











Cardiac Cachexia: A Well-Known but Challenging Complication of Heart Failure

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Abstract: Heart failure (HF) is a common complication of various cardiac diseases, and its incidence constantly increases. This is caused mainly by aging of populations and improvement in the treatment of coronary artery disease. As HF patients age, they tend to develop comorbidities, creating new problems for health-care professionals. Sarcopenia, defined as the loss of muscle mass and function, and cachexia, defined as weight loss due to an underlying illness, are muscle wasting disorders of particular relevance in the heart failure population, but they go mostly unrecognized. The coexistence of chronic HF and metabolic disorders facilitates the development of cachexia. Cachexia, in turn, significantly worsens a patient's prognosis and quality of life. The mechanisms underlying cachexia have not been explained yet and require further research. Understanding its background is crucial in the development of treatment strategies to prevent and treat tissue wasting. There are currently no specific European guidelines or recommended therapy for cachexia treatment in HF ("cardiac cachexia").

Keywords: cardiac cachexia, heart failure, nutritional status

Introduction

Heart failure (HF) is considered a cardiovascular disease whose incidence increases constantly. The number of hospitalizations due to HF is still rising, and it has tripled over the last three decades. Over one million hospitalizations with a primary diagnosis of HF occur each year in the U.S.¹ similar to Europe.² This is related both to the demographics, ie, aging population, and to the improved treatment of acute cardiac diseases that eventually leads to the development of chronic HF. Chronic HF is a complex syndrome accompanied by changes in various organs. Most importantly, there are changes within muscular tissue, which facilitate the development of frailty syndrome. Chronic HF is a catabolic state that may lead to cachexia when the physiological balance between anabolic and catabolic processes is impaired.³

Cachexia is a well-known problem in patients with end-stage chronic HF, and it is a risk factor of death for the patients at this stage of the disease.⁴ It is estimated to affect between 5% and 15% of HF patients, especially those with HF with reduced ejection fraction (HF_{rEF}).⁵ However, neither left ventricular ejection fraction (LVEF) nor the New York Heart Association (NYHA) functional class is directly associated with cachexia development.⁶ In 34% of HF patients during a 48-month follow-up $\geq 6\%$ of body weight loss was reported, while 10.5% of optimally treated outpatients with no underlying diabetes had $>5\%$ weight loss.⁷

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Cachexia is related to malnutrition, which frequently accompanies chronic HF and has many negative consequences. There are associations between malnutrition and impaired wound healing, increased rate of post-operative complications, and mortality.⁸ What is important, cardiac cachexia is associated with poor outcomes and unfavorable reactions to pharmacological treatment, and poor quality of life.⁹ The overall prevalence of cachexia in the industrialized world increases with a greater incidence of chronic diseases. Currently, this problem affects approximately 6–12 million people. It is estimated that 1.5–2 million people die every year due to cachexia. The annual mortality due to cardiac cachexia is 20–40%.¹⁰ Although the cardiac cachexia problem is well known and well documented, it is still difficult to develop a specific therapy for its prevention and treatment due to the multifactorial myocardial injury.

Cachexia in Heart Failure – Definition

Several definitions of cachexia due to HF were proposed. Historically, cachexia was defined as a loss of body mass (taking fluid imbalance into account) of more than 6% in the absence of any other significant illness.¹¹ Nowadays, a multidisciplinary approach is commonly accepted. Cachexia is a multifactorial and multiple organ metabolic disorder¹² that is often observed in patients affected by chronic diseases, including HF. Currently, it is primarily defined as a loss of body mass (taking fluid imbalance into account) of more than 5% in 12 months (or BMI <20 kg/m²) with accompanying conditions like decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormalities in blood biomarkers (elevated C-reactive protein and/or elevated interleukin (IL)-6, Hb <12 g/dL, or low serum albumin (<3.2 g/dL));^{12–15} at least three of the above must coexist. Cachexia is a generalized process involving adipose tissue, ie, energetic reserves, and other tissues, especially skeletal muscles and bones.¹² Cachexia should also be understood as a nutritional syndrome because, to reverse cachexia, nutrients such as protein and calories are needed. Also, the anorectic components represent a nutritional disorder.¹³

Cachexia is accompanied by malnutrition, systemic nutritional deficiencies, elevated inflammatory cytokines, immune system hyperactivity, and neurohormonal alterations.¹⁶ This process results in a syndrome involving

loss of body weight, fatigue, dyspnea, tachycardia, dyspepsia, and appetite loss.

Muscle wasting is an important component of cachexia. It often precedes cachexia development and can also predict poor results in HF. Interesting data shows that a handgrip test is a useful tool for detecting muscle function changes in advanced heart failure after the implantation of a ventricular assist device, which can help to better plan interventional tests in cachexia.^{7,17}

Seeking optimal biomarkers of cachexia to facilitate diagnosis is very important. Methods of prevention and treatment are needed. Pre-albumin seems to be a biomarker of cachexia, a potential indicator of malnutrition, low-cholesterol levels, and worse prognosis in chronic HF patients.¹⁸ Appetite regulating hormones (cholecystokinin and ghrelin) can play an important role as potential biomarkers of cardiac cachexia (ie, cachexia due to heart disease). In Wang et al, plasma cholecystokinin levels and expression in the heart muscle increased in rats with cardiac cachexia and positively correlated with BNP (brain natriuretic peptide) concentrations and were significantly negatively correlated with LVEF.⁹ Compared to the control group, plasma-ghrelin levels in the cardiac cachexia group decreased dramatically, and the expression of ghrelin in the myocardium was also decreased, which was negatively associated with BNP levels and positively associated with the ejection fraction.⁹

Nutritional Status and Metabolic Processes in Heart Failure

HF is a syndrome accompanied by multiple changes. HF patients show impaired kidney function caused by a neurohormonal disorder in the renin-angiotensin-aldosterone system (RAAs). Electrolyte disorders, calcium-phosphate imbalance, lung diseases, and anemia may also be observed.¹⁹ Progression of HF involves remodeling of cardiac tissue, including metabolic changes such as a slower ATP synthesis, mitochondrial dysfunction, or elevated free fatty acid concentration.²⁰ Microelements play a crucial role in metabolic processes as co-factors. One of the most important is co-enzyme Q10 (CoQ10), a natural antioxidant for a human body that takes part in ATP synthesis. There is a high concentration of CoQ10 in the myocardium. It relieves oxidative stress and stabilizes cell membranes.²¹ According to research dating from 2010, decreased CoQ10 intake is associated with disease advancement as assessed using NYHA classification,

decreased LVEF, and elevated NT-proBNP.²² Interestingly, it was proved more than 20 years ago, that beta-blockers and statins decrease CoQ10 concentration.²³ Unfortunately, based on the available data, it is still impossible to determine whether CoQ10 has a sufficiently positive influence on biochemical and echocardiographic parameters to recommend its supplementation. The research on its influence on the state of health of HF patients is ongoing.

HF is often accompanied by calcium-phosphate metabolic disorders associated with secondary hyperparathyroidism and vitamin D deficiency, which in turn is caused by the impairment of kidney function.^{21,24,25} It also seems that elevated TNF-alpha concentration due to HF is associated with lower calcitriol and vitamin D synthesis, which results in elevated renin, which may play a role in promoting cachexia.²¹ This is why supplementation of vitamin D in HF is growing more popular. Moreover, research shows that vitamin D supplementation decreases aldosterone concentration, which is often elevated in HF.^{21,24,25}

It is important to keep normal iron concentration in HF patients. They often show iron deficiency (somewhat more frequent in women than in men), and inflammatory states may reduce iron absorption by 40% in these patients.^{26,27} One of the causes of iron deficiency in cachectic HF patients may also be loss of appetite. As a result, microcytic anemia develops, and subsequently, fatigue, dyspnea, and tachycardia in more severe cases. Anemia is a recognized cause of exacerbation of HF.^{26,27} It seems that intravenous iron supplementation is more effective than oral. It increases tolerance of exertion, improves the quality of life, and reduces symptoms of HF.²⁷

New potential factors to aid HF treatment are discussed, which can be even more critical when cardiac cachexia occurs. They include thiamin (vitamin B1), creatine, amino acids, taurine, and carnitine. Supplementation of taurine is already used in the treatment of HF in Japan.²¹ Carnitine seems to improve cardiac metabolism, left ventricle function, and has a protective effect on myocardium during ischemia.²⁷ It has been suggested that the addition of pentoxifylline to nutritional supplementation may reduce proinflammatory cytokine concentrations and increase anabolic processes,²⁸ which relieves HF symptoms.

Elevation of pro-inflammatory cytokines due to HF causes chronic generalized inflammation, including the alimentary tract. This inflammation results in the thickening of intestinal walls, increased bacterial growth, and, consequently, absorption disorders.²⁸ The newest theory attributes

the malnutrition in HF patients to impaired intestinal microcirculation. It was proposed that ischemia might cause dysfunction of intestinal epithelial cells, edema, and thickening of intestinal walls, and promote collagen depositing in small intestine walls. All the above-mentioned factors have a negative influence on the absorption of nutrients and microelements. Moreover, intestinal mucosa changes allow bacterial products to pass to circulation, thus increasing inflammatory reactions. These bacterial metabolites seem to promote myocardial hyperplasia and fibrosis.²⁹ Bacterial and functional changes may well play one of the most important roles in HF development. These changes result mainly in protein malnutrition and, consequently, muscle wasting, because muscle wasting causes elevation of serum amino acids to provide substrates for gluconeogenesis, which is much more intense in HF patients than in healthy individuals increased energy expenditure. This process may lead to the development of cardiac cachexia.^{29,30}

Obesity Paradox

Obesity is much more prevalent in patients with HF with preserved ejection fraction (HFpEF) compared to HF with reduced ejection fraction (HFrEF), where over 80% of patients with HFpEF have BMI overweight or obesity.³¹

The obesity paradox is a curious phenomenon in HF. Obesity is linked to lower circulating levels of B-type natriuretic peptide, suggesting the presence of a more favorable hemodynamic profile. However, loss of body mass in obese patients improves LVEF, NYHA class, and quality of life.^{32,33} Paradoxically, many authors reported that a significant loss of body mass, even in overweight or obese patients, makes the prognosis worse and increases the risk of cachexia.³³ Obesity measured by BMI and various other indicators have been associated with improved HF survival rates in many studies. What is more, HF patients with a BMI of over 30 kg/m² show better survivability rates than normal-weight patients.³⁴ The reason for this might be a high proportion of adipose tissue in obese patients. Thus, they would have more energetic reserves, which would be expected to decrease the risk of cachexia. There seems to be much ambiguous evidence in the research of the obesity paradox in HF. This phenomenon has not been thoroughly investigated yet.³⁵

Pathological Mechanisms in the Development of Cardiac Cachexia

A general overexpression of catabolic processes is crucial in the development of cardiac cachexia. This is caused by

various immunologic, metabolic, and neurohormonal changes.^{28,36,37} HF patients show increased energetic expenditure and a simultaneous decrease in energy intake.⁶ This results in compensatory proteolysis and a subsequent muscle wasting, the two processes are always associated with cachexia development.^{38,39}

The sequence of pathological processes involved in the development of cardiac cachexia includes hypoalbuminemia. HF patients demonstrate a negative nitrogen balance, which is a product of significant proteolysis. It seems that hypoalbuminemia provokes changes in the activity of inflammatory cytokines. It causes increased secretion of TNF-alpha (tumor necrosis factor), one of the main inflammatory cytokines of the human body. TNF-alpha has a negative impact on the endothelium, which leads to lower tissue blood flow and, consequently, decreased physical fitness and absorption of nutrients.^{38,39} Apart from TNF-alpha, also IL-1 and IL-6 are secreted, and all of them further activation of catabolic processes.^{36,40} Moreover, hypoalbuminemia seems to reduce the activity of anti-inflammatory cytokines IL-10 and TGF-beta (transforming growth factor).^{12,41} Hence, hypoalbuminemia is associated with muscular wasting. The exact cause and sequence of the above-mentioned changes are not known.

HF patients also show hormonal changes. Increased catabolic processes result in lower testosterone and elevated cortisol blood concentrations. This intensifies muscle wasting and proteolysis.¹² Loss of body weight provokes secretion of adiponectin, which increases lipid oxidation and tissue sensitivity to insulin. This results in lower lipid and glucose blood concentrations. Loss of body weight also increases leptin concentration. Leptin shows a similar action to adiponectin, by increased insulin sensitivity and lower lipogenesis.^{12,42} Nevertheless, HF patients show insulin resistance.⁴³ The main action of leptin is an activation of the satiety center, followed by the early feeling of satiety and lower intake of nutrients.⁴⁴ This may intensify cardiac cachexia.

Increased secretion of human growth hormone (hGH) with reduced IGF-1 (insulin-like growth factor) concentration may suggest that cachectic patients present tend to develop resistance to hGH.^{36,39} This is considered to be compensatory to ineffective action of GH on the tissue.^{12,39} The role of IGF-1 in HF and cardiac cachexia is still under investigation. Normally, IGF-1 plays a significant role in muscle regeneration and slows down muscular wasting.⁴⁵ It stimulates protein anabolism and activates muscular satellite cells. The latter include

progenitor and stem cells of muscular tissue.^{45,46} In a normal muscle, these cells are inactive. They are responsible for muscular fibers' regeneration, and their activity increases after an injury (or micro-injury).⁴⁶ Angiotensin II decreases the activity of these cells and TGF-beta, which may constitute another mechanism of muscular wasting in HF.³⁸

Increased energetic expenditure in cardiac cachexia results in an imbalance between the sympathetic and parasympathetic systems. Secretion of cortisol and activation of RAAs (renin-aldosterone-angiotensin system) and natriuretic peptide system increases.^{38,39} Angiotensin II plays a key role in cachexia. It promotes proteolysis in the muscular tissue by increased secretion of IL-6 and glucocorticosteroids and decreased secretion of IGF-1.³⁸ Some authors showed that the ubiquitin-dependent pathway of protein degradation plays a major role in the degradation of muscular fibril proteins in neoplastic cachexia.⁴⁷ Similar processes are also likely in cardiac cachexia. Their increased activity is associated with increased oxidative stress in muscular tissue, which is provoked by nicotinamide adenine dinucleotide phosphate (NADPH) activation by angiotensin II.^{38,39} Angiotensin II decreases the activation of muscular satellite cells, thus disturbing regeneration of injured muscular fibers. It also increases degradation of lysosome and proteasome proteins,³⁸ stimulates secretion of corticoid releasing hormone (CRH), and decreases secretion of neuropeptide Y (NPY) and orexin.³⁹ Hence, it causes a feeling of satiety and decreases appetite.

Sarcopenia

Cachexia is defined as weight loss due to an underlying illness, the sarcopenia is defined as the loss of muscle mass and function, and they both are muscle wasting disorders. Primary sarcopenia is age-related, whereas secondary sarcopenia is associated with various chronic diseases, including heart failure.⁴⁸ Sarcopenia is a significant issue in chronic HF patients. Sarcopenia is characterized by muscle loss and decreased muscle fibers, which leads to reduced muscle strength and physical performance in symptomatic HF patients compared to healthy subjects.⁴⁹ According to the European Working Group on Sarcopenia in Older People (EWGSOP) the definition of sarcopenia is both loss of muscle mass and function.⁵⁰ Sarcopenia is mainly age-related,⁵¹ but it is also observed in HF patients, especially in advanced chronic HF. It may lead to reduced exercise capacity and frailty syndrome.^{52,53} Sarcopenia is

a marker of worse prognosis in HF patients.⁵⁴ Some studies show that up to 20% of HF patients may develop a significant muscular wasting.¹⁶ Another study reported that 40% of the study participants (patients with chronic HF) were at risk of or already suffered from loss of muscular strength.^{8,55} Sarcopenia may also develop in obese HF patients, which shows that its pathology is complex.⁵¹ Impaired myocardial relaxation in HFpEF is a reliable and independent predictor of the ability to perform aerobic exercise, and HFpEF patients simultaneously show a high incidence of sarcopenic obesity,⁵⁶ which is independently associated with worse outcomes and increased mortality in chronic HF.^{57–60} Loss of muscle mass is associated with reduced fitness and quicker deterioration of a patient's state. HF patients with sarcopenia require hospitalizations more often, and their risk of death is greater than those without sarcopenia.^{50,61} Increased catabolic stress in the skeletal muscles of chronic HF (CHF) patients results in effort intolerance, ventilatory inefficiency, chronotropic incompetence and insulin resistance, which suggests a significant influence catabolic status mechanism on the limited functional status of the patient. It has been suggested that skeletal muscle density is an independent marker of clinical outcomes.⁵⁶ It has recently been shown that dilution of D3-creatine is more accurate in measuring muscle mass and more strongly associated with physical performance.⁴⁸

The gold standard in diagnostics of sarcopenia is dual-energy X-ray (DXA). Also, bioelectrical impedance spectroscopy, a safer alternative, is available.^{16,62} The simplest method of assessing patients with sarcopenia is the measurement of muscle strength using a hand dynamometer.⁵⁰ The search for effective methods of treatment is ongoing. Currently, strength training and amino-acid-based drugs are recommended. The effectiveness of other drugs, including testosterone, is currently under investigation.¹⁶ The essence of screening for sarcopenia should be emphasized. SARC-F is a simple, 5-point questionnaire that aims to identify people with high-risk complications due to sarcopenia. SARC-F contains five components: strength, assistance walking, rising from a chair, climbing stairs, and falls. SARC-F items were selected to reflect the consequences of sarcopenia. Cross-sectional SARC-F correlates with grip strength and frailty.⁶³ According to general recommendations, sarcopenia management should start with screening, by deepening the evaluation with a dynamometric measurement or walking gait speed. If the screening test is positive, the in-depth assessment

should be based on MRI, DXA. For the diagnosis of sarcopenia, physical exercise and an adequate protein supply are recommended: 1–1,5 g/kg per day.⁶⁴

Clinical Interplay in Heart Failure – Cachexia, Sarcopenia, Frailty

Due to a common pathophysiological pathway, patients with heart failure often suffer from a frailty syndrome with sarcopenia as a component and cardiac cachexia as the last stage. It is noteworthy that cachexic older adults are co-morbid for sarcopenia, but those who are sarcopenic are rarely co-morbid for cachexia.⁶⁵ Sarcopenia in HF may ultimately progress to cardiac cachexia.⁵⁶ Sarcopenia is a contributor toward the frailty syndrome, strictly physical and geriatric condition of frailty. However, frailty represents a broader age-related decline in reserve and function across multiple physiologic systems resulting in physical, cognitive, and social impairments that increase vulnerability to stressors.^{64,66} Frailty syndrome is an independent predictor of early disability, long-term mortality, and readmission in heart failure patients. It is important to understand that sarcopenia and cachexia may require different therapeutic approaches, even though they overlap on some points (Figure 1).

Clinical Significance of Cachexia in Heart Failure Patients and Treatment Options

There are still no European guidelines for dealing with cardiac cachexia. In the Recommendation for managing cardiac cachexia and Sarcopenia by Heart Failure Society of America Scientific Statements Committee, the most important points relate to:

- perform annual screening tests for unintentional weight loss due to the strong relationship between cachexia and adverse clinical outcomes;
- define cachexia as unintentional edema-free weight loss >7.5% from 6 to 12 months or BMI <20 kg/m² for documented sarcopenia, cachexia or abnormal biochemical indicators;
- refer patients meeting the above criteria to an in-depth nutritional assessment;
- sarcopenia diagnosis based on screening using SARC-F (≤ 4 points), walking speed test (≤ 0.8 m/s), grip strength <27 kg for men or <16 kg for women;

Clinical Interplay between Cachexia, Sarcopenia and Frailty*

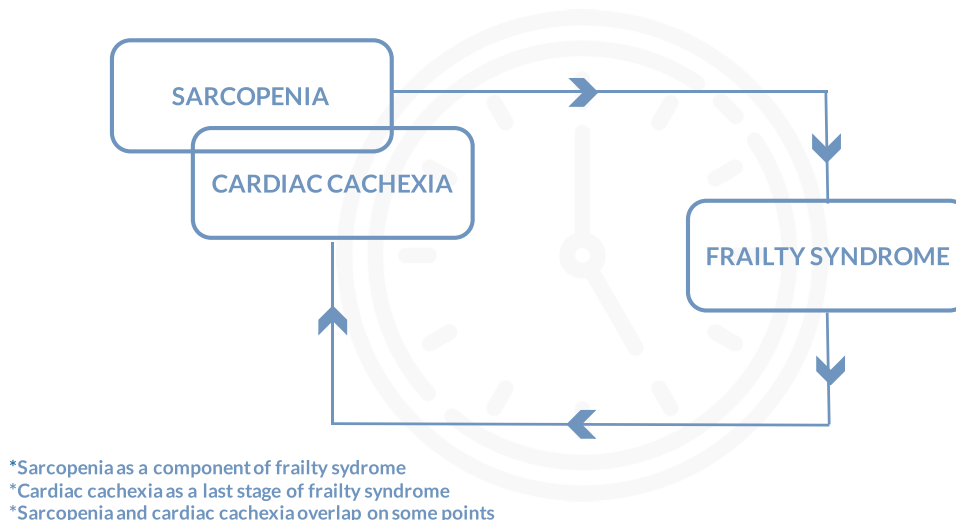


Figure 1 Clinical Interplay between Cachexia, Sarcopenia and Frailty. *Sarcopenia as a component of frailty syndrome; *Cardiac cachexia as a last stage of frailty syndrome
 *Sarcopenia and cardiac cachexia overlap on some points.

- protein supply in patients with identified cachexia or in the cachexia risk group at an amount ≥ 1.1 g/kg daily;
- special evaluation of patients with cachexia or malnutrition referred to cardiac surgery or patients with terminal status for enteral or parenteral nutritional support.^{66,67}

Potential therapeutic methods target different cardiac cachexia pathogenesis mechanisms, including neurohormonal abnormalities, immune activation and inflammation, metabolic, hormonal imbalance, and gastrointestinal disorders.⁶⁸ In patients with cardiac cachexia, long-term use of beta-blockers resulted in increased weight gain, decreased plasma noradrenaline levels, and partial reversal of cachexia. Growth hormone is an anabolic hormone that participates in protein synthesis and is associated with muscle mass gain. In studies of patients with non-ischemic HF, ghrelin administration within three weeks increased food intake, GH, left ventricular mass, LVEF, muscle strength, and lean muscle mass. While multifactorial effects of ghrelin show potential for the treatment of myocardial cachexia, further, well-controlled studies are needed.⁶⁸

Currently, both prevention and treatment of cachexia bases on non-pharmacological methods. Regular physical activity combined with an appropriate diet and nutritional supplementation seems the most important. Promising results of fat-rich and protein-rich diets have been

reported.⁶⁹ Some authors argue that carnitine shows a positive effect on skeletal muscles. This however has never been demonstrated for the cardiac muscle.⁷⁰ The most effective type of physical activity for HF patients is aerobic training. It has been proved to reduce the negative remodeling of the heart and to improve ventricular function and tolerance of exertion.^{7,71} Aerobic training reduces oxidative stress and catabolic processes within muscles. What is more, it promotes protein synthesis. Out of pharmacological treatment, intravenous iron usage in anemia²⁷ and ACEi/ARB (angiotensin converting enzyme inhibitor/angiotensin receptor blocker)⁷² shows some promise in cachectic patients though the efficacy of such a treatment has not been proven yet. It has been suggested that both ACEi and ARB may also have some influence on muscle wasting.^{11,38,72} The analysis of the COPERNICUS trial has shown that carvedilol has the potential to stop and partially reverse muscle wasting in cachectic patients with severe chronic HF (LVEF $<$ 25% and dyspnea at rest or during minimal activity).⁷³ The effects of other supplements, including essential amino acids, omega-3 polyunsaturated fatty acids, or pharmacological agents like immunomodulators, anabolic hormones, appetite stimulants, and other new drugs, are currently under investigation.⁷⁴ Table 1 summarizes the results of randomized controlled trials on supplementation in HF patients.

Currently, two management options are under serious consideration: anti-TNF-alpha therapy and appetite stimulants.¹² A research of thalidomide to treat cardiac

Table 1 The Summary of Randomized Controlled Trials on Supplementation in HF Patients

Authors	Country	Type of Study	Analyzed Population	Age (Years)	Method of Treatment	Follow Up	Findings
Fumagalli et al (2011) ⁷⁰	Italy	Randomized, double-blind, placebo-controlled trial	67 patients with HFREF	72±6 71±6 (placebo)	Oral supplementation with coenzyme Q10 and creatine	2 months	Supplementation improve exercise tolerance and HRQL.
Rozentryt et al (2010) ⁶⁹	Poland	Randomized, double-blind, placebo-controlled trial	29 cachectic patients with HFREF	52±10 49±12 (placebo)	High-caloric protein-rich oral nutritional supplement (additional 600 kcal/day)	6 weeks	Supplementation has a beneficial impact on quality of life, dry body weight and body composition.
Wicham et al (2010) ²⁴	United Kingdom	Randomized, double-blind, placebo-controlled trial	105 patients with HF with vitamin D insufficiency	78.8±5.6 80.6±5.7 (placebo)	Oral supplementation with vitamin D	20 weeks	Supplementation did not improve functional capacity or quality of life in this group of patients, despite a high increase in 25-hydroxyvitamin D level.
Boxer et al (2013) ²⁵	USA	Randomized double-blind placebo-controlled trial	64 patients with HF	65.8±10.6 66.0±10.4 (placebo)	Oral supplementation with vitamin D and calcium	6 months	Supplementation did not improve aerobic capacity or skeletal muscle strength.
Clark et al (2017) ⁷³	UK, Australia, USA, Germany, Switzerland	Randomized double-blind placebo-controlled trial (COPERNICUS trial)	2289 patients with HFREF	67.4±12.1 (BMI<22) 64.5±11.6 (BMI 22 to <25) 63.1±10.8 (BMI 25 to <30) 59.7±11.1 (BMI≥30)	Carvedilol treatment	29 months	Carvedilol reduced a risk of further weight loss and also attenuate the development of cardiac cachexia or even cause a reversal of cachexia.

cachexia is ongoing because of its potential to reduce the secretion of TNF- α and to relieve the symptoms of wasting.^{7,12} Studies of megestrol and testosterone in therapy to improve appetite are ongoing.⁷ However, according to many authors, targeting ghrelin for the treatment of anorexia and cachexia shows the greatest promise. Ghrelin is an adipokine that induces hunger by stimulation of the hypothalamic feeding center. Normally, it is synthesized in the stomach while fasting. It decreases secretion of TNF- α , IL-1, and IL-6, and it increases the secretion of IL-10. Moreover, ghrelin has been shown to improve the function of the left ventricle and tolerance of exertion and promote mass muscle gain.^{7,37} Also, it should be emphasized that the method for bioimpedance analysis can provide valuable measurements of body composition in the context of cachexia, sarcopenia, and frailty.⁷⁵

It was also shown that such predictors as brain natriuretic peptide (BNP), estimated plasma volume status (ePVS), bioimpedance vector analysis (BIVA), and blood urea nitrogen/creatinine ratio (BUN/Cr) could provide independent and complex prognostic information in patients with HF and, importantly, in combination with them, explain the 40% risk of death in these patients regardless of the acute or chronic HF.⁷⁶

There is a need for large, well-controlled studies to determine the most appropriate approach in cardiac cachexia. There is still limited evidence that anabolic therapies, combined with a caloric-protein supplement, have better outcomes.¹³

Summary

Despite new treatment options in HF, the survival of chronic HF patients is still lacking. Moreover, many affected patients, especially those with more advanced chronic HF, also suffer from metabolic disorders. A combination of chronic HF and metabolic disorders increase the risk of muscle wasting, sarcopenia, and eventually cachexia. A patient's nutritional status and cardiac cachexia require more attention from medical professionals as these conditions are associated with worse prognosis of chronic HF patients. Impaired absorption of nutrients due to HF may lead to malnutrition, anemia, and microelement deficiency. More effort is needed to improve our understanding of the role of metabolic disorders in muscle wasting and cachexia in HF patients. The search for specific therapies and methods of identification of patients at risk of cachexia is

ongoing. At present, individualized therapy and a multidisciplinary approach are required to optimize the treatment of patients with HF and cachexia in everyday practice.

Abbreviations

BIVA, bioimpedance vector analysis; BNP, brain natriuretic peptide; BUN/Cr, blood urea nitrogen/creatinine ratio; CHF, chronic heart failure; CoQ10, co-enzyme Q10; CRH, corticoid releasing hormone; DXA, dual-energy X-ray; ePVS, estimated plasma volume status; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hGH, human growth hormone; IGF-1, insulin-like growth factor; IL-1, interleukin 1; IL-6, interleukin 6; IL-10, interleukin 10; LVEF, left ventricular ejection fraction; NADPH, nicotinamide adenine dinucleotide phosphate; NPY, neuropeptide Y; NYHA, New York Heart Association; RAAs, renin-angiotensin-aldosterone system; TNF- α , tumor necrosis factor- α .

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