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MEETING REPORT

Cachexia in heart disease: highlights from the ESC 2010

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Abstract Cardiac cachexia is a co-morbidity that may develop in terminal stages of chronic heart failure (CHF). Up to 15% of ambulatory patients with heart failure are affected. Over the last decades, cardiac cachexia and alterations in muscle metabolism in heart disease have received increasing research interest. This article highlights some recent studies of cardiac cachexia that were presented at the annual meeting of the European Society of Cardiology in September 2010 in Stockholm, Sweden. Studies presented here were focused on effects of exercise training and protein degradation, particularly into the role of the ubiquitin–proteasome complex and its ubiquitin ligases MuRF-1 and MAFbx. Exercise training in patients with CHF was found to increase maximal oxygen consumption and to reduce MuRF-1 expression. Lysosomal muscle degradation does not seem to play a major role in patients with CHF, however, inflammatory cytokines such as tumor necrosis factor-a trigger muscle protein degradation. Other studies found that the serum levels of the adipokine adiponectin are elevated in patients with CHF and that these levels may be correlated with muscle mass, muscle strength in the arms, or with trunk fat mass. Another study showed that the expression of myostatin in skeletal muscle, a negative regulator of muscle growth that is essential for normal regulation of muscle mass, is decreased in spontaneously hypertensive rats with heart failure compared with control animals. This is also true for follistatin, a powerful antagonist, and its potential as a biomarker of muscle wasting. These findings may pave the way for effective treatment approaches to cardiac cachexia.

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1 Introduction

This year's meeting of the European Society of Cardiology (ESC) was held in the beautiful city of Stockholm, Sweden. With a total of 27,547 registered participants, it is the largest medical event in the world related to disease of the heart and the vasculature. Attendance was not as high as that in Barcelona in 2009, but still 12% above the level recorded in 2005 when the congress was last held in Stockholm. With 936 accepted abstracts, German scientists were the front-runners in scientific presentations (9.8%), closely followed by Italy (913 abstracts, 9.6%) and Japan (8.2%). Professor Roberto Ferrari, current president of the ESC, said that particularly Japanese participation made the ESC meeting a congress of the world.

Although heart failure is receiving increasing research interest, cardiac cachexia as its terminal stage remains a neglected clinical entity, even though between 5% and 15% of patients with heart failure are affected [1, 2]. Therapeutic approaches are limited to exercise training [3], nutritional

support [4–6], and drugs, although particularly the latter remain restricted to clinical studies [7–9]. Some interesting new studies regarding pathophysiology, treatment, and prediction of prognosis in cachexia and muscle metabolism among patients with cardiovascular diseases were presented at the ESC conference and are summarized here.

2 Exercise and different degradation pathways

Stephan Gielen (Heart Center, University of Leipzig, Germany) presented data about differential responses of MuRF-1 and MAFbx expression in skeletal muscle to training interventions in heart failure patients. Both proteins are E-3 ubiquitin ligases that covalently bind ubiquitin to the target protein; hence, their activity is limiting the rate of protein degradation by the proteolytic ubiquitin–proteasome system (Fig. 1). The expression of MuRF-1 and MAFbx is regulated by transcription factors like FOXO and NF–κB, which makes them inducible by cytokines like tumor necrosis factor-α (TNFα) or interleukin (IL) 1. Gielen explained that muscle wasting in chronic heart failure (CHF) is an independent predictor of mortality, and it has already been shown that the activation of the proteolytic ubiquitin–proteasome system is associated with increased expression of the muscle-specific ubiqitin ligase MuRF-1 [10]. Substrates of Murf-1 include myosin in muscle and troponin I in heart and are essential for ubiquitination and subsequent degradation of myofibrillar proteins in the course of cachexia [11]. But, it is still unclear if the second muscle-specific E3-ligase MAFbx is also involved in the muscle wasting process and how MuRF-1 and MAFbx respond to endurance training in patients with CHF of different age groups. Sixty patients with CHF and 60 healthy controls were randomized to 4 weeks of bicycle ergometer training at 70% of their respective heart rate reserve 4×20 min/day or to a control group. Before and after the intervention, spiroergometry, echocardiography, and a vastus lateralis muscle biopsy were performed. Expression of the E3 ligases MuRF-1 and MAFbx as part of the ubiquitin–proteasome system was quantified by real-time polymerase chain reaction (PCR) standardized for 18S-rRNA and Western blot. In younger CHF patients (n=15, age 45±3 years, body mass index [BMI] 26.8±2.7, left ventricular ejection fraction [LVEF] 26.8±2.6%), training improved maximum oxygen consumption (peak VO_2) by 36% from 13.3±1.6 to 18.1±1.5 mL/min*kg (p=0.008 vs. control). In elderly CHF patients (n=15, age 68±4 years, BMI 25.3±2.9, LVEF 27.4±3.0%), increased peak VO_2 by 33% from 12.9±1.4 to 17.1±1.1 mL/min*kg (p=0.01 versus control). At baseline, MuRF-1 mRNA expression in CHF patients was significantly elevated versus healthy subjects at 624±59 versus 401±25 relative units (p=0.007) and protein expression at 0.82±0.09 versus 0.57±0.04 relative units (p=0.01). MAFbx expression as measured by mRNA and Western blot was similar in CHF patients and healthy subjects and did not change with age. Training induced a reduction of MuRF-1 expression by 34.3% (p=0.02) in younger CHF patients and a reduction of 24.3% (p<0.05) in elderly. MAFbx did not show any significant

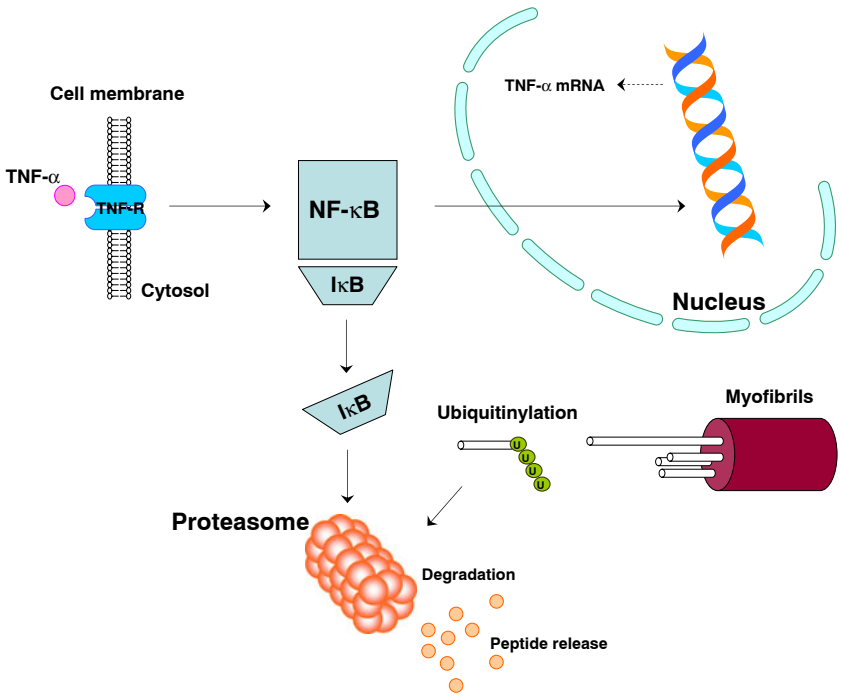

Fig. 1 Protein degradation by the ubiquitin–proteasome system: TNFα stimulation leads to protein degradation by the ubiquitin–proteasome complex and activation of NF–κB. Phosphorylation of IκB activates NF–κB. IκB and the proteins to be degraded are marked by a poly-ubiquitin chain. After ubiquitination, marked proteins and IκB are degraded by the proteasome complex. NF–κB can then signal into the nucleus, and transcription of the affiliated gene is induced

changes after training intervention (young CHF, 1.1±0.3 versus 0.8±0.2 relative units; elderly CHF, 0.8±0.1 versus 0.7±0.1 relative units). Gielen concluded that exercise training improves peak VO_2 significantly in both younger and older patients with CHF and that these results underline the importance of exercise-based rehabilitation programs to prevent CHF-related muscle wasting. On a molecular level, this study confirms that muscle wasting is mediated by selective activation of MuRF-1. On the other hand, MAFbx levels seem to remain unchanged by both the disease process and the training intervention.

In another session, Dr. Gielen also presented results of two different protein degradation pathways. These pathways were analyzed in skeletal muscle biopsies of patients with CHF. Expression of MuRF-1 as part of the ubiquitin–proteasome system was compared with cathepsin L as a marker of lysosomal proteolysis. Again, 60 CHF patients and 60 healthy controls were randomized to 4 weeks of bicycle ergometer training at 70% of heart rate reserve 4×20 min/day or to a control group. Before and after the intervention, spiroergometry, echocardiography, measurement of quadriceps force endurance, and vastus lateralis muscle biopsy were performed. Expression of Murf-1 was quantified by real-time PCR standardized for 18S-rRNA and Western blot. Cathepsin L was measured by real-time PCR. In younger CHF patients (n=15, age 45±3 years, BMI 26.8±2.7, LVEF 26.8±2.6%), training improved peak VO_2 by 23% from 14.7±3.1 to 18.1±3.0 mL/min*kg (p=0.008 vs. controls) and force endurance by 47% from 22.8±2.5 to 33.6±2.9 s (p=0.002 vs. control). In elderly CHF patients (n=15, age 68±4 years, BMI 25.3±2.9, LVEF 27.4±3.0%), training increased peak VO_2 by 17% from 15.2±2.6 to 17.8±2.4 mL/min*kg (p=0.01 vs. control, p=0.06 vs. younger trained CHF patients). Force endurance improved by 44.2% from 23.5±4.2 to 33.9±4.1 s (p=0.01 vs. control, p=NS vs. younger trained CHF patients). Murf-1 mRNA expression at baseline in CHF patients was significantly elevated vs. healthy controls at 593±68 vs. 410±27 relative units (p=0.013) and protein expression at 0.90±0.08 vs. 0.62±0.05 relative units (p=0.018). Cathepsin L was not different between both groups. Training induced a reduction in Murf-1 expression by 34.3% (p=0.02) in younger CHF patients and a reduction of 24.3% in elderly (p<0.05, p=0.15 vs. younger CHF patients). Otherwise, cathepsin L expression remained unchanged. Gielen summarized that muscle wasting in CHF is mediated via the ubiquitin–proteasome system and that the lysosomal system does not seem to play a major role in skeletal muscle. Furthermore, Gielen concluded that exercise training significantly improves maximum exercise capacity and forced muscular endurance, however, the relative gain in exercise capacity was slightly attenuated in elderly patients. We should think of more prolonged or higher intensive training programs for elderly CHF patients to achieve the same clinical benefit as compared with younger patients.

3 Adiponectin

Adiponectin is an anti-inflammatory, insulin-sensitizing, and anti-atherogenic adipocytokine, which plays a fundamental role in energy homeostasis [12]. Adiponectin comprises 244 amino acids, and it is synthesized and secreted in large quantities from adipose tissue [13]. The protein regulates lipid and glucose metabolism at the level of the skeletal muscle [14]. Low adiponectin levels have been associated with increased risk for coronary artery disease [15]. However, this risk does not seem to apply for the development of CHF [16].

M. van Berendoncks (Department of Medicine, University of Antwerp, Antwerp, Belgium) presented the results of a study that investigated whether adiponectin levels in CHF were associated with muscle mass and function. Ten male patients with CHF (LVEF 27±4%, mean±standard error of mean) were compared with seven healthy male controls of similar age and BMI. All subjects underwent a thorough clinical investigation including collection of anthropometric data, cardio-pulmonary exercise testing, measurement of upper and lower limb strength, and an assessment of their quadriceps muscle cross-sectional area (CSA) by computerized tomography scanning. Finally, circulating adiponectin levels were analyzed using enzyme-linked immunosorbent assay. It could be shown that, compared with the control group, patients with CHF had impaired exercise capacity (peak VO_2, peak maximal workload) and muscle strength (all p<0.01). Whilst quadriceps CSA was significantly lower in patients with CHF compared with the control subjects (57.7±4.5 vs. 84.1±5.1 cm^2; p<0.002), thigh circumference and BMI were similar in the two groups. Strength/muscle CSA did not differ between groups. Patients with CHF had significantly higher adiponectin levels than healthy controls (16.5±5.1 mg/L vs. 4.6±0.7 mg/L; p=0.025). Adiponectin levels were negatively correlated with thigh circumference (r=−0.665; p=0.036), quadriceps strength (r=−0.670; p=0.048), and quadriceps muscle CSA (r=−0.673; p=0.033). In addition, a negative correlation was also apparent between adiponectin and muscle strength of the upper limbs (r=−0.892; p=0.003) and muscle mass expressed as difference in median arm circumference during contraction and relaxation (r=−0.739; p=0.015). Van Berendoncks concluded that high adiponectin levels in patients with CHF are associated with decreased muscle mass and impaired muscle strength and that these results corroborate the hypothesis that adiponectin may be a marker of muscle wasting in CHF.

Another study regarding adiponectin as a marker of cardiac functional class and impaired energy metabolism in

patients with chronic heart failure was presented by Dr. Tibor Szabó (Department of Cardiology, Charite Medical School, Berlin, Germany). Szabó et al. assessed circulating adiponectin levels in 181 stable CHF patients and 35 healthy controls of similar age and BMI. Detailed analysis of body composition was performed by dual energy X-ray absorbtiometry; insulin sensitivity was assessed by Homeostasis Model Assessment (HOMA) and exercise capacity by spiroergometry. A total of 164 patients suffered from CHF with reduced ejection fraction (LVEF 36±1%, peak VO_2 18.0±0.5 mL/min*kg) and 17 patients from CHF with preserved ejection fraction (LVEF 33±4%, peak VO_2 21.2±1.3 mL/min*kg). In patients, plasma adiponectin concentrations increased stepwise with increasing New York Heart Association functional class (I/II/III, 8.3±1.2/10.2±0.9/17.5±2.1 mg/dL; ANOVA $p<0.001$) and discriminated cachectic from non-cachectic CHF patients (17.9±3.4 vs. 11.7±0.7 mg/dL; $p=0.01$). Commonly observed gender differences were confirmed in controls (female/male, 13.6±1.9/9.3±0.9 mg/dL; $p<0.05$) but were not detectable in patients with CHF ($p>0.9$). Adiponectin levels correlated inversely with BMI ($r=-0.31$, $p<0.001$) and specifically with trunk fat tissue (percent fat, $r=-0.40$; $p<0.001$). In addition, patients with CHF were found to have impaired insulin sensitivity compared with controls (HOMA, 3.0±0.2 vs. 1.5±0.2 $p<0.001$), and adiponectin correlated weakly with HOMA ($r=-0.21$, $p=0.01$). Correlations for high-density lipoprotein (HDL) cholesterol and triglycerides were less pronounced in patients with CHF compared with controls ($r=0.61$ vs. 0.36 and $r=-0.41$ vs. −0.26, all $p<0.05$). Furthermore, adiponectin correlated with peakVO_2, O_2 at anaerobic threshold and slope ($r=-0.20$; −0.30; 0.36; all $p<0.05$). Szabó concluded that elevated adiponectin levels were significantly associated with advanced disease state, symptomatic status, and metabolic impairment. The alleviated relation between adiponectin versus triglyceride and HDL concentrations in CHF patients may contribute to the development of insulin resistance, unfavorable energy efficiency, and elevated risk profile in this population.

4 Myogenic transcription factors, myostatin, and follistatin

Ricardo L. Damatto (Department of Internal Medicine, Sao Paulo State University, Botucatu Medical School, Botucatu, Brazil) explained in his presentation that changes in myosin heavy-chain isoforms and muscle atrophy have been frequently observed in patients with heart failure. Damatto presented a study testing the hypothesis that skeletal muscle phenotype changes are related to myogenic regulatory factors like myogenin, MyoD, and myogenic regulatory factor 4 (MRF4) and myostatin or follistatin expression in spontaneously hypertensive rats with heart failure. Myogenin, MyoD, and MRF4 are muscle-specific transcription factors, which belong to a large family of basic helix–loop–helix proteins. These factors were first isolated in the 1980s [17]. Myostatin, also known as growth differentiation factor-8, is expressed almost exclusively in skeletal muscle. It is a negative regulator of muscle growth and essential for normal regulation of muscle mass [18]. Under normal conditions, myostatin inhibits myoblast proliferation and thus acts as a negative regulator of muscle bulk [19]. Follistatin has emerged as a powerful antagonist of myostatin that can increase muscle mass and strength [20]. Several studies that support this approach demonstrate the potential of blocking the myostatin pathway [21] and may therefore represent an interesting therapeutic avenue to cachexia treatment (Fig. 2).

Damatto and colleagues investigated 18-month-old spontaneously hypertensive rats (SHR) twice weekly to

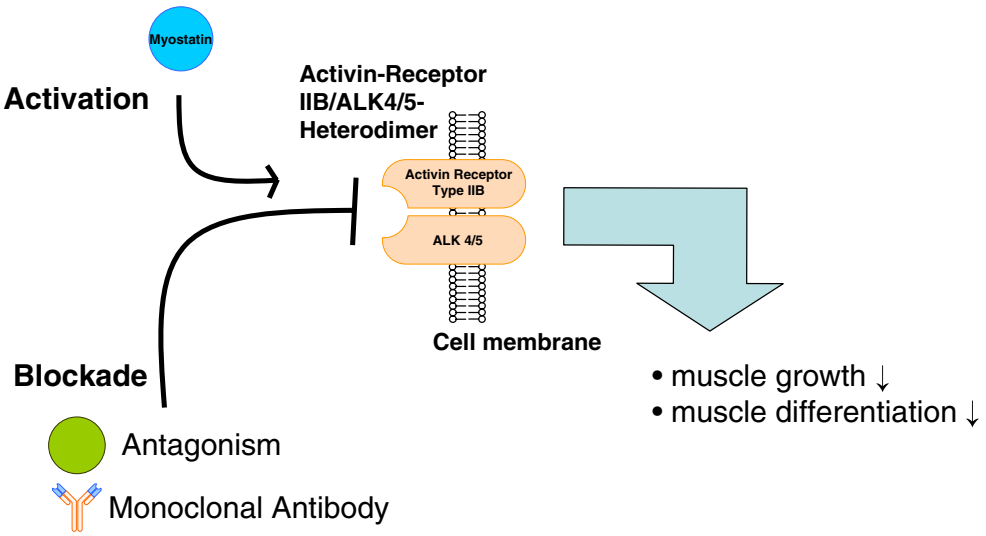

Fig. 2 Myostatin pathway: myostatin levels regulate skeletal muscle cell homeostasis. Myostatin is synthesized and secreted by muscle cell; it signals through the activin receptor IIB/ALK4/5 heterodimer to activate different pathways including Smad2/3 and MAPK (ERK1/2, p38MAPK) resulting in the regulation of gene expression. Myostatin stimulation results in inhibition of muscle growth and muscle differentiation

identify tachypnea, weight loss, and apathy as clinical features of heart failure. After the detection of heart failure, animals underwent transthoracic echocardiogram and were subsequently euthanized on the following day. During euthanasia, pathological evidence of heart failure such as pleuropericardial effusion, ascites, left atrial thrombi, right ventricular hypertrophy, and lung congestion were recorded. Age-matched Wistar-Kyoto (WKY) rats were used as controls. Soleus muscle morphometry was analyzed in hematoxylin and eosin and picro-sirius red stained sections, and myosin heavy-chain (MyHC) isoforms were evaluated by protein electrophoresis. Myogenic regulatory factors, myogenin, MyoD, and MRF4, and myostatin and follistatin protein levels were analyzed by Western blot.

All spontaneously hypertensive rats presented tachypnea and right ventricular hypertrophy. Other heart failure evidence had frequencies between 38% and 88%. None of the Wistar-Kyoto control rats presented any evidence of heart failure. Echocardiographic evaluation showed left chamber dilation, left ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction in those rats with hypertension. Soleus weight was lower in SHR than in control animals ($p<0.001$). Fiber cross-sectional areas were lower (WKY 3,615±412; SHR 2,035±224 μm^2; $p<0.001$), and collagen fractional area was higher (WKY 2.61±0.39; SHR 4.88±0.98%; $p<0.001$) in hypertensive rats. Protein electrophoresis showed decreased IIa MyHC isoform expression in SHR. Myogenin, myostatin, and follistatin protein expression was lower in SHR than in control animals. MyoD protein expression was similar in both groups and MRF4 was higher in SHR. Myogenin and follistatin expression positively correlated with fiber cross-sectional areas, and MRF4 expression negatively correlated with IIa MyHC isoform. Damatto concluded that, while reduced myogenin and follistatin protein expression participates in muscle atrophy, increased MRF4 protein expression modulates myosin heavy-chain isoform shift in skeletal muscle of spontaneously hypertensive rats with heart failure.

5 Inflammation

It has been known since the 1990s that elevated levels of pro-inflammatory cytokines are present in patients with cardiac cachexia [22]. In one of the first studies, Levine et al. had demonstrated elevated serum levels of TNFα in affected patients; not only serum levels of TNFα are elevated but also those of its soluble receptors 1 and 2 (sTNFR-1 and sTNFR-2), all of which are associated with poor survival in heart failure [23].

Norman Mangner (Heart Center, University of Leipzig, Leipzig, Germany) presented data about the force reduction in the diaphragm of mice mediated via TNFα. The signaling pathway of TNFα through NF–κB and the degradation of proteins by the ubiquitin–proteasome system are shown in Fig. 1. In his introduction, Mangner explained that TNFα induces the expression of atrogin-like muscle-specific ubiquitin E3-ligases in skeletal muscle, presumed to mediate the onset of muscle atrophy. The influence of TNFα on muscle function in respiratory muscles, e. g., diaphragm is not well understood. Therefore, Mangner et al. examined the influence of TNFα on muscle function and the expression of MuRF1 in diaphragm of female and male mice. TNFα (100 ng/g body weight) or saline were injected into the peritoneum of C57Bl6 mice of either sex ($n=10$ per group). After 16–24 h, the expression of MuRF1 in the diaphragm was quantified using real-time PCR. Muscle function was measured in an organ bath. Force and power generation were determined in diaphragm bundles. Results were adjusted to muscle cross-sectional area, which was calculated by dividing diaphragm strip weight by strip length times specific density. Animals injected with TNFα showed no higher MuRF1 mRNA expression in diaphragm than saline-injected littermates (saline female vs. TNFα female, 8.5±1.9 vs. 8.4±2.5 arb. units; saline male vs. TNFα male, 5.4±0.7 vs. 7.3±1.1 units). TNFα reduced force development at 150 Hz by ~50% in C57Bl6 animals (saline female vs. TNFα female, 10.3±1.3 vs. 5.2±1.1 N/cm^2; $p=0.01$). Also, maximum power was reduced in female animals injected with TNFα as compared with sham injected littermates (saline female vs. TNFα female, 42.0±6.7 vs. 19.9±5.9 Watt, $p<0.03$). In male mice, no force or power reduction was detectable under TNFα exposure. Mangner concluded that the results of this study demonstrate, for the first time, a gender-specific force reduction of the diaphragm after TNFα administration. Mangner mentioned that they were previously able to show that TNFα leads to an induction of MuRF1 and a consecutive ubiquitination of troponin T accompanied by impaired muscle function in soleus muscle. In contrast, MuRF1 seems not to be essential for the TNFα-induced force reduction in the diaphragm of female mice.

Another study regarding possible anti-inflammatory effects of HDL cholesterol to improve insulin sensitivity in human skeletal muscle was presented by Bronwyn A. Kingwell (Baker IDI Heart and Diabetes Institute, Melbourne, Australia). Kingwell said, recent studies indicate that HDL reduces blood glucose through multiple actions including enhanced insulin secretion and increased glucose uptake into skeletal muscle. The responsible pathway is the AMP-activated protein kinase signaling pathway [24]. Kingwell et al. tested the hypothesis that HDL may improve insulin sensitivity via lipid removal and anti-inflammatory actions in macrophages associated with excess adiposity/ectopic lipid deposition. A variety of

macrophage cell models including the murine RAW 264.7 cell line, the human monocytic cell line THP-1 and primary human macrophages from healthy participants were incubated separately with lipid challenges including palmitate (0.5 mM) and acetylated low-density lipoprotein (LDL, 100 μg/mL), then co-treated with either HDL (50 μg/mL) or vehicle (18 h). Macrophage cultures were subsequently incubated in fresh media (4 h) and conditioned media (CM) applied (1:10) to primary human skeletal muscle cell cultures derived from unmedicated patients with type 2 diabetes mellitus for 24 h and insulin-mediated glucose uptake (2-deoxy glucose) and insulin signaling (pAkt) assessed (n=7, all in triplicate). HDL treatment ameliorated cytokine release (TNFα/IL1β) from macrophages in response to lipid challenges by 50% through suppression of the JNK pathway (39% reduction in JNK phosphorylation). In skeletal muscle cultures treated with THP-1 CM, acetylated LDL treatment reduced insulin-mediated glucose uptake by 31.3±4.1% (p=0.04). Co-treatment with HDL restored insulin-mediated glucose uptake to control levels (51.0±13.4% greater than acetylated LDL treatment alone; p=0.002). Results from two cell lines, the murine RAW cell line and the human monocytic cell line THP-1 macrophages, were recapitulated in primary human macrophages and demonstrate that HDL-mediated improvements in skeletal muscle glucose uptake relate to phosphorylation of the key insulin signaling protein Akt, which in turn phosphorylates and thereby inactivates negative regulators of protein synthesis, such as GSK-3 4E-PB or the transcription factor FOXO, which drives expression of MuRF-1 and MAFbx. AKT activates protein synthesis by phosphorylating and activating mTOR and downstream targets like p70S6K. Kingwell concluded that macrophage inflammation associated with excess/ectopic adiposity is reduced by HDL, and these effects may contribute to improved insulin sensitivity and glucose homeostasis. These findings, said Kingwell, together with a growing body of evidence linking HDL to glucose metabolism, suggest that therapeutics aimed at elevating plasma HDL levels may provide efficacy in preventing and treating type 2 diabetes. HDL might have beneficial effects as an anti-inflammatory agent and should be further investigated.

6 Conclusion

Several pathways have been shown to play crucial roles in muscle wasting in cardiac cachexia. These pathways include overexpression of MuRF-1, an E3-ubiquitin ligase that facilitates myofibril degradation via the ubiquitin–proteasome pathway. Importantly, while this pathway seems to be the most important one in muscle wasting, other pathways such as the lysosomal cathepsin pathway do not appear to be crucially involved. The over-activity of inflammatory mediators fuels the activity of the ubiquitin–proteasome pathway. Exercise training may have important effects in that it reduces the expression of MuRF-1. This buttresses the view that exercise training is beneficial and should be mandated in patients with heart failure [10]. This is particularly true for patients with reduced muscle mass and muscle strength; the term sarcopenia has been suggested for this state, however, its presence remains underdiagnosed and is usually neglected by clinicians [25]. The availability of biomarkers to easily detect muscle loss or even muscle wasting in affected patients would provide a means for daily clinical practice to make reaching this diagnosis easier. Adiponectin may have potential in this regard.

Both cachexia and sarcopenia deserve more attention in daily clinical work and have not received enough research endeavors so far. Prospective studies into understanding the development, phenotype, and the progression of these perturbations are needed. One such study, the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF), is currently ongoing [26]. In the hope that more research into this area will be presented here, we are eagerly awaiting the next meeting of the ESC, which will take place in Paris, France, in August this year.

Acknowledgment The authors of this manuscript certify that they comply with the Principles of Ethical Publishing in the *Journal of Cachexia, Sarcopenia, and Muscle* [27].

Conflict of interest The authors declare that they have no conflict of interest.

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