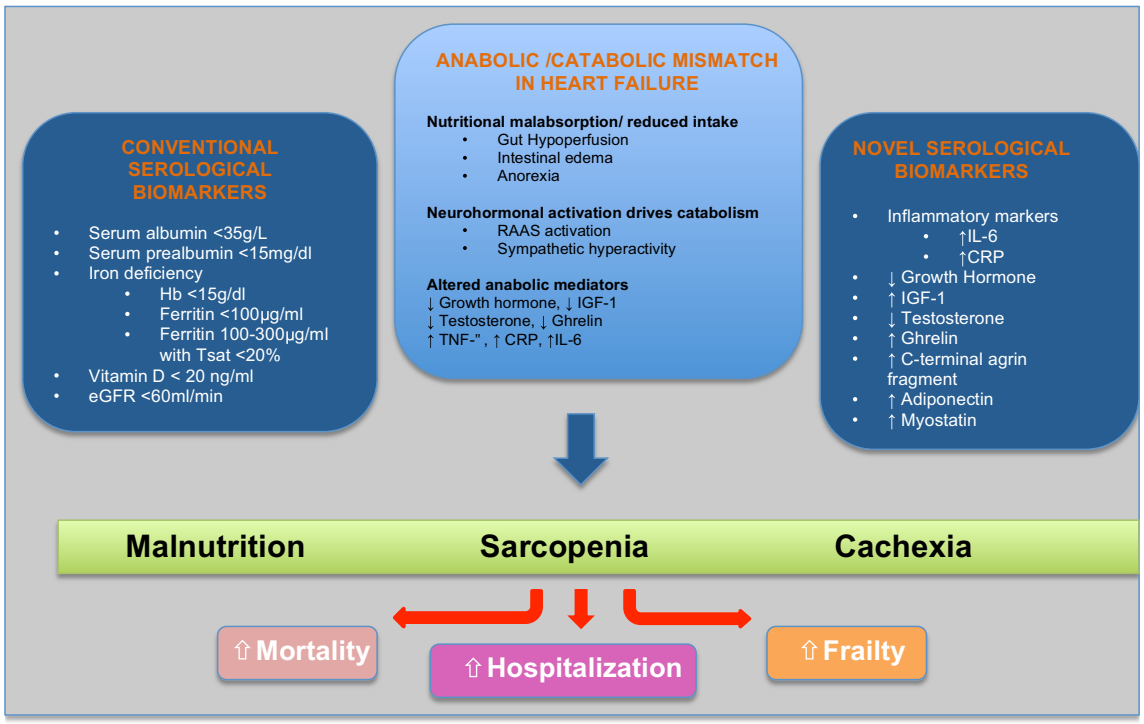

Fig. 1 Serological clues to nutritional deficiency in heart failure: a number of pathophysiological processes in heart failure result in nutritional deficiencies which can be detected by conventional and novel serological biomarkers with the resultant effect of malnutrition, sarcopenia, and cachexia and ultimately increased mortality, hospitalization, and frailty in this already vulnerable group. CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, Hb: hemoglobin, IGF-1: insulin-like growth factor-1, IL-6: interleukin-6, RAAS: renin-angiotensin-aldosterone system, TNF-α: tumor necrosis factor-alpha, Tsat: transferrin saturation

Table 1 Summary of methods to detect substrates

Malnutrition			
Clinical detection:	Components:		Results:
NRS 2002 [10, 11]	BMI < 20.5 kg/m^2:	Yes/No	BMI, weight loss % over time, food intake % normal (score 0–3)
	Weight loss in last 3 months:	Yes/No	Severity of disease: mild–severe (score 0–3)
	Reduced dietary intake in last week:	Yes/No	Age > 70 years–add 1 point
	Is the patient severely ill?	Yes/No	Score > 3 points requires nutritional intervention
MNA [12]	Dietary intake decline in last 3 months due to anorexia/GI disturbance/ chewing/swallowing difficulties: *None/moderate/severe decrease* Weight loss in last 3 months: *None/1–3 kg/> 3 kg* Mobility: *No dysfunction* *Can get out of chair/bed, does not go out of house, Bed/Chair bound* Psychological stress/acute disease in last 3 months: *Yes/No* Neuropsychological assessment: *None/mild dementia/severe dementia or depression* BMI (kg/m^2): *< 19/19–21/21–23/> 23* Calf circumference (cm): *> 31 or < 31*		Normal assessment: 12–14 points At risk of malnutrition: 8–11 points Malnourished: 0–7 points
SNAQ [13]	Unintentional weight loss: •> 6 kg in last 6 months ••• •> 3 kg in last month •• Decreased appetite in last month? • Supplemental drinks or tube feeding in the last month? •		• No intervention •• Moderately malnourished, nutritional intervention ••• Severely malnourished: nutritional interventional and treatment dietician
Sarcopenia			
DEXA [14]	Appendicular skeletal muscle mass = the sum of muscle mass of the four limbs indexed to height in m^2		< 5.45 kg/m^2 women abnormal < 7.26 kg/m^2 men abnormal
CT [15•, 16]	Psoas muscle area measured on axial images at level of L3/L4 vertebrae		Lowest tertile psoas muscle area: < 12.0 cm^2 men/< 6.5 cm^2 women
MRI [17•]	Thoracic muscle cross-sectional area on chest magnetic resonance images		Strongest correlation between lower pectoralis major muscle mass and increased mortality
SPPB [18]	Side by side stand (10 s) Semi-tandem stand (10 s) Tandem stand (10 s) Gait speed test to walk 4 m Time taken for × 5 chair stands		Increased risk of death associated with lower scores. Score 0: hazard ratio: 6.06 (CI: (2.19–16.76) Score 1–4: hazard ratio: 4.78 (CI: 1.63–14.02) Score: 5–8: hazard ratio: 1.95 (CI: 0.67–5.70)
Hand grip strength [19]	Jamar dynamometer 3 attempts with 5 s between each attempt Dominant and non-dominant hands measured with averages for each taken		< 25% body weight abnormal
Cachexia			
Definition [20]	≥ 5% edeme free body weight loss in previous 12 months ↓muscle strength, fatigue, anorexia, ↓at free mass index, ↓hemoglobin ↓albumin ↑inflammatory markers		

BMI body mass index, *CI* confidence interval, *CT* computed tomography, *DEXA* dual-energy x-ray absorptiometry, *MNA* Mini Nutritional Assessment, *MRI* magnetic resonance imaging, *NRS 2002* Nutritional Risk Score 2002, *SNAQ* Short Nutritional Assessment Questionnaire, *SPPB* short physical performance battery

fact be malnourished, highlighting the importance of careful volume status assessment in these patients.

Malnutrition screening can consist of both clinical and serological markers (Table 1).

The Nutritional Screening 2002 (NRS2002) tool identified a prevalence of nutritional risk of 57% in chronic HF inpatients, which was associated with an increased incidence of complications and prolonged length of stay in this group [10]. A meta-analysis looking at nutritional and screening tools in HF patients identified an even higher prevalence of malnutrition in patients with ADHF or advanced HF (75–90%) and found that the Mini-Nutritional Assessment was the strongest predictor of mortality in the HF studies [12]. The Short Nutritional Assessment Questionnaire (SNAQ) provides an assessment of nutritional status based on patients' own reported weight loss and dietary intake [13]. Further details of these assessment tools are provided in Table 1 below.

Sarcopenia is defined as loss of skeletal muscle mass and strength associated with the normal process of aging but exacerbated by chronic disease states, including HF [21]. In ambulatory HF patients, the prevalence of sarcopenia is 20% [22]. Strikingly for a condition more typically associated with advancing age, an even higher prevalence of 47% has been documented in younger patients < 55 years with dilated cardiomyopathy [14]. Classically, sarcopenia predominantly affects postural rather than non-postural muscles. Sarcopenia can be assessed using a variety of methods—clinically using lower extremity strength and function measures or radiologically using dual-energy X-ray absorptiometry (DEXA) which is the GOLD standard for assessment. Other imaging measures including computed tomography (CT) or magnetic resonance imaging (MRI) have also been used. Thresholds for defining sarcopenia in previous studies in HF patients detected by these measures are provided in Table 1. Hand grip strength has been used as an isolated surrogate marker for muscle strength, can be assessed even in non-ambulatory HF patients, and has been associated with increased mortality, post-operative complications, and length of stay in advanced HF patients undergoing left ventricular assist device (LVAD) implantation [19, 23].

The wasting continuum in HF infers that muscle is lost before fat tissue, and thereby sarcopenia may progress into cachexia, which is associated with generalized loss of both lean, fat, and bone tissue [24]. Formally, cachexia is defined as 5% or more edema-free body weight loss in the previous 12 months in patients with an underlying chronic illness and is associated with abnormalities in either clinical or biochemical criteria including reduced muscle strength, fatigue, anorexia, low FFMI with or without increased inflammatory markers, anemia, and low serum albumin [25]. Cardiac cachexia is estimated to have a prevalence of anywhere between 5 and 15% in HF patients [26]. It has significant prognostic implications with an 18-month mortality of 50% [27], highlighting the importance of identifying biomarkers and treatments in this patient cohort.

Clinical Consequences of These Three Phenotypes in Heart Failure

Malnourished Patients

Malnutrition identified in HF patients represents an adverse prognosis in a variety of HF presentations. Malnutrition is associated with a significant increase in mortality in both acute HF patients as well as an increased risk of hospitalization and death in stable chronic HF outpatients [28, 29]. Advanced HF patients who were enrolled in the ESCAPE trial and were identified as being at high malnutrition risk prior to discharge had an increased mortality at 6 months compared to those not at high risk [30].

Sarcopenia

Sarcopenia is associated with increased disease severity in patients admitted with ADHF [31]. Lower extremity strength and function, as measured by the Short Physical Performance Battery (SPPB), has been shown to predict long-term survival in patients hospitalized with HF [18]. Sarcopenia in chronic HF patients has been associated with an increased risk of cardiac events [32]. One small study in younger patients aged < 55 years with dilated cardiomyopathy showed that sarcopenia identified using DEXA was associated with lower left ventricular ejection fraction (LVEF), reduced 6-min walk distance (6MWD), and increased New York Heart Association (NYHA) class in this group [14]. In the advanced HF population, one study of 333 patients undergoing LVAD implantation found that sarcopenia, defined as the lowest tertile psoas muscle area by gender identified on CT, was associated with an increase in the composite outcome of inpatient mortality or prolonged length of stay [15•]. This association between psoas muscle area and increased mortality and major adverse post-operative events was also found to be true in patients following heart transplantation [16].

Cachexia

Cardiac cachexia is important prognostically as it has been shown to be independently associated with mortality and adverse cardiovascular and non-cardiovascular outcomes in two studies with a combined patient cohort of 11,712 patients, regardless of age, HF severity, or LVEF [20]. Melenovsky identified that cardiac cachexia was found in almost 20% of advanced HF patients undergoing advanced therapy assessment and was strongly related to the degree of right ventricular dysfunction (RVD). Higher grades of RVD were associated with higher amounts of weight loss. Cachexia was not only associated with worse outcomes (defined as death, transplantation, or need for VAD), but the combination of cardiac cachexia and RVD has the most adverse impact on prognosis

[33]. This study suggests that the two conditions are probably mechanistically linked and have a bidirectional relationship, through known mechanisms such as venous congestion and related anorexia but also through cytokines, increased TNF-α and IL-6, and increased oxidative stress.

Biomarkers of Nutritional Status in Heart Failure

Classic Biomarkers

Serum Albumin/Prealbumin

Albumin is the body's most common serum binding protein and accounts for the majority of plasma colloid oncotic pressure. Low serum albumin (< 35 g/L) has historically been used as a marker of nutritional status. However, its use in functionally impaired elderly patients has been questioned, with > 80% in one study being wrongly identified as malnourished [34]. Albumin needs to be considered in combination with CRP assessment, given its role as a negative acute-phase protein, meaning that its synthesis is suppressed in inflammatory settings. Albumin has been identified as a useful marker of adverse prognosis in advanced HF patients. Low serum albumin levels were found to correlate with increased mortality and post-operative complications in 72 patients undergoing LVAD implantation. Albumin levels were also found to correlate with the degree of frailty identified by low handgrip strength in this group [19].

Prealbumin is a rapid turnover visceral protein with a half life of 2–3 days which is less sensitive to hydration status than albumin, and therefore, it is being recognized as a better marker of protein nutrition. It is also a negative acute phase reactant; therefore, CRP also needs to be taken into account; however, in contrast to albumin, even in the setting of an elevated CRP, it can be used to monitor changes within the same patient. Prealbumin is cleared by the kidneys; therefore, it accumulates in patients with renal dysfunction and clinicians need to be aware of this fact [35]. In one study, 514 patients admitted with ADHF who had prealbumin levels measured at discharge were stratified according to a cut-off < 15 mg/dL, based on a previous study from the same group which showed that this cut off predicted in-hospital mortality. Prealbumin levels below this cut-off were found to be associated with reduced survival and increased rates of all-cause and HF readmission at 6-month follow-up [36].

Serum Iron/Iron Indices

Iron deficiency in HF is defined as hemoglobin < 15 g/dL as well as ferritin < 100 μg/mL or ferritin 100–300 μg/mL if transferrin saturation is < 20% [37]. Iron deficiency is estimated to affect between 37 and 61% of patients with HF, including those who do not have overt anemia [38]. Iron is a vital micronutrient with important roles in tissue oxygenation and metabolism and in recent years has had increased attention in the HF arena. A total of 10–15% of iron in the body is stored in skeletal muscle [39]. Previous animal studies have demonstrated that iron depletion in skeletal muscle results in a number of different detrimental metabolic changes which result mostly in a decrement of oxidative capacity [40]. These effects are borne out clinically with a significant reduction in exercise capacity in HF patients with iron deficiency, regardless of overt anemia or LVEF [41]. In these malnourished patients who already have sarcopenia and muscle wasting, iron deficiency further impairs the optimal functioning of the remaining skeletal muscle and should be a therapeutic target in this cohort.

Vitamin D

Vitamin D is essential for skeletal muscle and mineral homeostasis. Vitamin D deficiency is defined as 25-dihydroxyvitamin (OH) D < 20 ng/mL with vitamin D insufficiency being 21–29 ng/mL [42]. It is highly prevalent in HF with up to 73% being classed as vitamin D deficient in one UK study [43]. The age-related decline in vitamin D receptor expression and 1,25(OH)D activity affects proinflammatory cytokines in the skeletal muscle, and vitamin D deficiency enhances bone marrow adipogenesis and intramuscular adipose tissue, which reduces functionality in skeletal tissues [44]. In studies in a Dutch elderly population, low 25 OH vitamin D < 25 nmol/L was associated with more than double the rates of sarcopenia, defined by either a 40% reduction in grip strength or appendicular mass detected on DEXA scan at 3-year follow-up [45]. This same group also found an impact in functional outcomes, with patients with vitamin D < 25 ng/mL performing worse on physical assessments (sum score of walking test, chair stands, and tandem stand) compared to those with 25 OH vitamin D > 30 ng/mL [46]. The clinical consequences of low vitamin D in HF include increased hospitalizations [47] and increased mortality in patients with HF with reduced ejection fraction (HFrEF) [43].

Renal Function/Creatinine

Chronic kidney disease (CKD), generally defined as an estimate glomerular filtration rate (eGFR) < 60 mL/min/1.72 m^2, is often present in the setting of HF, with a prevalence of 63.6% identified in patients admitted with ADHF [48]. Patients with CKD have a higher prevalence of traditional HF risk factors, while also being associated with malnutrition, acid-based alterations, uremic toxins, renal osteodystrophy, and anemia, further contributing to the risk of HF [49].

From a cross-sectional analysis of the Cardiovascular Health Study of 5888 community dwelling adults aged > 65 years, the prevalence of frailty was more than 2.5 times increased in those with CKD versus those without, even when adjusted for co-morbidity [50]. For patients post-LVAD implantation, a reduced eGFR was the only parameter associated with a lack of improvement in frailty phenotype [51]. Impaired renal function on admission (both acute and chronic) has been associated with increased in-hospital mortality for HF patients and has been shown to have a negative impact on physician adherence to guideline-directed medical therapy [52]. The link between CKD and anemia is also well-established, with negative prognostic outcomes with respect to quality of life, cognitive impairment, cardiovascular disease, hospitalizations, and mortality [53]. In one study of 148 CKD stage 3–5 patients, loss of lean muscle mass detected on DEXA scanning was significantly related to GFR decline [54]. Another study found that sarcopenia identified using the lowest tertile of hand grip strength and bioelectrical impedance measures was an independent predictor of mortality in a similar cohort of patients [55]. Impaired renal function is therefore a serological marker of worse outcome in these patients which is mediated by multi-factorial factors, many of which relate to nutritional status, wasting, and frailty.

Common Pathophysiological Biomarkers

Inflammation

Inflammatory markers including IL-6, CRP, and TNF-α have been noted to be significantly elevated in HF patients [56], particularly those suffering from cachexia and sarcopenia [57, 58]. Increased levels of IL-6 and CRP have been associated with low handgrip strength in people older than 65 years, further supporting the relationship between muscle wasting and inflammation [57]. With regards to clinical effects, one study of 1680 patients admitted with ADHF found that those identified as being malnourished had elevated CRP and TNF-α levels and had higher mortality [59]. Inflammatory markers can be used as biomarkers and have also been therapeutic targets as outlined later in this article.

Glucose Metabolism Disorders

GH has multiple effects on cardiac function, including regulating cardiac growth, decreasing wall stress and vascular resistance, and stimulating myocardial contractility [60]. Abnormalities in the GH/IGF-1 axis have previously been identified in cachectic patients with chronic HF, with significantly elevated levels of GH and a pattern of GH resistance, with lower IGF-1/GH ratios and trends toward lower IGF-1 levels compared with healthy controls [61]. The prevalence of GH deficiency following growth hormone releasing hormone plus arginine stimulation test was reported in nearly 40% of HF patients in one study [62]. GH levels have been shown to be an independent predictor of 1-year outcome, either death or HF re-admission, in patients with HFrEF admitted with ADHF [63].

IGF-1 levels have yielded conflicting results with one study reporting no effect on death/hospital readmission in a group with mild-moderate HF [60], but another reporting that low IGF-1 levels act as a prognostic marker in HF [64]. The use of GH replacement therapy has raised concern over potential side effects including edema, arthralgia, and gynaecomastia when used in otherwise healthy elderly men [65]. There is no consensus as to how best to assess the GH/IGF-1 axis biochemically; therefore, until agreements can be made on this, then their use as biomakers for wasting syndromes in HF remains limited.

Hormonal Disturbances/Testosterone

Testosterone deficiency is defined as the association of low serum testosterone levels with consistent clinical symptoms or signs [66]. Low testosterone levels have been reported in 13–39% of men with chronic HF [67, 68]. Low testosterone levels in HF serve as an independent predictor of reduced peak V02 and are associated with muscle wasting, reduced functional capacity, and reduced survival [69–71].

Novel Biomarkers

Ghrelin

Ghrelin is a peptide hormone which stimulates the release of growth hormone from the pituitary gland. It is primarily released from the stomach and results in appetite stimulation [72]. Low baseline ghrelin levels were found to be associated with worsening nutritional status at 2 years, either by weight loss, grip strength, or nutritional scores in one cohort study of 313 unselected patients aged over 70 years [73]. Ghrelin levels have been found to be elevated in patients with HF and cardiac cachexia compared with those with HF alone [74].

C-Terminal Agrin Fragment

C-terminal agrin fragment (CAF) is produced by the enzyme neurotrypsin and has been investigated as a potential biomarker of muscle wasting. In the SICA-HF study, patients identified as having muscle wasting on DEXA scanning had higher levels of CAF, with a calculated sensitivity of 78.9% and low specificity (43.7%). In this study, CAF was also found to correlate with functional measures including handgrip and quadriceps strength, peak oxygen consumption, and 6MWD [75].

Adiponectin

Adiponectin is an adipose tissue hormone and is elevated in cardiac cachexia, correlating with brain natriuretic peptide (BNP) and weight loss [76]. Patients with chronic HF who had adiponectin levels above the mean had a 3.4 times increase in mortality compared with those with adiponectin levels below the mean [77].

Myostatin

Myostatin, also known as growth differentiation factor 8, is a cytokine primarily found in skeletal muscle and inhibits skeletal muscle growth [78]. Myostatin has been shown to be upregulated in chronic HF patients with an attendant loss in skeletal muscle mass [79].

Serological Biomarkers of Poor Nutrition as Therapeutic Targets in HF

General and Disease-Modifying Treatments

Treatment and reversal of the underlying pathophysiological processes leading to HF and malnutrition require a multidisciplinary approach across a number of different targets. Involvement of a registered dietician with expertise in HF is crucial and is one of the key recommendations outlined in the recent Consensus Statement from the Heart Failure Society of America on nutrition, obesity, and cachexia in HF [80].

Oral protein supplementation has also been examined in chronic HF patients to replace the protein/calorie deficit in patients with cardiac cachexia. Twenty-nine patients were randomized to a regimen of high protein (20 g) high calorie (600 kcal) oral supplement in addition to their usual diet. An improvement in quality of life and reduced TNF-α levels,

Table 2 Biomarker targeted treatments in HF

Biomarker	Population	Patients	Study Duration	Intervention	Outcome
Vitamin D	Elderly, sarcopenia [92]	380	13 weeks	Vitamin D and whey-rich protein supplement BD	↑ Handgrip strength ↑ Lower extremity function
TNF-α	HFrEF < 35% NYHA III-IV [93]	150	28 weeks	Infliximab 5 mg/kg or 10 mg/kg at 0, 2, and 6 weeks or placebo	↑ Risk of hospitalization ↑ Mortality
	HFrEF < 30% NYHA II-IV [94]	1059 925	24 weeks Stopped early	Etanercept 25 mg once or twice weekly or placebo Etanercept 25 mg twice or three times weekly or placebo	in higher dose (10 mg/kg) group No effect on clinical status No effect on death/re-hospitalization
hsCRP	Previous MI ↑ hsCRP [95]	10,061	3.7 years	Canakinumab 50 mg, 150 mg, 300 mg or placebo 3 monthly	Dose dependent ↓ in HF-related hospitalization and ↓ composite of mortality and HF-related hospitalization
Testosterone	Men, chronic HF [96]	70	12 weeks	IM testosterone every 6 weeks or placebo	↑Peak VO2, 6MWD, body weight
	Women, chronic HF [97]	36	6 months	Transdermal testosterone patch or placebo	↑ 6MWD, quadriceps muscle strength
	Men, chronic HF [98]	41	12 weeks	IM testosterone + exercise or exercise alone	↑Peak VO2, leg strength, QoL
SARM: enbosarm	Cancer cachexia [99]	100	113 days	PO Enbosarm 1 mg *or* 3 mg *or* placebo	↑lean body mass
GH	Chronic HF, GH deficiency [62]	56	6 months	GH 0.012 mg/kg SC every second day or placebo	↑Peak VO2, exercise duration, QoL ↑LVEF, ↓NT pro-BNP
Ghrelin	Chronic HF [100]	10	3 weeks	IV Ghrelin 2 μg/kg IV BD	↑ muscle strength, lean muscle mass, peak VO2 ↑ LVEF ↓ Norepinephrine
	Non-small cell lung cancer cachexia, Japanese patients [101]	174	12 weeks	PO Ghrelin (Anamorelin) 100 mg OD	↑ lean muscle mass, improved anorexia symptoms
Myostatin	Sarcopenia [102]	253	12 weeks	REGN1033 100 mg SC 4 weekly *or* 300 mg SC 4 weekly *or* 300 mg SC alternate weeks *or* placebo	↑ lean body mass in all groups
	COPD, reduced skeletal muscle mass [103]	67	24 weeks	Bigramumab (activin type II blocker) receptor 30 mg/kg BD weeks 0, 8 or placebo	↑ lean body mass No change in functional capacity or 6MWD

BD twice daily, *COPD* chronic obstructive pulmonary disease, C-reactive protein, *GH* growth hormone, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *hsCRP* high sensitivity, *IM* intramuscular, *IV* intravenous, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NYHA* New York Heart Association, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide, *OD* once daily, *PO* orally, *QoL* quality of life, *REGN1033* anti-myostatin antibody, *SARM* selective androgen receptor modulator, *SC* subcutaneous, *TNF-α* tumor necrosis factor-alpha, *VO2* maximal oxygen consumption, *6MWD* 6-min walk distance

with associated improvements in body size and composition, was seen in the treatment group [81]. Another small study found that amino acid supplementation improved exercise capacity and peak maximal oxygen consumption (VO_2) in elderly HF patients [82•]. The HFSA consensus statement recommends an even higher goal of protein intake of 1.1 g/kg/day in patients with malnutrition and cachexia [80].

Exercise training is the most effective proven treatment for sarcopenia [83]. Exercise in cachexia reduces inflammatory markers, decreases protein catabolism and reactive oxygen species, and increases protein synthesis [84]. It has also been shown to reduce myostatin expression in both skeletal and cardiac tissue in patients with chronic HF [85].

Treatment of congestion with diuretics will enhance absorption of nutrients, improve symptoms like anorexia, and encourage more oral intake. The only proven treatment for cachexia is standard beta blocker therapy with carvedilol, which has been shown to arrest the progression of cachexia and even partially reverse it in patients with HF [86]. In chronic HF, angiotensin-converting enzyme inhibitors were also shown to reduce the risk of weight loss and attendant risk of mortality [87]. A study by Maurer et al. of 29 frail patients with advanced HF undergoing LVAD implantation found improvements in frailty as assessed by the Fried phenotype in nearly half of patients after 6 months of LVAD therapy, a finding that was also associated with improved quality of life scores [51]. Confirmation as to the highly beneficial effects of continuous-flow LVAD implantation on muscle structure and metabolism was provided in an experimental study of 31 HF patients who had blood and rectus abdominis muscle samples analyzed at both implant and explant of the device. Between both time points, multiple positive effects had occurred, including increased muscle fiber cross-sectional area and increased ratio of type I versus type 2 oxidative fibers [88].

Biomarker Targeted Treatments

The benefits of intravenous iron in HF have been well established with improvements in exercise capacity, 6MWD, and patient global assessment, supporting its use in sarcopenic HF patients [89, 90]. Notably, a recent randomized clinical trial from the Heart Failure Clinical Research Network found that among 225 HFrEF participants with iron deficiency, high-dose oral iron did not improve exercise capacity over 16 weeks [91]. A summary of other published studies and reports evaluating established and novel serological biomarkers of nutrition and metabolism in HF is provided in Table 2.

Conclusion

While HF management and the availability of novel and advanced therapeutics have significantly evolved in recent years, the downstream effects of this success have now become apparent, with an increasing number of older, frail patients with multiple comorbidities and coexisting conditions such as malnutrition, sarcopenia, and cachexia. Identification of these patients is essential, both for appropriate healthcare utilization and also to reverse the muscle wasting at the sarcopenic stage, prior to progression to cachexia, which has to date proven largely irreversible. Markers for nutritional status include serological markers as well as physical assessments of frailty. Serological markers with proven prognostic implications include increased inflammatory markers (CRP, IL-6, and TNF-α), iron deficiency, hypoalbuminemia, and chronic kidney disease in HF patients. Serological markers of nutritional status have the potential to obviate the need for more expensive imaging studies to diagnose and monitor response to treatments and therefore should continue to be an area of further scientific and clinical research interest into malnutrition and wasting syndromes in the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke Statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146–603. https://doi.org/10.1161/cir.0000000000000485.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606–19. https://doi.org/10.1161/HHF.0b013e318291329a.
3. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail. 2016;18(6):613–25. https://doi.org/10.1002/ejhf.566.
4. Raposo André T, Lopes-Santos A. I GN. Cardiac Cachexia syndrome. Eur Med J Cardiol. 2017;5(1):101–7.
5. Goyal P, Almarzooq ZI, Horn EM, Karas MG, Sobol I, Swaminathan RV, et al. Characteristics of Hospitalizations for Heart Failure with Preserved Ejection Fraction. Am J Med. 2016;129(6):635.e15–26. https://doi.org/10.1016/j.amjmed.2016.02.007.
6. McNallan SM, Chamberlain AM, Gerber Y, Singh M, Kane RL, Weston SA, et al. Measuring frailty in heart failure: a community

perspective. Am Heart J. 2013;166(4):768–74. https://doi.org/10.1016/j.ahj.2013.07.008.
7. Vidan MT, Sanchez E, Fernandez-Aviles F, Serra-Rexach JA, Ortiz J, Bueno H. FRAIL-HF, a study to evaluate the clinical complexity of heart failure in nondependent older patients: rationale, methods and baseline characteristics. Clin Cardiol. 2014;37(12):725–32. https://doi.org/10.1002/clc.22345.
8. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56. https://doi.org/10.1093/gerona/56.3.m146.
9. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr (Edinburgh, Scotland). 2015;34(3):335–40. https://doi.org/10.1016/j.clnu.2015.03.001.
10. Tevik K, Thurmer H, Husby MI, de Soysa AK, Helvik AS. Nutritional risk screening in hospitalized patients with heart failure. Clin Nutr (Edinburgh, Scotland). 2015;34(2):257–64. https://doi.org/10.1016/j.clnu.2014.03.014.
11. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiencydagger. Eur Heart J. 2015;36(11):657–68. https://doi.org/10.1093/eurheartj/ehu385.
12. Lin H, Zhang H, Lin Z, Li X, Kong X, Sun G. Review of nutritional screening and assessment tools and clinical outcomes in heart failure. Heart Fail Rev. 2016;21(5):549–65. https://doi.org/10.1007/s10741-016-9540-0.
13. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). Clin Nutr (Edinburgh, Scotland). 2005;24(1):75–82. https://doi.org/10.1016/j.clnu.2004.07.015.
14. Hajahmadi M, Shemshadi S, Khalilipur E, Amin A, Taghavi S, Maleki M, et al. Muscle wasting in young patients with dilated cardiomyopathy. J Cachexia Sarcopenia Muscle. 2017;8(4):542–8. https://doi.org/10.1002/jcsm.12193.
15.• Iwakami N, Nagai T, Furukawa TA, Sugano Y, Honda S, Okada A, et al. Prognostic value of malnutrition assessed by controlling nutritional status score for long-term mortality in patients with acute heart failure. Int J Cardiol. 2017;230:529–36. https://doi.org/10.1016/j.ijcard.2016.12.064 **This study highlights the importance of assessing nutritional status in acute HF patients due to the significant association with increased mortality identified in this group.**
16. Sargento L, Satendra M, Almeida I, Sousa C, Gomes S, Salazar F, et al. Nutritional status of geriatric outpatients with systolic heart failure and its prognostic value regarding death or hospitalization, biomarkers and quality of life. J Nutr Health Aging. 2013;17(4):300–4. https://doi.org/10.1007/s12603-013-0030-y.
17.• Lewis GD, Malhotra R, Hernandez AF, SE MN, Smith A, Felker GM, et al. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical TrialOral Iron for Heart FailureOral Iron for Heart Failure. JAMA. 2017;317(19):1958–66. https://doi.org/10.1001/jama.2017.5427 **The results for IV iron have previously been promising with improvements in exercise capacity in HF patients however, this study examines the use of oral iron and found it to be of little benefit in the treatment group.**
18. Chiarantini D, Volpato S, Sioulis F, Bartalucci F, Del Bianco L, Mangani I, et al. Lower extremity performance measures predict long-term prognosis in older patients hospitalized for heart failure. J Card Fail. 2010;16(5):390–5. https://doi.org/10.1016/j.cardfail.2010.01.004.
19. Chung CJ, Wu C, Jones M, Kato TS, Dam TT, Givens RC, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail. 2014;20(5):310–5. https://doi.org/10.1016/j.cardfail.2014.02.008.
20. Adejumo OL, Koelling TM, Hummel SL. Nutritional risk index predicts mortality in hospitalized advanced heart failure patients. J Heart Lung Transplant : the official publication of the International Society for Heart Transplantation. 2015;34(11):1385–9. https://doi.org/10.1016/j.healun.2015.05.027.
21. Santilli V, Bernetti A, Mangone M, Paoloni M. Clinical definition of sarcopenia. Clin Cases Mineral Bone Metab : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases. 2014;11(3):177–80.
22. Fulster S, Tacke M, Sandek A, Ebner N, Tschope C, Doehner W, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). Eur Heart J. 2013;34(7):512–9. https://doi.org/10.1093/eurheartj/ehs381.
23. Yost G, Bhat G. Relationship between handgrip strength and length of stay for left ventricular assist device implantation. Nutr Clin Pract : official publication of the American Society for Parenteral and Enteral Nutrition. 2017;32(1):98–102. https://doi.org/10.1177/0884533616665926.
24. Anker SD, Sharma R. The syndrome of cardiac cachexia. Int J Cardiol. 2002;85(1):51–66.
25. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr (Edinburgh, Scotland). 2008;27(6):793–9. https://doi.org/10.1016/j.clnu.2008.06.013.
26. Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. J Cachexia Sarcopenia Muscle. 2013;4(3):173–8. https://doi.org/10.1007/s13539-013-0105-y.
27. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet (London, England). 1997;349(9058):1050–3. https://doi.org/10.1016/s0140-6736(96)07015-8.
28. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr (Edinburgh, Scotland). 2003;22(3):321–36.
29. Heberton GA, Nassif M, Bierhals A, Novak E, LaRue SJ, Lima B, et al. Usefulness of psoas muscle area determined by computed tomography to predict mortality or prolonged length of hospital stay in patients undergoing left ventricular assist device implantation. Am J Cardiol. 2016;118(9):1363–7. https://doi.org/10.1016/j.amjcard.2016.07.061.
30. Bibas L, Saleh E, Alkharji S, Chetrit J, Mullie L, Cantarovich M, et al. Sarcopenia and mortality after heart transplantation. Can J Cardiol. 2017;33(10):S71–S2. https://doi.org/10.1016/j.cjca.2017.07.145.
31. Kumar A, Ansari BA, Kim J, Suri A, Gaddam S, Yenigalla S, et al. Axial muscle size as a strong predictor of death in subjects with and without heart failure. J Am Heart Assoc. 2019;8(4):e010554. https://doi.org/10.1161/jaha.118.010554.
32. Rossignol P, Masson S, Barlera S, Girerd N, Castelnovo A, Zannad F, et al. Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from the GISSI-HF and Val-HeFT trials. Eur J Heart Fail. 2015;17(4):424–33. https://doi.org/10.1002/ejhf.240.
33. Tsuchida K, Fujihara Y, Hiroki J, Hakamata T, Sakai R, Nishida K, et al. Significance of Sarcopenia Evaluation in Acute Decompensated Heart Failure. Skeletal Muscle Mass Index versus Fat-Free Mass Index. Int Heart J. 2018;59(1):143–8. https://doi.org/10.1536/ihj.17-057.

34. Narumi T, Watanabe T, Kadowaki S, Takahashi T, Yokoyama M, Kinoshita D, et al. Sarcopenia evaluated by fat-free mass index is an important prognostic factor in patients with chronic heart failure. Eur J Int Med. 2015;26(2):118–22. https://doi.org/10.1016/j.ejim.2015.01.008.
35. Melenovsky V, Kotrc M, Borlaug BA, Marek T, Kovar J, Malek I, et al. Relationships between right ventricular function, body composition, and prognosis in advanced heart failure. J Am Coll Cardiol. 2013;62(18):1660–70. https://doi.org/10.1016/j.jacc.2013.06.046.
36. Kuzuya M, Izawa S, Enoki H, Okada K, Iguchi A. Is serum albumin a good marker for malnutrition in the physically impaired elderly? Clin Nutr (Edinburgh, Scotland). 2007;26(1):84–90. https://doi.org/10.1016/j.clnu.2006.07.009.
37. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, et al. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterol Rep (Oxf). 2016;4(4):272–80. https://doi.org/10.1093/gastro/gow013.
38. Lourenço P, Silva S, Friões F, Alvelos M, Amorim M, Couto M, et al. Low prealbumin is strongly associated with adverse outcome in heart failure. Heart. 2014;100(22):1780–5. https://doi.org/10.1136/heartjnl-2014-305747.
39. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. JACC Heart failure. 2019;7(1):36–46. https://doi.org/10.1016/j.jchf.2018.07.015.
40. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al. Iron deficiency across chronic inflammatory conditions: international expert opinion on definition, diagnosis, and management. Am J Hematol. 2017;92(10):1068–78. https://doi.org/10.1002/ajh.24820.
41. Boulton FE. The myoglobin content of human skeletal muscle. Br J Haematol. 1973;25(2):281.
42. Stugiewicz M, Tkaczyszyn M, Kasztura M, Banasiak W, Ponikowski P, Jankowska EA. The influence of iron deficiency on the functioning of skeletal muscles: experimental evidence and clinical implications. Eur J Heart Fail. 2016;18(7):762–73. https://doi.org/10.1002/ejhf.467.
43. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. Acta Cardiol. 2018;73(2):115–23. https://doi.org/10.1080/00015385.2017.1351239.
44. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30. https://doi.org/10.1210/jc.2011-0385.
45. Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of vitamin D on cardiac function in patients with chronic HF: the VINDICATE study. J Am Coll Cardiol. 2016;67(22):2593–603. https://doi.org/10.1016/j.jacc.2016.03.508.
46. Sanders KM, Scott D, Ebeling PR. Vitamin D deficiency and its role in muscle-bone interactions in the elderly. Curr Osteoporos Rep. 2014;12(1):74–81. https://doi.org/10.1007/s11914-014-0193-4.
47. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the longitudinal aging study Amsterdam. J Clin Endocrinol Metab. 2003;88(12):5766–72. https://doi.org/10.1210/jc.2003-030604.
48. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab. 2007;92(6):2058–65. https://doi.org/10.1210/jc.2006-1525.
49. Costanzo S, De Curtis A, Di Castelnuovo A, Persichillo M, Bonaccio M, Pounis G, et al. Serum vitamin D deficiency and risk of hospitalization for heart failure: prospective results from the Moli-sani study. Nutr Metab Cardiovasc Dis : NMCD. 2018;28(3):298–307. https://doi.org/10.1016/j.numecd.2017.11.008.
50. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail. 2007;13(6):422–30. https://doi.org/10.1016/j.cardfail.2007.03.011.
51. Tuegel C, Bansal N. Heart failure in patients with kidney disease. Heart. 2017;103(23):1848–53. https://doi.org/10.1136/heartjnl-2016-310794.
52. Shlipak MG, Stehman-Breen C, Fried LF, Song X, Siscovick D, Fried LP, et al. The presence of frailty in elderly persons with chronic renal insufficiency. Am J Kidney Dis : the official journal of the National Kidney Foundation. 2004;43(5):861–7.
53. Maurer MS, Horn E, Reyentovich A, Dickson VV, Pinney S, Goldwater D, et al. Can a left ventricular assist device in individuals with advanced systolic heart failure improve or reverse frailty? J Am Geriatr Soc. 2017;65(11):2383–90. https://doi.org/10.1111/jgs.15124.
54. Jenkins R, Mandarano L, Gugathas S, Kaski JC, Anderson L, Banerjee D. Impaired renal function affects clinical outcomes and management of patients with heart failure. ESC heart failure. 2017;4(4):576–84. https://doi.org/10.1002/ehf2.12185.
55. KDOQI. Clinical practice guidelines and clinical practice recommendations for Anemia in chronic kidney disease. Am J Kidney Dis : the official journal of the National Kidney Foundation. 2006;47(5 Suppl 3):S11–145. https://doi.org/10.1053/j.ajkd.2006.03.010.
56. Zhou Y, Hellberg M, Svensson P, Hoglund P, Clyne N. Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3-5. Nephrol Dialysis Transplant : official publication of the European Dialysis and Transplant Association - European Renal Association. 2018;33(2):342–8. https://doi.org/10.1093/ndt/gfw466.
57. Pereira RA, Cordeiro AC, Avesani CM, Carrero JJ, Lindholm B, Amparo FC, et al. Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. Nephrol Dialysis Transplant : official publication of the European Dialysis and Transplant Association - European Renal Association. 2015;30(10):1718–25. https://doi.org/10.1093/ndt/gfv133.
58. Anker SD, Ponikowski PP, Clark AL, Leyva F, Rauchhaus M, Kemp M, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. Eur Heart J. 1999;20(9):683–93. https://doi.org/10.1053/euhj.1998.1446.
59. Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2004;59(3):242–8. https://doi.org/10.1093/gerona/59.3.m242.
60. Bian AL, Hu HY, Rong YD, Wang J, Wang JX, Zhou XZ. A study on relationship between elderly sarcopenia and inflammatory factors IL-6 and TNF-alpha. Eur J Med Res. 2017;22(1):25. https://doi.org/10.1186/s40001-017-0266-9.
61. Yoshihisa A, Kanno Y, Watanabe S, Yokokawa T, Abe S, Miyata M, et al. Impact of nutritional indices on mortality in patients with heart failure. Open heart. 2018;5(1):e000730. https://doi.org/10.1136/openhrt-2017-000730.

62. Castellano G, Affuso F, Conza PD, Fazio S. The GH/IGF-1 Axis and heart failure. Curr Cardiol Rev. 2009;5(3):203–15. https://doi.org/10.2174/157340309788970306.
63. Anker SD, Volterrani M, Pflaum CD, Strasburger CJ, Osterziel KJ, Doehner W, et al. Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. J Am Coll Cardiol. 2001;38(2):443–52.
64. Cittadini A, Saldamarco L, Marra AM, Arcopinto M, Carlomagno G, Imbriaco M, et al. Growth hormone deficiency in patients with chronic heart failure and beneficial effects of its correction. J Clin Endocrinol Metab. 2009;94(9):3329–36. https://doi.org/10.1210/jc.2009-0533.
65. Bhandari SS, Narayan H, Jones DJ, Suzuki T, Struck J, Bergmann A, et al. Plasma growth hormone is a strong predictor of risk at 1 year in acute heart failure. Eur J Heart Fail. 2016;18(3):281–9. https://doi.org/10.1002/ejhf.459.
66. Hassfeld S, Eichhorn C, Stehr K, Naegele H, Geier C, Steeg M, et al. Insulin-like growth factor-binding proteins 2 and 3 are independent predictors of a poor prognosis in patients with dilated cardiomyopathy. Heart. 2007;93(3):359–60. https://doi.org/10.1136/hrt.2006.090092.
67. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med. 2007;146(2):104–15.
68. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med. 2013;10(1):245–84. https://doi.org/10.1111/j.1743-6109.2012.02783.x.
69. Kalicinska E, Wojtas K, Majda J, Doehner W, von Haehling S, Banasiak W, et al. Anabolic deficiencies in men with systolic heart failure: do co-morbidities and therapies really contribute significantly? Aging Male : the official journal of the International Society for the Study of the Aging Male. 2013;16(3):123–31. https://doi.org/10.3109/13685538.2013.807427.
70. Wu HY, Wang XF, Wang JH, Li JY. Testosterone level and mortality in elderly men with systolic chronic heart failure. Asian J Androl. 2011;13(5):759–63. https://doi.org/10.1038/aja.2011.26.
71. Jankowska EA, Filippatos G, Ponikowska B, Borodulin-Nadzieja L, Anker SD, Banasiak W, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. J Card Fail. 2009;15(5):442–50. https://doi.org/10.1016/j.cardfail.2008.12.011.
72. Jankowska EA, Biel B, Ponikowska B, Borodulin-Nadzieja L, Petruk-Kowalczyk J, Banasiak W, et al. 679 Reduction in serum testosterone deteriorates exercise capacity in men in the course of chronic heart failure. Eur J Heart Fail Suppl. 2007;6(S1):148. https://doi.org/10.1016/S1567-4215(07)60413-5.
73. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006;114(17):1829–37. https://doi.org/10.1161/circulationaha.106.649426.
74. Loncar G, Springer J, Anker M, Doehner W, Lainscak M. Cardiac cachexia: hic et nunc. J Cachexia Sarcopenia Muscle. 2016;7(3):246–60. https://doi.org/10.1002/jcsm.12118.
75. Serra-Prat M, Palomera E, Roca M, Puig-Domingo M. Long-term effect of ghrelin on nutritional status and functional capacity in the elderly: a population-based cohort study. Clin Endocrinol. 2010;73(1):41–7. https://doi.org/10.1111/j.1365-2265.2009.03730.x.
76. Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H, et al. Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. Circulation. 2001;104(17):2034–8.
77. Steinbeck L, Ebner N, Valentova M, Bekfani T, Elsner S, Dahinden P, et al. Detection of muscle wasting in patients with chronic heart failure using C-terminal agrin fragment: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). Eur J Heart Fail. 2015;17(12):1283–93. https://doi.org/10.1002/ejhf.400.
78. Araujo JP, Lourenco P, Rocha-Goncalves F, Ferreira A, Bettencourt P. Adiponectin is increased in cardiac cachexia irrespective of body mass index. Eur J Heart Fail. 2009;11(6):567–72. https://doi.org/10.1093/eurjhf/hfp046.
79. Szabo T, Scherbakov N, Sandek A, Kung T, von Haehling S, Lainscak M, et al. Plasma adiponectin in heart failure with and without cachexia: catabolic signal linking catabolism, symptomatic status, and prognosis. Nutr Metab Cardiovasc Dis : NMCD. 2014;24(1):50–6. https://doi.org/10.1016/j.numecd.2013.04.015.
80. Breitbart A, Auger-Messier M, Molkentin JD, Heineke J. Myostatin from the heart: local and systemic actions in cardiac failure and muscle wasting. Am J Physiol Heart Circ Physiol. 2011;300(6):H1973–H82. https://doi.org/10.1152/ajpheart.00200.2011.
81. Lenk K, Schur R, Linke A, Erbs S, Matsumoto Y, Adams V, et al. Impact of exercise training on myostatin expression in the myocardium and skeletal muscle in a chronic heart failure model. Eur J Heart Fail. 2009;11(4):342–8. https://doi.org/10.1093/eurjhf/hfp020.
82.• Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, et al. Nutrition, Obesity, and Cachexia in Patients With Heart Failure: A Consensus Statement from the Heart Failure Society of America Scientific Statements Committee. J Card Fail. 2019;25(5):380–400. https://doi.org/10.1016/j.cardfail.2019.03.007 **This article suggests an approach to the assessment of HF patients (both inpatients and outpatients) with malnutrition in combination with either cachexia and obesity and a management strategy for each cohort.**
83. Rozentryt P, von Haehling S, Lainscak M, Nowak JU, Kalantar-Zadeh K, Polonski L, et al. The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: a randomized, double-blind pilot study. J Cachexia Sarcopenia Muscle. 2010;1(1):35–42. https://doi.org/10.1007/s13539-010-0008-0.
84. Aquilani R, Viglio S, Iadarola P, Opasich C, Testa A, Dioguardi FS, et al. Oral amino acid supplements improve exercise capacities in elderly patients with chronic heart failure. Am J Cardiol. 2008;101(11a):104e–10e. https://doi.org/10.1016/j.amjcard.2008.03.008.
85. Forbes SC, Little JP, Candow DG. Exercise and nutritional interventions for improving aging muscle health. Endocrine. 2012;42(1):29–38. https://doi.org/10.1007/s12020-012-9676-1.
86. Gould DW, Lahart I, Carmichael AR, Koutedakis Y, Metsios GS. Cancer cachexia prevention via physical exercise: molecular mechanisms. J Cachexia Sarcopenia Muscle. 2013;4(2):111–24. https://doi.org/10.1007/s13539-012-0096-0.
87. Lenk K, Erbs S, Hollriegel R, Beck E, Linke A, Gielen S, et al. Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. Eur J Prev Cardiol. 2012;19(3):404–11. https://doi.org/10.1177/1741826711402735.
88. Clark AL, Coats AJS, Krum H, Katus HA, Mohacsi P, Salekin D, et al. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. J Cachexia Sarcopenia Muscle. 2017;8(4):549–56. https://doi.org/10.1002/jcsm.12191.
89. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet (London,

England). 2003;361(9363):1077–83. https://doi.org/10.1016/s0140-6736(03)12892-9.

90. Khawaja T, Chokshi A, Ji R, Kato TS, Xu K, Zizola C, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. J Cachexia Sarcopenia Muscle. 2014;5(4):297–305. https://doi.org/10.1007/s13539-014-0155-9.
91. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361(25):2436–48. https://doi.org/10.1056/NEJMoa0908355.
92. Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc. 2015;16(9):740–7. https://doi.org/10.1016/j.jamda.2015.05.021.
93. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF therapy against congestive heart failure (ATTACH) trial. Circulation. 2003;107(25):3133–40. https://doi.org/10.1161/01.Cir.0000077913.60364.D2.
94. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the randomized Etanercept worldwide evaluation (RENEWAL). Circulation. 2004;109(13):1594–602. https://doi.org/10.1161/01.Cir.0000124490.27666.B2.
95. Everett Brendan M, Cornel Jan H, Lainscak M, Anker Stefan D, Abbate A, Thuren T, et al. Anti-inflammatory therapy with Canakinumab for the prevention of hospitalization for heart failure. Circulation. 2019;139(10):1289–99. https://doi.org/10.1161/CIRCULATIONAHA.118.038010.
96. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol. 2009;54(10):919–27. https://doi.org/10.1016/j.jacc.2009.04.078.
97. Iellamo F, Volterrani M, Caminiti G, Karam R, Massaro R, Fini M, et al. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. J Am Coll Cardiol. 2010;56(16):1310–6. https://doi.org/10.1016/j.jacc.2010.03.090.
98. Stout M, Tew GA, Doll H, Zwierska I, Woodroofe N, Channer KS, et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. Am Heart J. 2012;164(6):893–901. https://doi.org/10.1016/j.ahj.2012.09.016.
99. Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol. 2013;14(4):335–45. https://doi.org/10.1016/s1470-2045(13)70055-x.
100. Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, Shimizu W, et al. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. Circulation. 2004;110(24):3674–9. https://doi.org/10.1161/01.Cir.0000149746.62908.Bb.
101. Katakami N, Uchino J, Yokoyama T, Naito T, Kondo M, Yamada K, et al. Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients (ONO-7643-04). Cancer. 2018;124(3):606–16. https://doi.org/10.1002/cncr.31128.
102. Ebner N, von Haehling S. Unlocking the wasting enigma: highlights from the 8th Cachexia conference. J Cachexia Sarcopenia Muscle. 2016;7(1):90–4. https://doi.org/10.1002/jcsm.12106.
103. Polkey MI, Praestgaard J, Berwick A, Franssen FME, Singh D, Steiner MC, et al. Activin type II receptor blockade for treatment of muscle depletion in chronic obstructive pulmonary disease. A randomized trial. Am J Respir Crit Care Med. 2019;199(3):313–20. https://doi.org/10.1164/rccm.201802-0286OC.