Diet and Cardiovascular Disease: Heart Failure

Part II: Red Meat, Micronutrients, Special Diets, and Obesity

Abstract

Diet is a major modifiable factor in the prevention and management of cardiovascular diseases. Part I of this two-part manuscript on the relationship between diet and heart failure discussed several healthy dietary patterns. In general, a plant-based with seafood, lean meats, low-fat dairy products, and unsaturated fatty acid intake is helpful to prevent and manage heart failure. This part reviews several macronutrients that are harmful, the role of micronutrients and supplements in the pathogenesis and management of heart failure, and the impact of some special diets on this disease. Red meat and especially processed red meat is high in saturated fat and sodium which tend to worsen heart failure. Refined carbohydrates and sugar-sweetened beverages are also not good choices. Supplementation with some micronutrients such as iron and magnesium may be reasonable in these patients if clinically indicated. The role of Coenzyme Q10 is still unclear. Popular diets such as the Mediterranean, DASH, and vegetarian, are also reviewed in the context of this disease. The complex connection between obesity, cachexia, and HF is also discussed.

Introduction

Heart failure (HF) is a chronic disabling disease with high morbidity and mortality. It is estimated that the lifetime risk of developing HF is about 20%[1]. It is more common in females. Its prevalence increases with age. It is seen in less than 1% for those aged <55 years and in more than 10% in those aged 70 years or over. Causes are many and include coronary artery disease, hypertension, valvular disease such as aortic stenosis, atrial and ventricular arrhythmias, congenital heart defects, infective and drug related myocarditis, infiltrative diseases such as sarcoidosis and malignancy, storage disorders such as hemochromatosis, Fabry disease, Glycogen storage diseases, endomyocardial disease such as carcinoid, pericardial disease, metabolic diseases, vitamin B1, thiamine and selenium deficiencies, autoimmune diseases and neuromuscular diseases such as Friedreich's ataxia, and muscular dystrophy. HF is a progressive disease, and either with preserved (HFpEF) or reduced ejection fraction (HFrEF). Although several pharmacological and non-pharmacological treatment options are available for patients with HFrEF[2], for patients with HFpEF, no therapies have been shown to improve morbidity or mortality[3]. However, HFpEF generally provides a better survival than HFrEF. Heart failure is one of the most common reasons for hospitalization or rehospitalization[4]. Most patients with HF are hospitalized at least once a year. The risk of HF hospitalization is higher in women and in those with diabetics. HF patients with AF, a higher body mass index (BMI), and higher glycated hemoglobin (HbA1c), or a low estimated glomerular filtration rate (eGFR) are also hospitalized more often. Many of these comorbidities are common in these patients[5,6]. HF patients often present with acute decompensation, acute pulmonary oedema, right ventricular failure, and cardiogenic shock. Treatment may include exercise rehabilitation and heart transplantation. In

patients with HFpEF, no treatment has been shown to reduce mortality and morbidity. Overall, HF has an extremely poor prognosis and has a one-year fatality rate of 29.5%[7]. The health care costs attributable to HF are extremely high.

Discussion

Healthy lifestyles, such as a prudent diet, play a mitigating role in the development and progression of heart failure. Plant-based diets help reduce HF incidence and improve its prognosis[8]. However, certain ingredients derived from fruits and vegetables can be harmful. Alcohol, a vegetarian product, if imbibed in high doses may cause and worsen HF[9]. Although whole grains are helpful, refined grains have the bran and germ sections removed during milling, along with all beneficial nutrients. This robs away any benefits gained by the intake of the whole grains[10]. Eating processed red meat and saturated fats have a detrimental influence on the myocardium[11]. The relationship between red meat and HF is reviewed in this section. Certain micronutrients and their relationship with heart failure are also reviewed. Besides the quality of diet, excessive caloric intake may result in an abnormal increase in body weight. A BMI >30 kg/m^2 is diagnostic of obesity[12]. Obesity has a complex relationship with heart failure. Despite increasing the risk of heart failure[13], obesity appears to be associated with survival benefits in many patients[14]. On the other hand, advanced cases of heart failure may be associated with sarcopenic obesity[15], and this is associated with a poorer quality of life (QOL) and a higher mortality[16].

Red meat

Recent studies suggest that the highest category of processed meat and red meat raise the risk of coronary heart disease[17], stroke[18], cardiovascular mortality[19]. Studies have also associated red meat consumption with an increased risk of HF[20]. The association is primarily with processed red meat, and these studies find no statistical increase in HF with consumption of unprocessed meat. In a study of 21,120 physicians, high consumption of red meat was associated with a statistically significantly increased risk of HF (Hazard Ratio or HR=1.02) per serving/day[20]. The data indicated that the risk was higher (HR=1.24) for the highest versus the lowest quintile) of consumption. However, no distinction was made between unprocessed and processed red meat in this study. However, the association appears to be primarily with processed red meat, and most studies find no statistical increase in HF with consumption of unprocessed meat.

Unprocessed and processed red meats were analyzed in two cohorts by Kaluza et al. In a cohort of 37,035 Swedish men, the consumption of unprocessed red meat was not associated with an increased risk of HF (HR=0.99 with a median intake of 83.2 g/day vs. 17 g/day) or HF mortality[21]. However, the consumption of processed meat was associated with an increased risk of HF; for each 50 g per day increment in intake, the risk of HF increased by 8% (HR=1.08), and HF mortality increased by 38% (HR=1.38). In women (cohort of 34,057 Swedish women, 2806 of whom were diagnosed with HF during 13 years of follow-up) they reported similar findings. For each 50 g day^{-1} increase in processed red meat consumption, the risk of HF in women increased by 11%-19%[22]. In this study, unprocessed red meat was not statistically detrimental. Processed meat has higher amounts of sodium and food additives. High dietary sodium intake

boosts the risk of heart failure[23,24] mainly by raising blood pressure[25]. Trimethylamine N-oxide (TMAO) levels are also elevated in meat-eaters and people with HF[26]. TMAO levels correlate with B-type natriuretic peptide (BNP)[27] and are associated with HF severity[28] and HF mortality[29].

Fats

Fatty acids may have beneficial or detrimental effects on HF, depending on their type[30]. Most human studies have focused on trans fats and olive oil. Trans fats increase systemic inflammation as well as BNP levels in HF patients[31,32]. Fried foods are high in saturated fats and often have trans fats. In a large prospective study of 15,362 male physicians, there was a 103 % increase in HF risk in those with the highest versus the lowest levels of fried food consumption[33]. Olive oil (as consumed in the Mediterranean diet. or MedD) is rich in monounsaturated fats. In a study of 651 acute coronary syndrome patients, olive oil consumption was associated with a 65 % decrease in the risk of left ventricular systolic dysfunction[34].

Micronutrients

Micronutrient deficiency is common in patients with HF. Further, several micronutrients present in the body are significantly altered by treatment modalities used in heart failure. These include minerals like sodium, potassium, calcium, magnesium, and selenium. These may be altered by increased urinary excretion due to loop diuretics[35]. Diet may also be altered due to reduced appetite and taste disorders, with the use of Angiotensin-converting enzyme inhibitors[36]. These drugs may also cause zinc deficiency[37]. Other micronutrients that may be affected by heart failure include vitamins C, E vitamins B1, B6, B12, folate, and beta-carotene (precursor of vitamin A). Levels of carnitine, CoQ10, and creatine may also suffer[38]. Micronutrient deficiency in these patients is associated with a higher mortality[39,40]. Micronutrient supplementation in human trials has failed to improve survival or provide robust beneficial effects in these patients[41]. Therefore, supplementation is not routinely advised unless these micronutrients are found to be deficient, irrespective of the cause[42]. A nutrient-rich dietary pattern is the best source of micronutrients and should be adhered to by HF patients[43-45].

Thiamine

Thiamine deficiency can cause heart failure (especially in underdeveloped countries) due to poor nutrition. Thiamine deficiency is also more common in patients with heart failure[46]. Although HF is improved by thiamine supplementation in severe thiamine deficiency, it remains unclear if thiamine supplementation is useful in patients with heart failure at large[47].

Coenzyme Q10 (CoQ10)

The role of CoQ10 remains unclear. In a 2-year prospective study with 420 participants, CoQ_{10} 100 mg 3 times daily (or placebo) in addition to standard therapy showed that it significantly reduced major adverse clinical events (MACE), cardiovascular death by 43%, and all-cause mortality by 42%[48]. The patients also experienced an improvement in their New York Heart Association (NYHA) functional class. Mortensen and colleagues also reported that CoQ10 supplementation in moderate to severe HF was safe and well-tolerated. Although this study has

suggested that CoQ10 supplementation in patients with HF may be beneficial, further data is needed before it can be recommended routinely in HF patients[49].

Iron

Iron deficiency anemia is common in patients with HF[50]. Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in male adults and <12.0 g/dL in female adults[51]. Iron deficiency anemia in HF is associated with poor clinical status and worse outcomes[52]. Several trials such as the IRON-HF[53] and IRONOUT-HF[54] have shown that oral supplementation is unsuccessful in reducing MACE in HF patients. IV supplementation in HFrEF improves outcomes, as shown by the FAIR-HF[55] and CONFIRM-HF[56] trials. Currently, intravenous iron supplementation in patients with both HFrEF and iron deficiency is the only micronutrient supplementation strategy that has been shown to definitively improve outcomes in HF[57].

Sodium

Sodium restriction in HF has been recommended by the American College of Cardiology and the American Heart Association[58]. The Heart Failure Society recommends an intake of less than 2000 mg/day in moderate to severe HF. This is to prevent fluid overload. Although routinely followed, the data on clinical improvement, lower hospital readmission rates[59,60], and decreased mortality[61,62] with salt restriction remains unclear.

K+

In HF, the relationship between K^+ concentrations and adverse outcomes appears to be U-shaped, where both low-K^+ (<3.5 to 4.0 mmol/l) and high-K^+ (>5.5 to 6.0 mmol/l). levels are associated with adverse outcomes[63]. Although dietary intervention may help, a pharmacologic intervention will probably be needed in most cases[64].

Mg

Low magnesium levels and low magnesium intake has been associated with increased HF. Due to inconsistent benefits and potential adverse effects of magnesium (overload) in studies, magnesium supplementation is suggested only when hypomagnesemia has been proven or suspected as a cause for cardiac arrhythmias[65].

Mediterranean Diet

The MedD is characterized by high monounsaturated/saturated fat ratios, with olive oil as the main source of fat; high consumption of vegetables, fruits, legumes, and cereal products; moderate consumption of wine and dairy products; and low consumption of red and processed meat[66,67]. In a prospective study of 1,000 adults admitted with an acute coronary syndrome, there was a 7 % decrease in the likelihood of developing left ventricular systolic dysfunction during hospitalization. There was also a trend towards a 10 % lower risk of cardiac remodeling in those following the MedD, over 2 years[68]. Subsequent large prospective studies have also reported that MedD adherence was associated with decreases in HF incidence of 24 % in healthy adults[69], 21 % in healthy women[70], and 31 % in healthy men[71]. All studies reported that greater adherence conferred greater protection in a dose-dependent manner. In a recent meta-analysis of six studies

(n=10,950), the MedD reduced the risk of HF by 70 %[72]. Extra virgin olive oil has a high content of polyphenols and accounts for a significant fraction of this beneficial effect[73].

Some studies have questioned the beneficial effect of MedD on HF, especially in women. Papadaki et al found that in 7403 participants without prevalent HF (followed for a median of 4.8 years) there was no reduction in the risk of clinical cases of HF with MedD[74]. Strengers et al. in a recent study, found no risk reduction in women, while a 12% lower risk was noted in men[75]. In general, MedD with extra virgin oil and nuts is helpful in HF. MedD reduces several HF risk factors such as hypertension[76], type 2 diabetes mellitus (T2DM)[77], and obesity[78], and this helps in protecting against HF. MedD has been shown to beneficially decrease oxidative stress, reduce plasma N-terminal pro-BNP levels[79], and lower oxidized LDL-C levels[80].

DASH

The DASH diet emphasizes the intake of fruits and vegetables; lean protein such as poultry, fish, and nuts; fiber and whole grains; and low-fat dairy products. This diet provides adequate levels of micronutrients, such as potassium, calcium, and magnesium, deemed to lower blood pressure[81]. High blood pressure is a major cause of HF. While the DASH diet has been proven to effectively reduce blood pressure, the benefit of the DASH diet in patients with HF has been infrequently investigated. However, the consensus is that the DASH diet helps prevent and reduce HF, irrespective of gender. In a large Swedish study in postmenopausal women (36,019), aged 48 to 83 years, during a seven-year follow-up, those who had higher adherence to the DASH diet had a 37% lower rate of HF[82]. In a study of men, aged 45 to 79 years, over a nine-year follow-up, the highest quartile for the DASH diet adherence had a 22% lower rate of HF incidence[83]. A 2013 systematic review and meta-analysis including >144,000 adults reported that a DASH-like diet was associated with significant risk reduction against HF (29 %)[84]. Another prospective observational study conducted in 3,215 women with pre-existing HF found a 16 % decrease in mortality in those with the greatest DASH adherence after 4.6 years[85]. Besides the risk reduction, these patients improve clinically, with an improvement in exercise capacity and quality of life[86]. DASH diet intake has been shown to improve arterial elasticity, decrease arterial stiffness, and reduce BP[43,44,85]. Its adherence is also associated with a favorable end-diastolic volume, stroke volume, and ejection fraction[87]. There is a favorable decrease in 24-hour urinary sodium and BNP levels[86]. These changes are noted even if there is no associated weight loss. DASH diet beneficially modifies antioxidant capacity[88], inflammatory response, liver function, coagulation[89], natriuresis[90], sympathetic activation[91], and endothelial function[92], in these patients.

Vegetarian Diet:

Vegetarian diets are plant-based diets. A vegan diet does not contain any animal products (meat, fish, poultry, eggs, or dairy) and consists of plant-based foods, such as fruits, vegetables, whole grains, and legumes/beans. Lacto-ovo-vegetarians also consume dairy products and eggs[93]. Pesco-vegetarian (pescatarians) diet avoids meat or poultry but does allow fish and shellfish, eggs, and dairy. Semi-vegetarians or “flexitarians”– eat all foods, including meat, poultry, fish and shellfish, eggs, and dairy, in addition to plant-based foods, such as fruits, vegetables, whole grains, and legumes/beans – they however limit their red meat and poultry intake[94]. The

Mediterranean and DASH diets discussed above are high in plant-based foods as their components. Vegetarian diets are associated with lower blood pressure, reduced platelet aggregation, better weight management, and a reduced risk of developing T2DM. Vegetarian foods also inhibit oxidation of LDL cholesterol, raise HDL cholesterol, and reduce total cholesterol[95]. Pai et al. reported that a vegetarian diet, compared to the non-vegetarian diet, was associated with a lower prevalence of LV diastolic dysfunction (Odds Ratio or OR=0.42) and a lower prevalence of LV hypertrophy with (OR=0, 30)[96].

Obesity/Cachexia

Obese individuals have twice the risk of HF compared to those with a normal BMI[97]. The Framingham heart study found that there was a 5% increase in men and a 7% increase in women for the risk of developing HF per unit increase in BMI[98]. The longer the duration of morbid obesity the higher the prevalence of HF - 70% after 20 years and 90% after 30 years.[99]. Early age obesity also prognosticates future HF. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, a higher self-reported weight at 20 and 40 years of age resulted in an increased HF risk later in life[100]. A weight loss of 5-10% is recommended for HF patients with body mass index ≥ 35 kg/m2[101]. This improves cardiac function and clinical symptoms. Dietary calorie restriction helps reduce body weight by inducing a calorie deficit. However, certain dietary patterns have been associated with greater weight loss. Plant-based eating results in weight loss[102,103] and decreases weight gain[104]. Conversely, greater intake of animal-based foods results in a higher BMI[105,106]. Special diets such as MedD[107]and DASH diet[108] also help in weight reduction. The obesity HF link is related to the effects of obesity on inflammation, hypertension, T2DM, and dyslipidemia[109,110].

The relationship between body weight in patients with HF is however not that simple. HF patients often experience two other phenomenon – obesity paradox and sarcopenia/cachexia. In the obesity paradox, obese patients diagnosed with HF have significantly better survival than normal-weight HF patients, while underweight patients have a poor prognosis than normal-weight HF patients. This paradox in HF was first noticed by Horwich and colleagues[111]. Several subsequent studies have verified this observation. Kenchaiah et al. reported that in a randomized controlled trial of 7,599 symptomatic patients with HFrEF and HFpEF, overweight and obese patients had lower mortality when compared with those who were underweight or had a normal BMI[112]. In a meta-analysis of 9 observational studies (28,209 patients), Oreopoulos et al. concluded that overweight and obese HF patients had lower mortality compared with normal BMI patients[113]. Another systematic review of 6 studies found that overweight individuals had a lower risk for hospitalization and total and CVD mortality when compared to underweight patients with chronic HF[114]. Obesity paradox is an accepted phenomenon in patients with HF. The underlying mechanisms are not clear, but factors such as fat distribution, lean mass, and cardio-fitness levels are postulated to play a role[115].

Heart failure when severe, is accompanied by sarcopenia and cachexia. Sarcopenia is a loss of skeletal muscle quantity or quality with a decline in muscle strength and/or physical performance not necessarily due to weight loss[116]. HF patients may also develop cachexia as the disease progresses[117]. Cachexia results from increased protein catabolism and is characterized by severe

body weight, fat, and muscle loss[118]. Almost 20% of HF patients suffer from sarcopenia and cachexia, with a significant decrease in the quality of life and survival in these patients. Dietary intervention with excess protein intake (1.0–1.2 g/kg body weight/day) appears to help improve muscle mass and physical function in these patients[119].

Conclusion

Diet has a significant effect on heart failure. The two major causes of heart failure are coronary artery disease and diabetes mellitus and can be almost completely prevented by eating a prudent diet. In the first part of this manuscript, the benefits of a plant-based diet were discussed. These non-omnivore diets are high in antioxidants, micronutrients, dietary nitrate, and fiber and low in saturated/trans fats and sodium. This results in a decreased HF incidence/severity. Red meat and saturated fats increase inflammation, decrease antioxidant activity, and detrimentally modulate the gut microbiome. The restriction of salt to prevent fluid retention is generally followed, although its restriction remains controversial. Obesity is an enigma. Despite the complex relationship between the obesity paradox and sarcopenic obesity, a weight reduction of 5% to 10% is beneficial if the obesity exceeds a BMI of 35 kg/m2. The Mediterranean, DASH, and vegetarian diets are heart-healthy and help attenuate HF. As nutritional modification is a relatively low-risk and low-cost option, it is an attractive strategy for reducing HF incidence and progression.

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References

1. Metra M, Teerlink JR. Heart failure. The Lancet 2017; 390: 1981–1995.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.
3. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014; 370: 1383–1392.
4. https://www.cmshospitalchartbook.com/ (2020).
5. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, obesity, diabetes, and heart failure-free survival: the Cardiovascular Disease Lifetime Risk Pooling Project. JACC Heart Fail. 2016;4:911–919. DOI: 10.1016/j.jchf.2016.08.001.
6. Verhaert DVM, Brunner-La Rocca HP, van Veldhuisen DJ, Vernooy K. The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management

of both diseases. Europace. 2021 Apr 10;23(23 Suppl 2):ii40-ii45. doi: 10.1093/europace/euaa368.
7. Chang PP, Chambless LE, Shahar E, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study) Am J Cardiol. 2014;113(3):504–510. doi: 10.1016/j.amjcard.2013.10.032.
8. Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. JAMA. (2009) 302:394–400. 10.1001/jama.2009.1062.
9. Klatsky AL, Chartier D, Udaltsova N, et al. Alcohol drinking and risk of hospitalization for heart failure with and without associated coronary artery disease. Am J Cardiol. 2005;96:346–351.
10. Swaminathan S, Dehghan M, Raj JM, et al. Associations of cereal grains intake with cardiovascular disease and mortality across 21 countries in Prospective Urban and Rural Epidemiology study: prospective cohort study. BMJ 2021; 372:m4948. doi: https://doi.org/10.1136/bmj.m4948.
11. Kaluza J, Åkesson A, Wolk A. Long-term processed and unprocessed red meat consumption and risk of heart failure: a prospective cohort study of women. Int J Cardiol. 2015;193:42–6. doi: 10.1016/j.ijcard.2015.05.044.
12. Hirsch, J., Salans, L. B., Aronne, LJ. (2001) Obesity. Becker, KL eds. Principles and Practice of Endocrinology and Metabolism. 3rd ed. Lippincott, Williams, and Wilkins Philadelphia. 1239–1246.
13. Fliotsos M, Zhao D, Rao VN, Ndumele CE, Guallar E, Burke GL, et al. Body mass index from early-, mid-, and older-adulthood and risk of heart failure and atherosclerotic cardiovascular disease: MESA. J Am Heart Assoc. (2018) 7:e009599. 10.1161/JAHA.118.009599.
14. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156:13-22.
15. Rahman A, Jafry S, Jeejeebhoy K, Nagpal AD, Pisani B, Agarwala R. Malnutrition and Cachexia in Heart Failure. JPEN J Parenter Enteral Nutr. 2016 May;40(4):475-86. doi: 10.1177/0148607114566854.
16. Krysztofiak H, Wleklik M, Migaj J, et al. Cardiac Cachexia: A Well-Known but Challenging Complication of Heart Failure. Clin Interv Aging. 2020 Nov 2;15:2041-2051. doi: 10.2147/CIA.S273967.
17. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. Circulation. 2010;121(21):2271–2283. doi: 10.1161/CIRCULATIONAHA.109.924977.
18. Chen GC, Lv DB, Pang Z, Liu QF. Red and processed meat consumption and risk of stroke: a meta-analysis of prospective cohort studies. Eur J Clin Nutr. 2013;67(1):91–95. doi: 10.1038/ejcn.2012.180.

19. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Stampfer MJ, Willett WC, Hu FB. Red meat consumption and mortality: results from 2 prospective cohort studies. Arch Intern Med. 2012;172(7):555–563. doi: 10.1001/archinternmed.2011.2287.
20. Ashaye A, Gaziano J, Djoussé L. Red meat consumption and risk of heart failure in male physicians. Nutr Metab Cardiovasc Dis 2011; 21: 941– 6.
21. Kaluza J, Akesson A, Wolk A. Processed and unprocessed red meat consumption and risk of heart failure: prospective study of men. Circ Heart Fail 2014; 7: 552– 7.
22. Kaluza J, Åkesson A, Wolk A. Long-term processed and unprocessed red meat consumption and risk of heart failure: a prospective cohort study of women. Int J Cardiol. 2015;193:42–6. doi: 10.1016/j.ijcard.2015.05.044.
23. Geach T. Heart failure: Processed meat and heart failure. Nat Rev Cardiol. 2014 Aug;11(8):434. doi: 10.1038/nrcardio.2014.93.
24. Graudal NA, Hubeck-Graudal T, Jurgens G. Reduced Dietary Sodium Intake Increases Heart Rate. A Meta-Analysis of 63 Randomized Controlled Trials Including 72 Study Populations. Front Physiol. 2016;7:111. doi: 10.3389/fphys.2016.00111.
25. Cui K, Liu Y, Zhu L, Mei X, Jin P, Luo Y. Association between intake of red and processed meat and the risk of heart failure: a meta-analysis. BMC Public Health. 2019 Mar 29;19(1):354. doi: 10.1186/s12889-019-6653-0.
26. Tang WH, Wang Z, Fan Y et al. Prognostic value of elevated levels of intestinal microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis. J Am Coll Cardiol. 2014;64:1908–14. doi: 10.1016/j.jacc.2014.02.617.
27. Trøseid M, Ueland T, Hov JR et al. Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. J Intern Med. 2015;277:717–26. doi: 10.1111/joim.12328.
28. Trøseid M, Ueland T, Hov JR et al. Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. J Intern Med. 2015;277:717–26. doi: 10.1111/joim.12328.
29. Suzuki T, Heaney LM, Bhandari SS et al. Trimethylamine N-oxide and prognosis in acute heart failure. Heart. 2016;102:841–8. doi: 10.1136/heartjnl-2015-308826.
30. Fiaccavento R, Carotenuto F, Minieri M, et al. Alpha-linolenic acid-enriched diet prevents myocardial damage and expands longevity in cardiomyopathic hamsters. Am J Pathol. 2006;169:1913–1924.
31. Mozaffarian D, Rimm EB, King IB et al. Trans fatty acids and systemic inflammation in heart failure. Am J Clin Nutr. 2004;80:1521–5. doi: 10.1093/ajcn/80.6.1521.
32. Lennie TA, Chung ML, Habash DL, Moser DK. Dietary fat intake and proinflammatory cytokine levels in patients with heart failure. J Card Fail. 2005;11:613–8. doi: 10.1016/j.cardfail.2005.06.434.
33. Djoussé L, Petrone AB, Gaziano JM. Consumption of fried foods and risk of heart failure in the physicians? health study. J Am Heart Assoc. 2015. p. 4.
34. Chrysohoou C, Kastorini CM, Panagiotakos D et al. Exclusive olive oil consumption is associated with lower likelihood of developing left ventricular systolic dysfunction in acute coronary syndrome patients: the hellenic heart failure study. Ann Nutr Metab. 2010;56:9–15. doi: 10.1159/000261898.

35. Dunn SP, Bleske B, Dorsch M, Macaulay T, Van Tassell B, Vardeny O (2009) Nutrition and heart failure: impact of drug therapies and management strategies. Nutr Clin Pract 24(1):60–75. 10.1177/0884533608329299.
36. https://www.pharmaco-vigilance.eu/content/drug-induced-taste-and-smell-disorders - accessed Novmenber 30, 2021.
37. Dunn SP, Bleske B, Dorsch M, Macaulay T, Van Tassell B, Vardeny O (2009) Nutrition and heart failure: impact of drug therapies and management strategies. Nutr Clin Pract 24(1):60–75. 10.1177/0884533608329299,
38. Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. J Am Coll Cardiol. 2001 Jun 1;37(7):1765-74. doi: 10.1016/s0735-1097(01)01227-x.
39. LT A, Christina A, Kay RM, et al. Micronutrient Deficiency Independently Predicts Time to Event in Patients With Heart Failure. J Am Heart Assoc. 2018;7(17):e007251.
40. Song EK, Kang S-M. Micronutrient Deficiency Independently Predicts Adverse Health Outcomes in Patients With Heart Failure. J Cardiovasc Nurs. 2017;32(1).
41. Georgiopoulos G, Chrysohoou C, Vogiatzi G, et al. Vitamins in Heart Failure: Friend or Enemy? Curr Pharm Des. 2017;23(25):3731-3742. doi: 10.2174/1381612823666170321094711.
42. Dunn SP, Bleske B, Dorsch M, Macaulay T, Van Tassell B, Vardeny O (2009) Nutrition and heart failure: impact of drug therapies and management strategies. Nutr Clin Pract 24(1):60–75. 10.1177/0884533608329299..
43. Hummel SL, Seymour EM, Brook RD, et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. Circ Heart Fail. 2013;6(6):1165–1171.
44. Hummel SL, Mitchell SE, Brook RD, et al. Low-Sodium Dietary Approaches to Stop Hypertension Diet Reduces Blood Pressure, Arterial Stiffness, and Oxidative Stress in Hypertensive Heart Failure With Preserved Ejection Fraction. Hypertension. 2012;60(5):1200–1206.
45. Hummel SL, Wahida K, Gillespie B, et al. Home-Delivered Meals Postdischarge From Heart Failure Hospitalization. Circ Hear Fail. 2018;11(8):e004886.
46. Hanninen SA, Darling PB, Sole MJ, Barr A, Keith ME. The prevalence of thiamin deficiency in hospitalized patients with congestive heart failure. J Am Coll Cardiol. 2006;47:354–361. doi: 10.1016/j.jacc.2005.08.060.
47. Smithline HA, Donnino M, Blank FSJ, Barus R, Coute RA, Knee AB, Visintainer P. Supplemental thiamine for the treatment of acute heart failure syndrome: a randomized controlled trial. BMC Complement Altern Med. 2019 May 6;19(1):96. doi: 10.1186/s12906-019-2506-8.
48. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP; Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail. 2014 Dec;2(6):641-9. doi: 10.1016/j.jchf.2014.06.008.
49. https://www.cochrane.org/CD008684/VASC_coenzyme-q10-heart-failure.

50. Sîrbu O, Floria M, Dascalita P, Stoica A, Adascalitei P, Sorodoc V, Sorodoc L. Anemia in heart failure - from guidelines to controversies and challenges. Anatol J Cardiol. 2018 Jul;20(1):52-59. doi: 10.14744/AnatolJCardiol.2018.08634.
51. Nutritional anaemias . Report of a WHO scientific group. Geneva, World Health Organization, 1968. (WHO Technical Report Series, No. 405). http://whqlibdoc.who.int/trs/WHO_TRS_405.pdf.
52. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol. 2008;52:818–27.
53. Beck-da-Silva L, Rohde LE, Pereira-Barretto AC, et al. Rationale and design of the IRON-HF study: a randomized trial to assess the effects of iron supplementation in heart failure patients with anemia. J Card Fail. 2007 Feb;13(1):14-7. doi: 10.1016/j.cardfail.2006.09.007.
54. Lewis GD, Malhotra R, Hernandez AF, et al. NHLBI Heart Failure Clinical Research Network. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical Trial. JAMA. 2017 May 16;317(19):1958-1966. doi: 10.1001/jama.2017.5427.
55. Stefan D. Anker, Josep Comin Colet, Gerasimos Filippatos, et al. for the FAIR-HF Trial Investigators. Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency. N Engl J Med 2009; 361:2436-2448. DOI: 10.1056/NEJMoa0908355.
56. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al.; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015 Mar 14;36(11):657-68. doi: 10.1093/eurheartj/ehu385.
57. Anker SD, Kirwan B-A, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail. 2018;20(1):125–133.
58. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):e240–e327.
59. Aliti GB, Rabelo ER, Clausell N, Rohde LE, Biolo A, Beck-da-Silva L (2013) Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. JAMA Intern Med 173(12):1058–1064. 10.1001/jamainternmed.2013.552.
60. Damgaard M, Norsk P, Gustafsson F, Kanters JK, Christensen NJ, Bie P, Friberg L, Gadsboll N (2006) Hemodynamic and neuroendocrine responses to changes in sodium intake in compensated heart failure. Am J Phys Regul Integr Comp Phys 290(5):R1294–R1301. 10.1152/ajpregu.00738.2005.
61. Paterna S, Parrinello G, Cannizzaro S, Fasullo S, Torres D, Sarullo FM, Di Pasquale P (2009) Medium term effects of different dosage of diuretic, sodium, and fluid

administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. Am J Cardiol 103(1):93–102. 10.1016/j.amjcard.2008.08.043.
62. Paterna S, Fasullo S, Parrinello G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). Am J Med Sci 342(1):27–37. 10.1097/MAJ.0b013e31820f10ad.
63. Shiyovich A., H. Gilutz, Y. Plakht. Potassium fluctuations are associated with inhospital mortality from acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAMI-II) project. Angiology, 69 (2018), pp. 709-717.
64. Ferreira JP, Butler J, Rossignol P, et al. Abnormalities of Potassium in Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Jun 9;75(22):2836-2850. doi: 10.1016/j.jacc.2020.04.021.
65. Tangvoraphonkchai K, Davenport A. Magnesium and Cardiovascular Disease. Adv Chronic Kidney Dis. 2018 May;25(3):251-260. doi: 10.1053/j.ackd.2018.02.010.
66. Trichopoulou A. Lagiou P. Healthy traditional mediterranean diet: an expression of culture, history, and lifestyle. Nutr Rev. 2009; 55 ([Internet]): 383-389.
67. https://academic.oup.com/nutritionreviews/article-lookup/doi/10.1111/j.1753-4887.1997.tb01578.x.
68. Chrysohoou C, Panagiotakos DB, Aggelopoulos P, et al. The Mediterranean diet contributes to the preservation of left ventricular systolic function and to the long-term favorable prognosis of patients who have had an acute coronary event. Am J Clin Nutr. 2010;92:47–54. doi: 10.3945/ajcn.2009.28982.
69. Wirth J, di Giuseppe R, Boeing H, Weikert C. A Mediterraneanstyle diet, its components and the risk of heart failure: a prospective population-based study in a non-Mediterranean country. Eur J Clin Nutr. 2016;70:1015–21. doi: 10.1038/ejcn.2016.140.
70. Tektonidis TG, Åkesson A, Gigante B et al. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: A population-based cohort study. Atherosclerosis. 2015;243:93–8. doi: 10.1016/j.atherosclerosis.2015.08.039.
71. Tektonidis TG, Åkesson A, Gigante B et al. Adherence to a Mediterranean diet is associated with reduced risk of heart failure in men. Eur J Heart Fail. 2016;18:253–9. doi: 10.1002/ejhf.481.
72. Liyanage T, Ninomiya T, Wang A et al. Effects of the Mediterranean diet on cardiovascular outcomes ? a systematic review and meta-analysis. PLoS One. 2016;11:e0159252. doi: 10.1371/journal.pone.0159252.
73. Wongwarawipat T, Papageorgiou N, Bertsias D, Siasos G, Tousoulis D. Olive Oil-related Anti-inflammatory Effects on Atherosclerosis: Potential Clinical Implications. Endocr Metab Immune Disord Drug Targets. 2018;18(1):51-62. doi: 10.2174/1871530317666171116103618.
74. Papadaki A, Martínez-González MÁ, Alonso-Gómez A, et al. Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial. Eur J Heart Fail. 2017 Sep;19(9):1179-1185. doi: 10.1002/ejhf.750.
75. Strengers JG, den Ruijter HM, Boer JMA, Asselbergs FW, Verschuren WMM, van der Schouw YT, Sluijs I. The association of the Mediterranean diet with heart failure risk in a

Dutch population. Nutr Metab Cardiovasc Dis. 2021 Jan 4;31(1):60-66. doi: 10.1016/j.numecd.2020.08.003.
76. Toledo E, Hu FB, Estruch R, et al. Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: results from a randomized controlled trial. BMC Med 2013; 11:207.
77. Salas-Salvadó J, Bulló M, Babio N, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet. Diabetes Care 2011;34:14–19.
78. Estruch R, Martínez-González MA, Corella D, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. Lancet Diabetes Endocrinol 2016;4:666–676.
79. Liyanage T, Ninomiya T, Wang A et al. Effects of the Mediterranean diet on cardiovascular outcomes ? a systematic review and meta-analysis. PLoS One. 2016;11:e0159252. doi: 10.1371/journal.pone.0159252.
80. Fitó M, Estruch R, Salas-Salvadó J et al. PREDIMED Study Investigators. Effect of the Mediterranean diet on heart failure biomarkers: a randomized sample from the PREDIMED trial. Eur J Heart Fail. 2014;16:543–50. doi: 10.1002/ejhf.61.
81. Rifai L, Silver MA (2016) A review of the DASH diet as an optimal dietary plan for symptomatic heart failure. Prog Cardiovasc Dis 58(5):548–554. 10.1016/j.pcad.2015.11.001.
82. Levitan E.B., Wolk A., Mittleman M.A. Consistency with the DASH diet and incidence of heart failure. Arch. Intern. Med. 2009;169:851–857. doi: 10.1001/archinternmed.2009.56.
83. Levitan E.B., Wolk A., Mittleman M.A. Relation of consistency with the dietary approaches to stop hypertension diet and incidence of heart failure in men aged 45 to 79 years. Am. J. Cardiol. 2009;104:1416–1420. doi: 10.1016/j.amjcard.2009.06.061.
84. Salehi-Abargouei A, Maghsoudi Z, Shirani F, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH)- style diet on fatal or nonfatal cardiovascular diseases ? incidence: a systematic review and meta-analysis on observational prospective studies. Nutrition. 2013;29:611–8. doi: 10.1016/j.nut.2012.12.018.
85. Levitan EB, Lewis CE, Tinker LF et al. Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. Circ Heart Fail. 2013;6:1116–23. doi: 10.1161/CIRCHEARTFAILURE.113.000495.
86. Rifai L, Pisano C, Hayden J, Sulo S, Silver MA (2015) Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure. Proc (Bayl Univ Med Cent) 28(2):151–156.
87. Nguyen HT, Bertoni AG, Nettleton JA et al. DASH eating pattern is associated with favorable left ventricular function in the multi-ethnic study of atherosclerosis. J Am Coll Nutr. 2012;31:401–7. doi: 10.1080/07315724.2012.10720466.
88. Al-Solaiman Y., Jesri A., Zhao Y., Morrow J.D., Egan B.M. Low-sodium DASH reduces oxidative stress and improves vascular function in salt-sensitive humans. J. Hum. Hypertens. 2009;23:826–835. doi: 10.1038/jhh.2009.32.

89. Azadbakht L., Surkan P.J., Esmaillzadeh A., Willett W.C. The Dietary Approaches to Stop Hypertension eating plan affects C-reactive protein, coagulation abnormalities, and hepatic function tests among type 2 diabetic patients. J. Nutr. 2011;141:1083–1088. doi: 10.3945/jn.110.136739.
90. Akita S., Sacks F.M., Svetkey L.P., Conlin P.R., Kimura G. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on the pressure–natriuresis relationship. Hypertension. 2003;42:8–13. doi: 10.1161/01.HYP.0000074668.08704.6E.
91. Edwards K.M., Wilson K.L., Sadja J., Ziegler M.G., Mills P.J. Effects on blood pressure and autonomic nervous system function of a 12-week exercise or exercise plus DASH-diet intervention in individuals with elevated blood pressure. Acta Physiol. 2011;203:343–350. doi: 10.1111/j.1748-1716.2011.02329.x.
92. Blumenthal J.A., Babyak M.A., Hinderliter A., Watkins L.L., Craighead L., Lin P.H. Effects of the DASH diet al.one and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: The ENCORE study. Arch. Intern. Med. 2010;170:126–135. doi: 10.1001/archinternmed.2009.470.
93. U.S. Department of Health and Human Services and U.S. Department of Agriculture . eighth ed. 2015. –2020 dietary guidelines for Americans. http://health.gov/dietaryguidelines/2015/guidelines/ December 2015. Accessed July 17, 2020.
94. Leitzmann C. Vegetarian diets: what are the advantages? Forum Nutr. 2005;(57):147-56. doi: 10.1159/000083787.
95. Pilis W., Stec K., Zych M., Pilis A. Health benefits and risk associated with adopting a vegetarian diet. Rocz. Panstw. Zakl. Hig. 2014;65:9–14.
96. Pai R.G., Varadarajan P., Jabo B., Al-Mallah M.H. Vegetarianism is independently associated with Lower risk of left ventricular diastolic dysfunction and stage B heart failure burden [abstract] Circulation. 2015;132:A14601.
97. Allen KE, Gumber D, Ostfeld RJ. Heart Failure and a Plant-Based Diet. A Case-Report and Literature Review. Front Nutr. 2019;6:82. Published 2019 Jun 11. doi:10.3389/fnut.2019.00082.
98. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. J Am Coll Cardiol 2010;55:283-293.
99. Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM, Panayiotou H, Mukerji V. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol 1997;80:736-740.
100. Fliotsos M, Zhao D, Rao VN, Ndumele CE, Guallar E, Burke GL, et al. Body mass index from early-, mid-, and older-adulthood and risk of heart failure and atherosclerotic cardiovascular disease: MESA. J Am Heart Assoc. (2018) 7:e009599. 10.1161/JAHA.118.00959.
101. https://covid19-data.nist.gov/pid/rest/local/paper/implications_of_obesity_across_the_heart_failure_continuum – Accessed November 30, 2021.

102. Turner-Mcgrievy GM, Davidson CR, Wingard EE, Wilcox S, Frongillo EA. Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets. Nutrition. (2015) 31:350–8. 10.1016/j.nut.2014.09.002.
103. Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian diets and weight reduction: a meta-analysis of randomized controlled trials. J Gen Intern Med. (2016) 31:109–16. 10.1007/s11606-015-3390-7.
104. He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. Int J Obes Relat Metab Disord. (2004) 28:1569–74. 10.1038/sj.ijo.0802795,
105. Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians, and vegans. Int J Obes Relat Metab Disord. (2003) 27:728–34. 10.1038/sj.ijo.0802300.
106. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care. (2009) 32:791–6. 10.2337/dc08-1886.
107. Mancini JG, Filion KB, Atallah R, Eisenberg MJ. Systematic Review of the Mediterranean Diet for Long-Term Weight Loss. Am J Med. 2016 Apr;129(4):407-415.e4. doi: 10.1016/j.amjmed.2015.11.028.
108. Razavi Zade M, Telkabadi MH, Bahmani F, Salehi B, Farshbaf S, Asemi Z. The effects of DASH diet on weight loss and metabolic status in adults with non-alcoholic fatty liver disease: a randomized clinical trial. Liver Int. 2016 Apr;36(4):563-71. doi: 10.1111/liv.12990.
109. Thakker GD, Frangogiannis NG, Bujak M, Zymek P, Gaubatz JW, Reddy AK, et al. Effects of diet-induced obesity on inflammation and remodeling after myocardial infarction. Am J Physiol Heart Circ Physiol. 2006;291:H2504–H2514.
110. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med. 2002;347:305–313.
111. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001;38:789-795.
112. Kenchaiah S, Pocock SJ, Wang D, et al. CHARM Investigators. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007;116:627-636.
113. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156:13-22.
114. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D, Lazar JM. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. Am J Cardiol 2015;115:1428-1434.
115. Kokkinos P, Faselis C, Franklin B, et al.. Cardiorespiratory fitness, body mass index and heart failure incidence. Eur J Heart Fail 2019; 21(4):436–444. doi:10.1002/ejhf.1433.

116. Cruz-Jentoft A.J., Bahat G., Bauer J., Boirie Y., Bruyère O., Cederholm T., Cooper C., Landi F., Rolland Y., Sayer A.A., et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16–31. doi: 10.1093/ageing/afy169.
117. Rahman A, Jafry S, Jeejeebhoy K, Nagpal AD, Pisani B, Agarwala R. Malnutrition and Cachexia in Heart Failure. JPEN J Parenter Enteral Nutr. 2016 May;40(4):475-86. doi: 10.1177/0148607114566854.
118. Muscaritoli M., Anker S.D., Argilés J., et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics" Clin. Nutr. 2010;29:154–159. doi: 10.1016/j.clnu.2009.12.004.
119. Holeček M. Beta-hydroxy-beta-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions. J. Cachexia Sarcopenia Muscle. 2017;8:529–541. doi: 10.1002/jcsm.12208.