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Review

Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure

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Abstract

Chronic heart failure is a complex catabolic state that carries a devastating prognosis. The transition from stable disease to cardiac cachexia is not well understood. Mechanisms that maintain the wasting process involve neurohormones and pro-inflammatory cytokines, which contribute to an imbalance in anabolic and catabolic pathways. A decrease in food intake alone rarely triggers the development of a wasting process, but dietary deficiencies in micronutrients and macronutrients contribute to the progression of the disease. Malabsorption from the gut as a result of bowel wall edema and decreased bowel perfusion also plays an important role. This article describes the complex interplay of hormonal systems in energy balance in patients with chronic heart failure as well as other factors such as malabsorption and dietary deficiencies that contribute to the wasting process. Finally, therapeutic approaches are discussed. These include dietary advice, ongoing studies, and future possibilities.

Keywords: Cachexia; Heart failure; Nutrition; Catabolism

1. Introduction

Chronic heart failure (CHF) is a major public health problem in western countries. CHF carries a devastating prognosis which resembles that of some types of malignant cancer [1]. Its incidence rises steadily from 0.02 per 1000 population per year in those aged 25 to 34 years to 11.6 in those aged 85 years or older [2]. Despite substantial improvements in the management of the disease, the prognosis remains poor especially in advanced stages of the disease. About half the patients diagnosed with CHF die within 4 years of diagnosis [3]. The prognosis worsens considerably once cardiac cachexia has been diagnosed. Importantly, the occurrence of cachexia establishes a poor prognosis in patients with CHF, independently of whether the heart failure is regarded as mild or advanced. Mortality at 18 months in unselected patients with CHF in whom cardiac cachexia had been diagnosed was as high as 50% compared to 17% in non-cachectic patients from the same study population [4]. However, cachexia is not a unique feature of CHF, but is also seen in terminal stages of other chronic illnesses, including cancer, sepsis, rheumatoid arthritis, and AIDS. Consequently, the pathophysiology of cachexia in CHF is to some degree similar to that of cachexia in other illnesses.

The transition from clinically and body weight stable, ambulatory CHF to cardiac cachexia is not well understood, and the timelines differ widely between patients. Up to 68% of patients with CHF have evidence of muscle atrophy [5]. Osteoporosis has also been observed in advanced stages of CHF [6]. Profound metabolic perturbations, initially meant to isolate and neutralize the insult, contribute to the development and the progression of cardiac cachexia. Cellular hypoxia, possibly a consequence of the activation of neurohormones and cytokines, as well as nutritional factors certainly plays an important part.

The aim of this review is to provide an overview of nutritional aspects that contribute to the wasting progress and

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to summarize available data on micronutrient and macronutrient supplementation in CHF and cardiac cachexia. Furthermore, we describe the complex interplay between metabolic and neurohormonal systems involved in appetite and substrate utilization and finally give dietary and therapeutic recommendations for patients with CHF with and without cardiac cachexia.

1.1. Aging and energy expenditure

In human beings, significant changes in body composition occur during the aging process. It has been estimated that elderly persons lose between 0.1 and 0.3 kg of lean body mass per year [7,8]. Simultaneously, lipid stores increase contributing to a net increase in body weight [9]. This is the 'normal' pathophysiology of aging. Total energy expenditure declines with aging: at age 75 a much lower daily energy intake is needed to maintain weight compared to the age 20, even if the level of physical activity remains the same [10]. The resting energy expenditure accounts for approximately 60–75% of the total energy expenditure. Resting energy expenditure is increased in some, but not all patients with CHF [11–13]. This might be due to an increased cardiac and ventilatory work, and an increased resting peripheral oxygen consumption [14]. Thus, CHF shows a number of catabolic features that can ultimately lead to cardiac cachexia. A major obstacle for the development of effective therapies is the fact that many different – and redundant – pathways are involved in the development of this syndrome.

2. Definition of cardiac cachexia

It is important to differentiate cachexia from malnutrition and anorexia. In contrast to cachexia, both are reversible once food is supplied. With these perturbations, weight loss is the result of fat mass being consumed for energy yield while muscle mass is mostly spared. There is currently no agreement on how to define cachexia. Cachectic CHF patients not only lose muscle mass, but they also have reductions in total fat mass and bone mineral density [15]. A multitude of definitions have been used in different studies, which make it difficult to reconcile study results from different groups of workers. In cardiac cachexia, the presence of edema further complicates the assessment of weight loss, which highlights the importance to assess changes in body weight in the non-edematous state. Established measures of disease severity in CHF, for example, left ventricular ejection fraction, New York Heart Association (NYHA) disease severity class, or exercise duration are not strongly associated with the severity of cachexia [16]. In two independent studies we showed that the presence of cachexia in CHF is not associated with structural cardiac changes as assessed by echocardiography [17] or magnetic resonance imaging [18].

The defining clinical characteristic of cachexia is the *process* of losing weight. This has two consequences, first that weight loss of a defined degree and possibly over a defined time-course should be part of any cachexia definition, and second, that any treatment for cachexia should be able to stabilise or even increase body weight to be considered as "anti-cachexia therapy". Using data from the Studies of Left Ventricular Dysfunction (SOLVD) database, Anker et al. suggested a definition for cardiac cachexia as documented non-edematous weight loss of >6% of the previous normal weight observed over a period of >6 months [19]. This definition was validated based on the assumption that a "best" definition should provide the highest sensitivity–specificity-product to predict subsequent mortality. In this context, the average weight prior to the onset of heart disease should be used as the previous normal weight.

3. Neurohormonal and immune activation

CHF is a complex catabolic state. A number of different mechanisms maintain the wasting process, most of which were found to be activated early in the development of CHF. Many of these pathways are initially activated to protect the heart and the circulation from damage and to compensate for impaired myocardial function. Mediators that have been implicated in this process include pro-inflammatory cytokines, catecholamines, cortisol, natriuretic peptides, and heat shock proteins [15,20].

Activation of the renin–angiotensin–aldosterone–system tends to follow the activation of pro-inflammatory cytokines in the course of CHF [21]. Whilst the first system is directed at maintaining renal and organ perfusion, the activation of the immune system is only incompletely understood. Elevated plasma levels of tumor necrosis factor-α (TNF-α) were first observed in cardiac cachexia in 1990 by Levine and colleagues [22]. Other pro-inflammatory cytokines including interleukin (IL)-1 and IL-6 are also activated. The activation of TNF-α is one of the candidates that has been suggested as a final common pathway in all forms of cachexia. TNF-α induces apoptosis via specific receptors on the cell surface and activates proteasome-dependent protein breakdown in striate muscle and other tissues thus maintaining the wasting process [23]. In CHF, plasma levels of soluble TNF-α receptors are associated with a poor long- and short-term prognosis [24,25]. TNF-α is partially responsible for decreased blood supply to skeletal muscles as it worsens endothelial dysfunction [26]. This, in turn, yields reduced exercise endurance and lack of nutrient supply. However, direct antagonism of TNF-α in patients with CHF has largely failed in clinical trials [27]. But for many reasons this may not mean that anti-cytokine therapy may not be of benefit in CHF, if restricted to patients with evidence of inflammation [28].

The pro-inflammatory cytokine IL-6 most potently induces the acute phase response [29], whose maintenance requires an excess of essential amino acids. The need for amino acids yields loss of body proteins [30]. Because skeletal muscle accounts for almost half of the body's protein mass, this compartment is intensively affected. Moreover, both TNF-α and IL-6 are known to down-regulate albumin synthesis in the liver [31]. Both TNF-α and IL-1 are involved

in the inhibition of food intake [32]. The mechanisms behind this action await to be elucidated in more detail, however, it appears that circulating TNF-α and IL-1 act, at least in part, directly on the brain [32]. Interestingly, the permeability of the blood–brain barrier is increased by these cytokines which thus promote their own uptake [33]. Peripheral intravenous injection of IL-1 activates a number of regions in the central nervous system that control eating behaviour [34]. Moreover, TNF-α increases the expression of the catabolic hormone leptin [35,36], whereas IL-1 has been shown to reduce hypothalamic mRNA levels of the food intake stimulating neurotransmitter neuropeptide Y (see below) [37].

4. Nutrition and neurohormones

A multitude of nutritional factors contribute to the pathogenesis of cardiac cachexia. These include alterations in food intake and appetite, an imbalance between anabolic and catabolic factors, as well as malabsorption in the gut. Lack of appetite alone can lead to malnourishment in up to 50% of patients with chronic illnesses, and this can certainly progress to anorexia-mediated cachexia. An adequate nutritional status is critical in providing patients with the means to recover from their illness and to withstand the detrimental metabolic effects of aggressive therapies [38].

4.1. Imbalance between anabolic and catabolic pathways

Numerous hormone systems contribute to the wasting process by altering appetite and energy expenditure as shown in Fig. 1. The derangement of these hormone systems, potentially triggered by the effects of pro-inflammatory cytokines [39], may be responsible for the development of satiety without adequate food intake.

4.1.1. Growth hormone

Growth hormone (GH) is a 191 amino acid peptide hormone released from the pituitary gland. This hormone exerts pleitropic actions on both growth and maturation of the body during the life span as well as on short-term regulation of energetic flux. Its anabolic effect and increased stimulation upon all types of stress and energy expenditure may be viewed as a regulative effort to restore and built up energy stores. GH exerts direct lipolytic effects, but its major mode of action is indirect and anabolic through the activation of the somatomedins and particularly through insulin-like growth factor-1 (IGF-1) [9]. IGF-1 is produced mainly by the liver but also by peripheral tissues [40]. GH levels have been found to be increased threefold in cachectic patients with CHF compared to non-cachectic and healthy subjects [16]. IGF-1, was found to be reduced in CHF and particularly so in cachectic CHF patients [41]. This biochemical condition indicates presence of acquired GH resistance, that has been observed in numerous catabolic diseases such as sepsis, trauma, surgery, cancer but also in chronic obstructive pulmonary disease, uremia, chronic liver disease and CHF [42]. GH resistance may explain why GH treatment failed to improve clinical status of patients with CHF due to dilated cardiomyopathy in randomized trials [43–45]. However, individual responses to GH had not been tested before enrolment in these trials. Thus, GH treatment might be unsuitable for unselected patients because individual GH responsiveness may vary considerably.

Theoretical possibilities to overcome GH resistance have been suggested. These include altered dosing regimens, the combination of GH with IGF-1 or the testing for individual GH responsiveness. Applying the latter option would mean to use GH therapy as a tailored option only in those individuals eligible. Whether there is a future for GH therapy

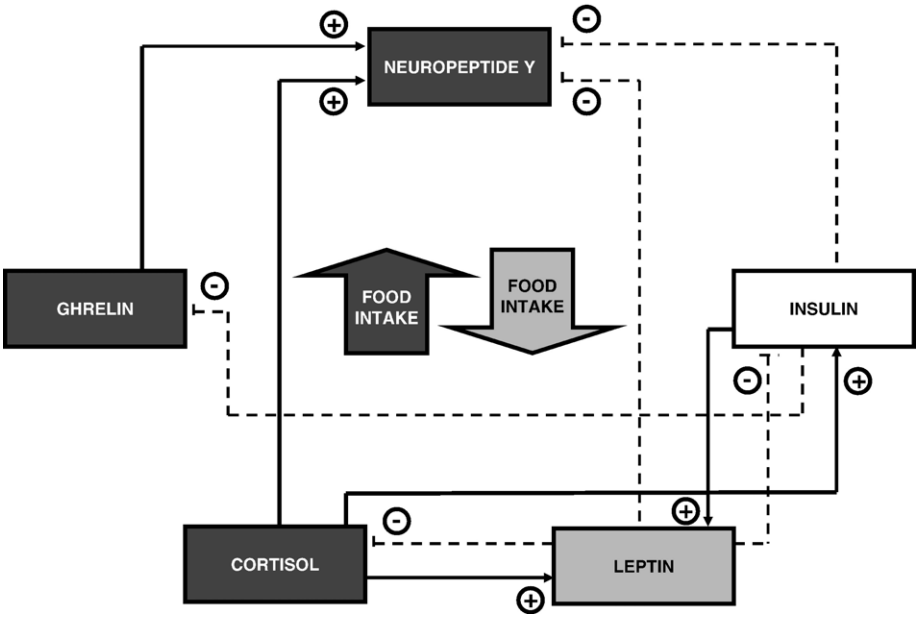

Fig. 1. Interplay between different players in energy balance in man. A full line denotes enhancement, a dashed line denotes inhibition.

in CHF is unclear and further studies have been discouraged by the data described above.

4.1.2. Neuropeptide Y

Neuropeptide Y is a 36-amino acid peptide with a molecular weight of 10.8 kDa that was initially discovered in 1982 [46]. It functions as a neurotransmitter and neuromodulator in the central and peripheral nervous system [47]. Its main site of accumulation is the hypothalamus. Neuropeptide Y is a potent stimulator of food intake. Therefore, its secretion in the hypothalamus is induced during fasting. Moreover, neuropeptide Y potently induces corticotropin-releasing factor, which results in the release of ACTH and cortisol (Fig. 1).

Only small amounts of neuropeptide Y cross the blood–brain barrier. The peptide is co-released with norepinephrine from sympathetic nerves and causes vasoconstriction. A study in 30 patients with CHF found elevated plasma levels of neuropeptide Y compared to 16 healthy controls ($p<0.01$) [48]. Patients with an LVEF<20% had similar plasma values like those with an LVEF of 20–35% [48]. Intravenous infusion of neuropeptide Y in seven healthy volunteers had no effect on central hemodynamic parameters [49].

4.1.3. Leptin

Leptin is a 16 kDa protein hormone with a direct inhibitory effect on neuropeptide Y. Thus, it exerts central effects on food intake and body energy balance. Its existence had originally been suggested from mutant mouse models (*ob*/*ob* mouse) and parabiosis experiments in the 1950's, but it was only in 1994 that the ob gene product had been identified [50], which had subsequently been termed leptin (from Greek "leptos", thin). Leptin is exclusively secreted from adipocytes [51]. In fact, it was the first adipocyte-derived hormone to be discovered, and its existence proved that fat tissue is actively involved in metabolic signalling rather that being a mere energy depot. Later studies identified other substances derived from adipocytes such as adiponectin. Leptin crosses the blood–brain barrier, and it was initially believed to be an inhibiting feedback link between adipose tissue and the central regulation of satiety and body composition (Fig. 1). Recent studies, however, demonstrated that leptin receptors are also expressed in several peripheral tissues such as pancreatic islets, liver, kidney, lung, skeletal muscle, and bone marrow suggesting a role in the periphery as well [52–54]. Importantly, leptin affects the balance of several metabolic and hormonal pathways, such as insulin sensitivity [55], GH signalling [56], and lipogenesis in adipose tissue. Leptin and adiponectin appear to work together in sensitizing peripheral tissues to insulin [57]. Leptin itself is under multihormonal control (via insulin, glucocorticoids, catecholamines), and its serum levels in women are higher than in men [58].

Being secreted from fat tissue, circulating leptin levels depend on the amount of fat tissue. Its main purpose is to control and maintain the balance of energy stores (*i.e.* fat depots). Accordingly, increased leptin release leads to a reduction in food intake and increases in energy expenditure through increased thermogenesis and physical activity. Food deprivation yields a rapid fall in leptin release. A 10% reduction in body weight leads to a 53% reduction in serum leptin levels in obese subjects [59]. Conversely, an increase in body weight by 10% results in a 300% increase in serum leptin levels [59].

In CHF, the amount of fat tissue similarly predicts leptin serum levels [13]. Disease related factors might, however, affect the balanced feed-back regulation as elevated leptin levels have been reported in CHF patients [55,60,61]. Lower levels of leptin in cachectic compared to non-cachectic patients might be expected in view of the reduced amount of fat tissue in cachectic patients. This has been confirmed in a number of studies [56,62,63]. Some controversy remains about leptin levels in CHF, because other studies reported normal leptin levels compared to controls [64]. This might be due to the selection of study subjects as these were different regarding sex distribution and the presence of cachexia between studies [65]. Leptin should therefore be normalized for fat tissue amount for comparison of study populations. Accordingly, the leptin levels in cachectic CHF patients were suggested to be viewed as "pseudo-normal" leptin levels. When fat tissue normalized leptin levels were analysed, both non-cachectic and cachectic CHF patients were found to be hyperleptinemic [55]. In any case, it appears that leptin levels in cachectic CHF are not higher than in non-cachectic patients, which argues against reduced appetite and food intake to be of particular importance for the development of cardiac cachexia.

4.1.4. Ghrelin

Ghrelin, originally identified in 1999 [66], is a 12.9 kDa peptide containing 28 amino acids. Ghrelin stimulates the secretion of growth hormone. It is predominantly produced by the stomach, although bowel, pancreas, kidney, hypothalamus and other tissues also contribute to its plasma concentration [67]. Ghrelin plays an important role in hunger and meal initiation. Ghrelin plasma levels rise with food deprivation causing increases in food intake and weight gain through increases in fat mass and decreases in fat use [68,69]. Healthy volunteers treated with ghrelin report hunger sensations [67]. On the other hand, ghrelin blocks leptin-mediated decreases in food intake. Not surprisingly, ghrelin levels are negatively correlated with body mass index (BMI) and body fat content [70], and ghrelin levels usually increase after weight loss.

Nagaya et al. studied plasma ghrelin levels in 28 cachectic (mean NYHA 3.3±0.1, LVEF 27±1%, BMI 17.9±0.4 kg/m^2) and 46 non-cachectic (NYHA 3.0±0.1, LVEF 29±1%, BMI 22.7±0.7 kg/m^2) patients with CHF [71]. Cachectic patients presented with significantly higher levels of plasma ghrelin than non-cachectic patients ($p<0.001$) [71]. Plasma ghrelin levels in this study correlated significantly with plasma levels of growth hormone ($r=0.28$, $p<0.05$) and TNF-α ($r=0.31$, $p<0.05$) [71]. Ten patients who developed cardiac cachexia during a mean follow-up of 12±1 months showed significant increases in plasma ghrelin levels ($p<0.05$) [71].

A small, uncontrolled study of intravenous infusion of ghrelin showed promising results [72]. In this study, 10 patients with CHF, predominantly cachectic patients in NYHA class III, were treated with ghrelin at a dose of 2 μg/kg over 30 min at a constant rate twice daily for three weeks. Ghrelin increased food intake and led to a non-significant increase in body weight (49.6±2.7 to 50.4±2.7 kg, $p=0.09$) [72]. Patients experienced a significant increase in lean body mass as assessed by dual X-ray absorptiometry (38.3±2.1 to 39.1±2.1 kg, $p<0.05$). Interestingly, ghrelin also led to an increase in LVEF (27±2 to 31±2%, $p<0.05$). Plasma levels of B-type natriuretic peptide decreased over the three week treatment period (238±59 to 190±60 pg/mL) [72]. Several studies are currently initiated to assess whether these results can be reproduced in double-blind placebo-controlled studies.

4.1.5. Insulin

Insulin has a pivotal role in the regulation of body composition for its two major functions: (i) regulation of energy flux and substrate utilization and (ii) anabolism. In CHF, diabetes mellitus is a common comorbidity with a prevalence of 20–25% (compared to 5% in the general population). Diabetes mellitus has been shown to be a predisposing factor for the development of CHF [73,74]. Insulin resistance – the underlying principle of type II diabetes – develops as a continuous process and occurs decades before the diagnosis of overt diabetes mellitus. Accordingly, sub-clinical impairment of glucose metabolism has been observed in a CHF population with a prevalence of 43% [75]. In patients with CHF, insulin resistance is a characteristic finding increasing in parallel to disease severity [76]. A direct impact of insulin resistance on impaired functional capacity of skeletal muscle has been shown [77,75]. Reduced glucose utilization is paralleled by an increase of free fatty acid consumption which implies reduced energetic sufficiency. Furthermore, recent evidence suggests prognostic significance of insulin resistance in CHF as it predicts impaired survival independently of established prognosticators [78]. The underlying mechanisms of insulin resistance in CHF and other chronic illnesses form a complex web of metabolic interrelations on the basis of age and genetic predisposition, including factors such as immune activation, neurohormonal activation, and hormonal imbalances (*e.g.* hyperleptinemia, GH resistance).

On the basis of the above it seems intriguing to test whether therapeutically targeting and restoring insulin sensitivity may exert additional beneficial effects on symptomatic status and potentially on prognosis in CHF and especially in cachectic patients. Thiazolidinediones are selective agonists of the peroxisome proliferator activated receptor-γ that modulate insulin-mediated glucose utilization by the skeletal muscle on a transcriptional level. The use of such insulin sensitizers in CHF has recently been debated, because they increase fluid retention and may contribute to increased edema. However, animal models suggest that the weight gain associated with the use of these substances may be blocked by amiloride [79].

4.2. Dietary deficiency and loss of nutrients

Patients with CHF are prone to reduced appetite and consequently reduced food intake [80]. The reasons are multifactorial but include changes in taste and smell, dietary advice on salt and calorie intake, social isolation, and derangements in bowel perfusion. However, only seldom is the decrease in food intake *per se* triggering the development of a wasting syndrome [9]. Deficiencies in both micronutrients and macronutrients, on the other hand, may contribute to the wasting process once triggered. Additionally, disease-associated metabolic perturbations hamper the optimal utilization of nutrients, which may have its reasons, for example, in hormonal derangements (see below). Large-scale studies on appetite and food intake in CHF are not available. In our clinical experience anorexia plays a significant role in cachexia pathophysiology only in a minority of patients with CHF, which contrasts findings in COPD or malignant cancer.

4.2.1. Micronutrients

A micronutrient is any essential dietary component present in a trace amount [81]. There is general agreement that a diet high in sodium is potentially harmful in CHF, as it may cause fluid overload and consequently acute decompensation. Deficiency in micronutrients, on the other hand, as a cause of heart failure is rare, but cases due to selenium and thiamine (vitamin B_1) deficiency have been reported [82]. Thiamine supplementation *per se* may improve cardiac function [83]. Levels of selenium have been reported to be low in CHF. In a study of 21 patients with CHF (NYHA class II–III, mean LVEF 29±6%), baseline selenium levels were approximately 20% lower than those in healthy control subjects ($p=0.0004$) [84]. Whereas plasma levels of copper were 19% higher in patients with CHF compared to controls ($p<0.05$), zinc levels were 9% lower ($p<0.05$) [84].

Patients with CHF are usually receiving loop diuretics which increase urinary excretion of micronutrients. Using multiple micronutrient supplementations, Witte et al. showed recently improvements in left ventricular ejection fraction (LVEF) and quality of life after 9 months of treatment [85]. In this placebo-controlled, randomized, double-blind study, a total of 30 patients with CHF received capsules containing thiamine (daily dose: 200 mg), vitamins C (500 mg) and E (400 mg), magnesium (150 mg), selenium (50 μg), zinc (15 mg), co-enzyme Q10 (150 mg), and various other substances. LVEF improved by 5.3±1.4% in the micronutrient group ($p<0.05$ *vs.* placebo). A possible explanation other than replacement of thiamine is the reduction of oxidative stress by the aforementioned substances, a significant contributor to morbidity in CHF and cardiac cachexia. Indeed, many micronutrients can scavenge free radicals [81]. This may ensue through direct action as with vitamins C and E although recent studies have questioned their "real life" efficacy in various conditions [86,87]. An indirect effect of micronutrients may ensue as components of anti-oxidant

enzymes like zinc in superoxide dismutase or selenium in glutathione peroxidase [88].

4.2.2. Macronutrients

Protein degradation by the proteasome plays an important role in the development and progression of cachexia. Therefore, amino acid supplementation has been studied in some but still only few models. Glutamine, for example, is a non-essential amino acid that is involved in cellular integrity and immune function. Low plasma levels of glutamine were found in critically ill patients and patients with chronic illness associated with muscle wasting [89,90]. In a randomized, placebo-controlled, double-blind study, the effect of treatment with a mixture of β-hydroxy-β-methylbutyrate (3 g/day), L-arginine (14 g/day), and L-glutamine (14 g/day) in 18 cachectic cancer patients was evaluated [91]. The placebo group received a mixture of non-essential amino acids. Patients in the active treatment group gained 0.95±0.66 kg compared to control subjects who lost 0.26±0.78 kg after four weeks. This change was due to a significant increase in fat-free mass in the active treatment group (+1.12±0.68 kg *vs* −1.34±0.78 kg, $p=0.02$) [91].

Branched-chain amino acids, namely leucine, isoleucine, and valine, have been suggested as a useful supplementation in the treatment of cachexia [38]. These amino acids appear to exert anabolic effects by promoting protein synthesis and by inhibiting proteolysis. This notion appears to be particularly true for leucine [92]. Stein et al. investigated the effect of amino acid supplementation during a 14-day period of bed-rest, which is known to involve protein loss from weight-bearing muscle [93]. During bed-rest, healthy volunteers received either a supplementation with the three branched-chain amino acids (30 mmol/day each) or a mixture of non-essential amino acids (glycine, serine, and alanine, 30 mmol/day each). Interestingly, the concentration of free amino acids in muscle biopsies was greater in the branched-chain amino acid treated group during bed-rest compared to the control group (0.21±0.07 *vs* 0.09±0.12 nmol/mg protein, $p<0.05$) [93]. Moreover, nitrogen retention, reflecting the body's protein pool, was greater in the branched-chain amino acid treated group (56±6 *vs* 26±12 mg nitrogen per kg per day, $p<0.05$) [93].

However, supplementation of *any* amino acid is certainly not beneficial. Homocysteine, for example, has been described to possess negative inotropic properties [94], and hyperhomocysteinemia is a well-established risk factor for cardiovascular diseases. In a substudy of the Framingham Heart Study, hyperhomocysteinemia was associated with a hazard ratio for the development of heart failure (adjusted for established risk factors) of 1.84 (95% CI 1.06–3.17) in men and 1.93 (95% CI 1.19–3.13) in women [95]. In association with relatively low levels of vitamins B_6, B_9 (folate), B_{12}, and magnesium, homocysteine levels were found to be increased in patients with established CHF compared to healthy controls (20.5±2.5 *vs.* 13.3±1.1 μmol/L, $p=0.01$) [88]. Indeed, circulating homocysteine levels are strongly influenced by vitamin status, because homocysteine degradation is dependent on the presence of vitamins B_6, B_9, and B_{12} [96]. This point is worth stressing, as Gorelik et al. have shown that the intake of vitamin B_9 did not reach the recommended daily amount (400 μg) in 57 hospitalized patients with CHF and 40 healthy controls (Table 1) [97].

Dietary supplementation with $n-3$ polyunsaturated fatty acids derived from fish oil has also been studied. In a canine model of heart failure, the effect of fish oil supplementation was studied [98]. 28 dogs, 15 of which were cachectic, were fed fish oil supplement or placebo for eight weeks. Active treatment decreased plasma levels of IL-1 ($p=0.02$) and

Table 1
Daily dietary intake data of patients with CHF and controls

	RDA or DRI	Patients with CHP ($n=57$)	Controls [a] ($n=40$)	p value	Dietary insufficiency, %	
					Patients	Controls
Energy, kcal	1890–1960 [b]	1602±530	1609±826	NS	67.6	70
Protein, g	50–63 [b]	74±22	72±31	NS	8.5	20
Vitamin A, μg retinol equivalents	800–1000	1210±1364	1528±1367	NS	47.3	40
Vitamin C, mg	60	137±126	124±80	NS	20.3	22.5
Thiamin, mg	1.1–1.2	1.0±0.5	0.8±0.3	NS	64.2	62.5
Riboflavin, mg	1.1–1.3	1.0±0.4	0.9±0.4	NS	77.7	80
Niacin, mg niacin equivalents	14–16	24±8	23±12	NS	8.5	15
Folic acid, μg	400	168±120	175±98	NS	65.9	55
Magnesium, mg	320–420	229±97	261±172	NS	81.1	72.5
Sodium, mg		1172±621	1030±635	NS		
Potassium, mg	1560–4690	2353±1078	2170±928	NS	18.6	30
Calcium, mg	1200	617±280	589±267	NS	81.1	72.5
Zinc, mg	12–15	5.7±2.8	5.6±3.6	NS	94.6	95
Copper, mg	1.5–3	0.9±0.5	0.9±0.5	NS	87.9	80
Manganese, mg	2–5	1.4±0.8	1.5±0.6	NS	82.8	77.5

Reproduced with permission from S. Karger AG [97].
[a] Values are means±SD.
[b] For 70 kg body weight.

improved cachexia ($p=0.01$) compared to the placebo group. Plasma concentrations of IGF-1 ($p=0.01$) and IL-1 ($p=0.02$) correlated with survival [98].

Rozentryt et al. studied the effects of enteral support in a small, randomized, placebo-controlled study [99]. A total of 29 patients with cardiac cachexia were randomized in a 3:1 fashion to an enteral support of 600 kcal daily in addition to their normal diet or placebo for six weeks. After the nutritional supplementation had been discontinued, patients were followed-up for an additional 12 weeks. Interestingly, weight increased in the active treatment group only (before nutritional support: 63.4±10 kg, after nutritional support: 66.0±11 kg, $p=0.001$), as did the 6-minute walking distance (before: 366±108 m, after: 433±106 m, $p=0.02$), and the total fat mass (before: 15.5±3 kg, after 17.2±4 kg, $p=0.007$). Thus, hypercaloric diets warrant further studies in larger trials.

4.3. Malabsorption and bowel permeability

Bowel wall permeability and thus absorption of nutrients from the gut in patients with CHF are thought to be influenced mainly by two factors: bowel perfusion and bowel edema. Indeed, the small and large intestines are highly vascularized and receive under normal conditions up to 25% of the cardiac output [100]. Relatively small changes in blood flow can lead to ischemia of the tips of the villi, which is the result of blood being shunted from arterioles to venules at low flow rates [101]. Such phenomena are observed in situations with low cardiac output, which may occur, for example, after coronary artery bypass grafting [102]. Bowel edema can lead to fat malabsorption [103] and protein loss [104]. Especially protein loss may contribute to the development of cardiac cachexia. Moreover, bowel wall edema may yield translocation of bacteria or endotoxin, a cell wall component from Gram-negative bacteria, through the gut wall into the circulation. Indeed, patients with edematous decompensation of CHF were found to have elevated plasma levels of endotoxin as compared to patients with stable disease (0.74±0.45 *vs* 0.37±0.23 endotoxin units [EU]/mL, $p=0.0009$) and controls (0.46±0.21 EU/mL, $p=0.02$). The elevated levels decreased after diuretic therapy. The endotoxin challenge may be the responsible stimulus that triggers the release of pro-inflammatory cytokines [105].

4.4. Lipoprotein–endotoxin-hypothesis

It has recently been suggested that cholesterol may inhibit the activity of endotoxin [106]. This may explain why high cholesterol values predict better (not worse) survival in patients with CHF [107,108]. Indeed, it has been demonstrated in a study in 114 patients with CHF that higher total serum cholesterol was a predictor of improved survival (hazard ratio 0.64, 95% CI 0.48–0.86), independent of CHF etiology, age, LVEF, and exercise capacity [107]. This study showed that total cholesterol ≤5.2 mmol/L (200.8 mg/dL) was the best cut-off value as a predictor of mortality after 12 months (sensitivity 80%, specificity 62.9%) (Fig. 2). Data from *in vitro* studies are in support of this view [109]. Thus, micelle formation by cholesterol around endotoxin could be beneficial in CHF. Indeed, earlier studies using highly purified plasma lipoproteins demonstrated that these can inhibit endotoxin activity in a time- and dose-dependent fashion [110]. It is not known if cholesterol values correlate with pro-inflammatory parameters.

5. Therapeutic approaches to cardiac cachexia

5.1. Prevention of weight loss

The treatment of CHF varies according to disease severity. The standard regimen currently comprises angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, β-blockers, and diuretics (thiazide or loop diuretics). Patients with more advanced stages of the disease should also receive an aldosterone antagonist. Particularly ACE inhibitors and β-blockers have recently been shown to exert beneficial effects on weight development in patients with CHF [19]. A re-analysis of the SOLVD database has shown that enalapril can prevent or delay weight loss in patients with CHF. 817 (42%) of the 1929 patients in SOLVD experienced weight loss of 5% or more over a period of 8 months (Fig. 3). Enalapril, used at a dose of 20 mg once daily, reduced the risk of weight loss compared to placebo (adjusted hazard ratio 0.81, 95% CI 0.70–0.94, $p=0.0054$) [19].

Carvedilol is a β-blocker that showed a reduction in mortality by 35% in patients with CHF compared to placebo in the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) [111]. In a recent re-analysis of these data it was shown that carvedilol (target dose: 25 mg twice daily) reduced the risk of weight loss [112]. A total of 2262 patients were analysed. 14.1% in the placebo group and 10.2% in the carvedilol group developed cachexia during follow-up ($p=0.005$). Moreover, there was a

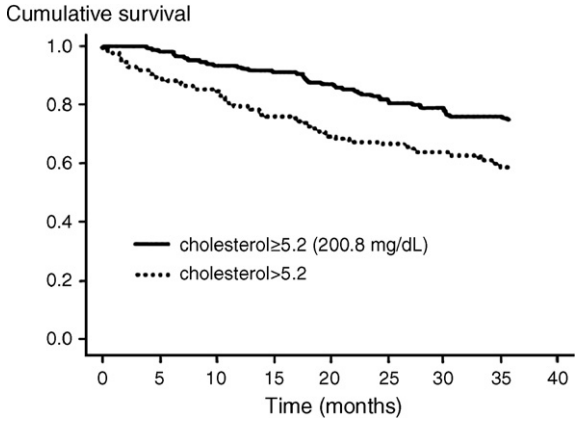

Fig. 2. Survival in 303 patients with CHF related to the best predictive value for serum cholesterol of 5.2 mmol/L. Log-rank $p=0.0011$ for the difference between groups. Reproduced with permission [107].

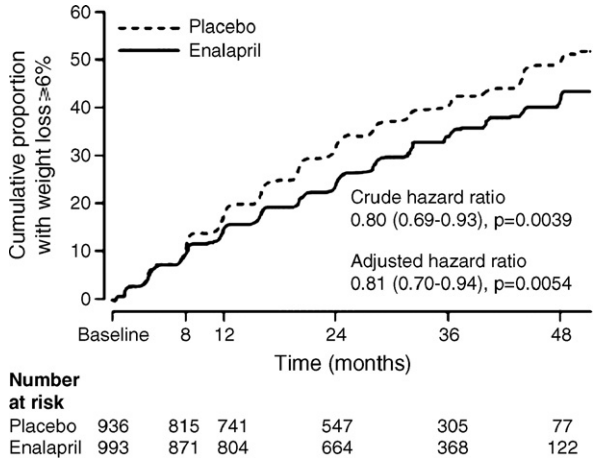

Fig. 3. Cumulative incidence of cachexia (weight loss ≥ 6%) in patients with chronic heart failure treated with enalapril or placebo in the SOLVD treatment study. Reproduced with permission [19].

decrease in mortality with increasing body mass index ($p<0.0001$), and in fact the risk of death decreased by 7.7% per unit increase in BMI. Importantly, only patients on carvedilol experienced a significant increase in body weight compared to placebo. At four months, the mean change in body weight in the carvedilol group was +0.5 kg *vs* −0.1 kg in the placebo group ($p=0.0002$). At 8 months, the corresponding numbers were +0.9 kg *vs* −0.1 kg ($p<0.0001$), and at 12 months +1.1 kg *vs* +0.2 kg ($p<0.0001$) [112].

Although the effect of carvedilol appears to be readily explained by the inhibition of catecholamine-induced lipolysis [113], it is not entirely clear whether these effects are class effects or apply only to specific substances. However, bisoprolol (target dose: 10 mg once daily) reduced the risk of weight loss in a subanalysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS) II database [114]. This subanalysis confirmed the aforementioned findings, as it showed a significant decrease of 3.5% in mortality with increase per unit of body mass index. Patients with CHF with a body mass index > 25 kg/m^2 had a 25% lower risk of death than patients with a body mass index ≤ 25 kg/m^2 (95% CI 8–39%). Patients on bisoprolol experienced an increase in weight compared to those on placebo after 12 months (+0.8 kg *vs* −0.04 kg, $p<0.0001$) and after 24 months (+1.2 kg *vs* + 0.03 kg, $p=0.0041$). It appears that β-blockers exert anti-cachexia effects by inhibiting lipolysis. A recent study found that approximately 70% of the weight increase that a β-blocker can induce is an increase in fat tissue mass [115].

5.2. Dietary supplementation

Patients with CHF, whether cachectic or not, should restrict their daily sodium intake to about 2 g [80]. Foods rich in salt such as cheese, sausages, crisps, tinned soup and vegetables, ham, bacon, tinned meat, and tinned or smoked fish should therefore be avoided [80]. Long periods of fasting are potentially harmful, and cachectic patients should be advised to eat small, frequent meals [9]. Fluid overload should be avoided, and in patients with severe symptoms or those requiring high doses of diuretics, fluid restriction (1.5–2.0 L per day) should be advised [80]. The evidence suggests that multiple micronutrient supplementation is potentially beneficial for cachectic patients [85], and it should contain anti-oxidant supplements and B-group vitamins. As stated above retrospective data indicate that low levels of total cholesterol, LDL and triglycerides are associated with poor outcome in CHF patients [116,117]. Nevertheless, statin therapy is associated with survival benefits in CHF, and hence statins may be beneficial in CHF patients not because but despite their cholesterol lowering effects [118].

As a general rule, food and lifestyle factors that trigger the acute phase response should be avoided. This comprises, for example, excess of carbohydrates or saturated fats, alcohol, and smoking [119]. Food that counteracts inflammatory processes can generally be recommended, for example fish oil supplements, olives, walnuts, flaxseed oil, any fruits or vegetables, garlic, ginger, turmeric, sunflower seeds, eggs, herring, or nuts [119]. Enteral nutrition should always be preferred over parenteral feeding. If parenteral nutrition becomes paramount, the general guidelines should be followed: 35 kcal per kg of body weight per day, 1.2 g of protein per kg per day, and a 70:30 glucose:lipid ratio for the non-protein energy [9].

5.3. Pharmacotherapy of cachexia

Some therapeutic approaches are currently pursued in order to reverse weight loss in patients with cachexia. Cardiac cachexia has not specifically been targeted and it appears important to note that none of the following treatments are currently approved for the treatment of cachexia in CHF or any other chronic illness (with the exception for use in AIDS cachexia). The therapeutic concepts comprise interventions with appetite stimulants, anabolic steroids, and growth hormone.

Appetite stimulants such as megestrol acetate and medroxyprogesterone acetate have been reported to stimulate appetite and weight gain. The optimal dose of megestrol appears to be 800 mg daily with doses ranging from 160 to 1600 mg daily. In a double-blind, randomized, placebo-controlled study in 107 patients with cancer, patients were assigned to one of three treatment groups: (i) megestrol acetate 160 mg daily ($n=37$), (ii) megestrol acetate 480 mg daily ($n=35$), or (iii) placebo ($n=35$) [120]. Weight gain was reported in 38% on the lower and 68% on the higher dose of megestrol acetate compared to 37% in the placebo group ($p<0.03$). Whilst the higher dose of megestrol acetate yielded a mean weight gain of 5.41 kg after 12 weeks of treatment, there was no change in the mean values of body weight in the lower megestrol acetate or the placebo group [120]. In another randomized, double-blind study, a total of 475 patients with cancer were assigned to one of three treatment arms as well: (i) dexamethasone 0.75 mg four times daily ($n=159$), (ii) megestrol acetate 800 mg once daily

($n=158$), or (iii) fluoxymesterone 10 mg twice daily ($n=158$). Fluoxymesterone enhanced appetite significantly less than the other two substances. Dexamethasone and megestrol acetate caused a similar degree of appetite enhancement, however, dexamethasone had a higher rate of drug discontinuation compared to megestrol acetate (36% *vs* 25%, $p=0.03$). Treatment with megestrol acetate, on the other hand, yielded a higher rate of deep vein thrombosis than dexamethasone (5% *vs* 1%, $p=0.06$). There is so far no data on the use of megestrol acetate or systemic steroid hormones in cardiac cachexia.

Anabolic steroids are another possible therapeutic approach to treat cardiac cachexia. Few clinical studies have been performed in patients with cachexia, none of them in patients with cardiac cachexia. In 12 patients with CHF due to idiopathic dilated cardiomyopathy, the administration of the anabolic steroid oxymetholone 5–10 mg daily for three months, led to significant decreases in left ventricular end-diastolic (from 68±2 to 63±2 mm, $p<0.001$) and end-diastolic (from 53±3 to 46±3 mm, $p<0.001$) diameters [121]. Left ventricular mass decreased from 381±37 g to 342±34 g ($p<0.001$). Interestingly, the reduction stopped six months after drug discontinuation. LVEF increased from 42±6% to 51±5% ($p<0.005$), and plasma B-type natriuretic peptide levels decreased from 96±9 to 46±7 pg/mL ($p<0.001$) [121]. Body weight did not change during the study period [121]. Pugh et al. investigated the acute hemodynamic effects of testosterone in 12 men with stable CHF [122]. In this double-blind, randomized, placebo-controlled cross-over trial, testosterone yielded a relative increase in cardiac output 180 min after application of testosterone (+10.6±4.6%, $p=0.035$ compared to baseline). Systemic vascular resistance was reduced with maximal effect at the same time point (−17.4±9.6%, $p=0.085$ compared to baseline) [122]. Thus, testosterone application may increase cardiac output via reduction of left ventricular afterload, but it remains unclear whether this is due to its anabolic efficacy.

A limited number of studies have addressed the use of growth hormone in patients with CHF. Fazio et al. were among the first to study this concept [123]. When they treated 7 patients with idiopathic dilated cardiomyopathy with recombinant human growth hormone 14 IU per week (4 IU every other day) for three months, they found a significant increase in cardiac output, particularly during exercise (from 7.4±0.7 to 9.7±0.9 L/min, $p=0.003$). Left ventricular end-diastolic and end-systolic dimensions decreased from 65±1 to 61±1 mm ($p<0.001$) and from 52±1 to 46±1 mm ($p<0.001$). LVEF increased from 34±1.5 to 47±1.9% ($p<0.001$) immediately after therapy. Like the left ventricular dimensions, LVEF decreased slightly three months after study termination (40±2.4%, $p=0.02$ compared to baseline). These promising effects, however, could only partially be reproduced in a larger cohort of patients with idiopathic cardiomyopathy [44]. In this study by Osterziel et al., LVEF was essentially unchanged three months after treatment initiation with 2 IU per day of recombinant human growth hormone administered subcutaneously in double-blind, randomized, placebo-controlled study in 50 patients. Left ventricular mass increased in the active treatment arm by 25.0±29.2 g (from 236 to 260 g, $p<0.001$). NYHA class and 6-minute walking distance did not change during the study period [44].

6. Conclusion

The pathophysiology of cardiac cachexia is exceedingly complex, and only slowly do we begin to understand the many different – and redundant – pathways involved in its pathogenesis. Of particular importance is to establish a commonly accepted definition of the syndrome [124]. Targets for future interventions include the deranged hormonal systems involved in energy balance as well as malabsorption from the gut and dietary supplementation with micronutrients and macronutrients potentially joined in some form of hypercaloric diet. Other targets involve the inhibition of proteasome-dependent protein degradation and the direct inhibition of pro-inflammatory pathways. The beneficial effects of ACE inhibitors and β-blockers in preventing or delaying the onset of a wasting syndrome merit further attention. Prospective randomized clinical trials are required in that respect. These will help to improve the patients' quality of life and possibly their survival.

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