Nutrient modulation in the management of disease induced muscle wasting - evidence from human studies

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Abstract

Purpose of Review

In addition to being essential for movement, skeletal muscles act as both a store and source of key macronutrients. As such, muscle is an important tissue for whole body homeostasis, undergoing muscle wasting in times of starvation, disease and stress e.g. to provide energy substrates for other tissues. Yet, muscle wasting is also associated with disability, co-morbidities and mortality. Since nutrition is so crucial to maintaining muscle homeostasis "in health", it has been postulated that muscle wasting in cachexia-syndromes may be alleviated by nutritional interventions. This review will highlight recent work in this area in relation to muscle kinetics, the acute metabolic (e.g. dietary protein), and longer-term effects of dietary interventions.

Recent Findings

Whole-body and skeletal muscle protein synthesis invariably exhibit deranged kinetics (favoring catabolism) in wasting states; further, many of these conditions harbor blunted anabolic responses to protein-nutrition compared to healthy controls. These derangements underlie muscle wasting. Recent trials of essential amino acid (EAA) and protein-based nutrition have shown some potential for therapeutic benefit.

Summary

Nutritional modulation, particularly of dietary-AA, may have benefits to prevent or attenuate disease-induced muscle wasting. Nonetheless, there remains a lack of recent studies exploring these key concepts to make conclusive recommendations.

200 words

Introduction

Skeletal muscle facilitates locomotion and is metabolically important in providing a large capacity for glucose and intramuscular lipid storage for energy production, as well as the body's largest reservoir of amino acids (AA) [1]. Clinically this makes muscle a vital support mechanism in times of need e.g. i) releasing AA for tissue repair in response to diseases, trauma and starvation, and ii) compensating for failing organs (i.e liver and kidneys). Both communicable infectious and non-communicable diseases are associated with skeletal muscle wasting; collectively known as "cachexia" syndromes these include: cancers [2], metabolic diseases such as diabetes [3], auto-immune/immune-deficiency diseases such as rheumatoid arthritis [4] in addition to organ failures, e.g. cirrhosis [5], chronic obstructive pulmonary disease (COPD) [6] congestive heart failure (CHF) [7]. Cachexia is defined as an involuntary and progressive weight loss primarily due to muscle wasting with or without associated loss of fat mass [8]. The mechanisms underlying muscle wasting include disease-led catabolism, co-morbidities, poly-pharmacy, physical inactivity and malnutrition [9]. Crucially, muscle wasting has been shown to be clinically important as it is a strong predictor of mortality in many clinical conditions [10]. Nonetheless, interventions to mitigate cachexia are limited, since pharmaceutical treatments to increase muscle mass are yet to show efficacy [11]. This has led to the search for nutritional support strategies.

Skeletal muscle mass is under tight homeostatic regulation with a precise diurnal balance being maintained between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). This equilibrium is dynamic across fasted-fed cycles. The intake of food enhances MPS and suppresses MPB via EAA-mediated stimulation of MPS [12] and insulin mediated suppression of MPB [13]. Yet, a key feature of cachexia is that it cannot be completely reversed with conventional nutritional support [9], suggesting a disturbance in these key homeostatic/proteostatic processes. Ultimately, this results in muscle wasting that *standard* nutritional provision cannot restore - hence, the search for nutritional/nutraceutical strategies. This timely review will summarise new knowledge into the metabolic basis of muscle wasting in diseases (note: where sufficient recent data exists), and associated nutrient therapies that have been trialed – all with a strict focus on clinical studies.

What's new in cancer nutritional management?

Cachexia is prevalent in nearly half of all cancer patients exhibiting ~10% body-weight loss, and accounts for ~20-25% of all cancer deaths [14]. In addition to inactivity and malnutrition, cachexia is driven by disease processes (e.g. inflammation [8]) and disease-modifying treatments e.g. chemotherapy [15]. Insights into the regulation of cancer cachexia have been achieved using protein kinetic measurements. For instance, it was recently shown that pancreatic cancer patients (weight loss >10%) exhibited increased whole body protein synthesis (WBPS) and whole body protein breakdown (WBPB) compared to controls in the fasted state, resulting in no difference in net balance (NB) [16]. In contrast, in non-cachectic advanced non-small cell lung

cancer (NSCLC) patients (stage III/IV unresectable), no differences in WBPS or WBPB were observed, yet overall, NSCLC displayed decreased NB [17]. Other studies have focused on how the feeding response is affected by cancer burden; one such study illustrated that sip-feeding over 4h (24g casein/86.4g carbohydrate/31.2g fat) had no effect on WBPS in pancreatic cancer patients. Nonetheless, similar improvements in NB were achieved compared to healthy controls through suppressed WBPB [16]. Conversely, 14g of leucine-enriched (40%) EAA increased WBPS and NB equally between NSCLC patients vs. healthy controls [17], similar to what was previously shown in NSCLC patients in response to hyperaminoacidemia [2]. Disparities in fasted and fed-state results between van Dijk et al. [16] and Engelen et al. [17] could be due to different type of cancers (pancreatic vs. NSCLC), with pancreatic cancer patients exhibiting greater cachexia as shown by van Dijk et al. (>10% vs. 0 in Engelen). That being said, both groups displayed elevated C-reactive protein (CRP) (8.3mg/ml and 9.8mg/ml respectively), while CRP positively correlated with MPB only in van Dijk et al. [16]. Overall these studies indicate high levels of EAA may provide benefits for increasing WBPS and NB in cancer patients. Yet the effectiveness at increasing muscle protein synthesis is difficult to interpret as measures of whole body protein kinetics include that of all organs that may also display altered protein metabolism.

Additional work has been performed looking at MPS via gold-standard direct incorporation methods. In cachectic colorectal cancer patients, fasted-state MPS was unchanged compared to controls, although leg MPB tended to be increased [18]. Moreover, in response to AA infusions over 2.5h

(102mg/kg/h), blunted increases in MPS were evident in cancer patients compared to controls [18]. In contrast to these results, a population of mixed advanced non-cachectic cancer patients showed increased MPS in response to a formulated medical food high in protein and free-leucine compared to a control medical food (40g vs. 24g protein, 4.16g vs. 0g free leucine respectively). Nonetheless, in the absence of a healthy control group comparison, whether this was an “overcoming of anabolic resistance” or simply a dose response phenomenon cannot be determined. Recently, cumulative MPS was measured using D_2O in upper gastrointestinal patients over 7-days. Intriguingly, MPS was the same as controls and was further *increased* in weight losing patients [19]; these results could be driven by elevated MPS, matched with an equal or greater increase in MPB (not measured). Further, activity and diet were not monitored, that will affect cumulative MPS [19–21].

Together these protein kinetic studies demonstrate that cancer may alter whole body protein kinetics, perhaps to an extent dependent upon cancer type and progression of cachexia. Further, protein synthesis (particular that of muscle) may in some instances exhibit anabolic resistance to protein feeding. This is confirmed by the fact that, 6-weeks after tumor resection, Williams et al. demonstrated the restoration of anabolic sensitivity in these patients [18]. That said, providing EAA enriched protein sources may provide benefits in overcoming anabolic insensitivity in muscle [17,22] – yet whether it can truly restore MPS to the same as controls remains to be confirmed. It is patently clear that larger are more tightly controlled studies are needed.

159 Recent guidelines on nutrition in cancer suggest that malnutrition
160 should be taken into consideration and avoided by providing/advising on
161 adequate nutritional intake. While optimal protein intake has not been
162 determined in cancer patients, a minimum of 1g/kg/day is suggested with a
163 target of 1.2-2g/kg/d [23]. Recently, colorectal cancer patients with weight loss
164 >1kg in the past 3-6 months received pre-operative oral supplementation of
165 24g protein/d (5-15 days), although this did not prevent further losses in fat
166 free mass index (FFMI) -0.345 $kg.m^2$ [24]. In another trial, newly diagnosed
167 oesophageal cancer patients were randomized to receive placebo or a
168 specially formulated medical food similar to that previously described [22].
169 Patients consumed 2x200ml; consisting of 9.9 g protein, 1.1 g free leucine,
170 0.6 g eicosapentaenoic acid (EPA), 0.3 g docosahexaenoic acid (DHA) and a
171 balanced mix of vitamins, minerals, and trace elements per 100ml for 4-
172 weeks. After supplementation, the specially formulated medical food resulted
173 in a significant increase in body weight (approximately 1.25kg) and functional
174 performance [25]. Energy dense high protein oral nutritional supplementation
175 or parental nutrition have shown efficacy at increasing weight, although this is
176 not always the case [26]. With cachectic patients having greater protein
177 needs, increased provision is likely to be beneficial. Variability between
178 studies is introduced by diverse individual cancer phenotypes rendering
179 interpretations difficult.

180 Further to protein, there are other nutraceutical interventions that may
181 herald benefits for increasing body weight in cancer. The primary anabolic
182 effects of protein arise from the EAA and leucine content, along with the
183 metabolite β-hydroxy-β-methylbutyrate (HMB). Nonetheless, supplementing

184 mixtures of HMB/arginine/glutamine in muscle wasting conditions has shown
185 both increases, or no effect on body weight [27,28]. Fish oil derived fatty
186 acids, particularly N-3 fatty acids, have many health benefits in both health
187 and disease. A recent review investigating the effect of purified EPA, or EPA
188 and DHA combined on body composition in cancer highlights studies
189 reporting an increase or stabilization of lean body mass and weight, along
190 with decreasing inflammation [23,29]. Nutritional support to increase energy
191 and protein intake, through nutritional counselling or supplementation is
192 recommended in cancer patients [23]. However, there is currently a lack of
193 strong consistent evidence that long term supplementation of e.g. protein, AA
194 (or metabolites of), or long chain N-3 fatty acids robustly improve lean mass
195 [23,28]. Nonetheless, there are multiple studies reporting increases in weight
196 when utilizing high EAA and high EPA interventions. Combined with the
197 promising results of EAA/protein on whole body and MPS, oral nutritional
198 support (ONS) strategies may hold clinical benefits in cancer patients [26].
199
200 **What's new in immune and metabolic disease nutritional management?**
201
202 Rheumatoid arthritis is an idiopathic autoimmune disease affecting synovial
203 joints. A complex network of chemokines and cytokines (particular TNFa and
204 IL-6) promote an inflammatory response that attracts immune cells to the
205 synovial fluid- stimulating osteoclast regeneration, bone and cartilage
206 degradation by matrix metalloproteinase and a perpetuation of inflammation
207 [30]. RA is commonly accompanied by muscle wasting of poorly defined
208 etiology, although chronic inflammation has been suggested to contribute [4].
209 Muscle protein kinetics have recently been investigated in non-cachectic RA

patients. In the fasted state there was no difference between MPS and MPB in RA patients vs. healthy age-matched controls [31]. Moreover, in response to whey protein (0.5g/kg/LBM) there was an equal increase in MPS and suppression in MPB. This group of individuals were described to be 'well functioning' and did not display reductions in muscle strength or mass. Further these patients were receiving disease modifying antirheumatic drug (DMARD), methotrexate and although exhibiting inflammation (TNFa, IL6, CRP) this was less than previous studies [31]. Overall this suggests anabolic resistance is not present in RA, although there are no studies to make comparisons to, and this may be different where overt cachexia is present.

Generally RA patients exhibit energy and protein requirements similar to age-matched controls [4]. Nevertheless, it was shown that mixtures of non-EAA (alanine, glutamic acid, glycine, and serine) vs. HMB, glutamine and arginine supplements were equally effective at increasing muscle mass in RA patients [4,32]. However, recent studies into the effects of nutritional supplementation on lean mass in RA patients are lacking. Interestingly 12-weeks of creatine supplementation was shown to increase lean mass in RA patients [33] potentially offering an effective way to restore muscle mass. Furthermore, with the preserved anabolic sensitivity, increased protein supplementation may help prevent or restore muscle mass losses, although again, larger and more controlled and detailed studies are needed.

Type I Diabetes (T1DM) is an auto-immune condition resulting in a lack of insulin production due to destruction of pancreatic beta cells and has a major negative impact on skeletal muscle [34]. A primary action of insulin on human muscle is the suppression of MPB [13]; as such reduced insulin action

on muscle may also exacerbate muscle wasting [3]. In support of this, without treatment most T1D individuals display dramatic weight loss, while weight loss and muscle mass can be much improved with insulin therapy [3]. Overall, T1DM results in an increase in both WBPS and WBPB. Increases in WBPB are greater than WBPS such that negative net balance occurs, with the majority of this coming from muscle protein sources [3]. With regard to feeding, supplementary leucine increased whole-body protein accretion in T1DM via suppression of protein breakdown [35].

T2D is primarily characterized by tissue insulin resistance (IR). Initially, insulin secretion increases, yet over time insulin secretion is inadequate to overcome IR [3]. T2D is a result of genetic and environmental factors, the risk being increased with obesity and physical inactivity. T2D is associated with a greater decline in muscle mass especially with ageing [36]. Nonetheless, WBPS, WBPB and NB were shown to be comparable between controls and T2DM patients and with no difference in MPS [37]. Additionally, obese T2D patients, with a lower percentile of appendicular lean mass, displayed no difference in fasted MPS [38]. Both of these studies further showed equal response to feeding as controls, with 20g casein [37] and 10/20g of EAA with maximal stimulation at 10g [38]. This suggests anabolic resistance is not the mechanism of muscle loss in T2D. Additionally, while there appears to be no major differences in protein kinetics, people with T2D maintain higher levels of insulin; whether this is needed to maintain equivalent WBPB is unclear [3].

What's new in organ failure nutritional management?

Chronic obstructive pulmonary disease (COPD) is characterized by long-term airflow limitation (“lung failure”) mainly caused by chronic exposure to cigarette smoke and air born pollutants [39]. Many COPD patients display cachexia with underlying hyper-metabolism, inflammation and reduced appetite [40]. COPD patients in the postabsorptive state have shown both increased or unchanged whole body protein turnover [6,41], yet the effect on MPS is unknown. Further, the effect of protein feeding has illustrated equal anabolic responses to healthy controls, with greater responses when a mixture of leucine enriched EAA (13g-40% leucine) was used compared to a mixture of total AA (13g-12% leucine) [42]. Overall, nutritional supplementation in COPD patients has shown increased body weight, with the use of EAA supplements showing greatest benefits at increasing fat free mass (FFM) [39].

Chronic kidney disease (CKD) describes the progressive loss of kidney function that results in end stage renal disease. This is accompanied by a progressive loss of muscle mass often referred to as protein energy wasting (PEW), although it has no obvious distinction from cachexia. Muscle loss is associated with many metabolic abnormalities in CKD including inflammation, insulin resistance, decreased nutrient intake and dietary restrictions, with muscle loss further enhanced by dialysis [43]. Whole body protein kinetics have been shown to be similar between CKD and healthy subjects, however in the fasted state specifically mixed MPS was lower [44]. The biggest effect of CKD on muscle kinetics is that through dialysis; resulting in rapid protein losses through increases in MPB that may persist for several hours after treatment [44]. In non-dialysis CKD patients, a protein diet of 0.6-0.8g/kg/day

has been recommended, as a low protein diet may slow the progression to renal failure. In CKD patients undergoing dialysis a much higher protein intake of >1.2g/kg/day is recommended [43], and to try and attenuate protein losses, many studies have provided intradialysis supplementation. Enteral nutritional support has previously shown effectiveness at attenuating catabolism [45]. However recently, CKD patients receiving a meal containing 30g of protein 90-min after the start of each treatment for 6-months did not prevent losses in lean mass [46]. Furthermore, consumption of either 27g whey protein, soy protein or placebo 15 minutes prior to the start of dialysis for 6 months had no effect on lean mass [47]. Similarly consumption of 3g of calcium-HMB per day for 6-months had no effects on lean body mass [27,48]. However, in both these studies lean mass remained stable in control and treatment groups. An additional option is the use of intradialytic parental nutrition, utilizing mixtures high in amino acids, glucose and lipids. Although showing benefits on nitrogen balance and body weight, recent studies focusing on muscle outcomes are limited, with intra-dialytic parenteral nutrition (IDPN) further seen as a short-term nutritional approach [45]. Both enteral and parental intradialytic supplementations offer a safe means to increase nutritional intake. However nutritional modulation in CKD should take individual characteristics and clinical condition into consideration [45].

Congestive heart failure (CHF) is impaired ventricular ejection and or filling capacity caused by structural or functional abnormalities. Accompanying heart failure is progressive involuntary weight loss, often referred to as cardiac cachexia [49]. Skeletal muscle loss is always the result of an imbalance between anabolic and catabolic factors, yet there is a lack of studies looking

at protein kinetics in heart failure, with only one study demonstrating that generally whole body protein turnover is unaffected [50]. As such the presence of anabolic resistance in HF is unknown. Malnutrition is often present in these patients and so nutritional support is recommended; yet there are no specific guidelines for protein and energy intake. The use of protein rich high calorie supplementation, and similarly EAA, have previously shown benefits in body weight in most patients [51].

Finally, acute multiple organ failure through the onset of acute illness and/or trauma is an often overlooked area of clinical nutrition. The accelerated loss of muscle in ICU patients (estimated at a striking 1-2%/d; [52]) through increased MPB and decreased MPS has devastating consequences on recovery, morbidity and mortality, even following discharge [53]. Due to the multifaceted causes of critical illness, alongside the extended periods of bedrest, nutritional management can be complicated. Of the few studies that have been performed, potential dietary manipulation with the EAA leucine and in particular its metabolite HMB have shown efficacy, improving nitrogen balance in trauma ICU patients [52]. Other anti-catabolic drugs and nutraceuticals (e.g. N-3 fatty acids, metformin) that have been tested in acute patients are discussed in detail in a recent review for this journal [54], however large RCT's are still lacking. Yet it is unlikely that any one nutritional intervention will be the "magic bullet" for preventing wasting in ICU patients, and nutritional therapies should be carefully individualized to each patient dependent on cause of admission.

Conclusions

Many chronic diseases described herein are associated with a significant and progressive wasting of muscle mass that increases the risk of mortality. There are common underlying abnormalities e.g. inflammation, hyper-metabolism, insulin/anabolic resistance - all contributing the irreversible nature of cachexia to standard nutrition. Despite the trialing of nutritional interventions, there is considerable inconsistencies and variability among results- assumably due to the type of disease. Acutely, protein feeding high in EAA content has shown to be effective at promoting a full anabolic response on the whole body and muscle level. Fulfilling energy requirements through high calorie/high protein nutritional approaches is therefore icily to be beneficial in many situations of disease-induced muscle wasting. However, recommendations should be specialized, as nutritional requirements and route of administration may vary considerably across disease state and progression. This review also highlights areas where lack of clinical progress is being made; including a number of the topics we cover herein, in addition to those with little-to no new data not covered e.g. chronic liver disease.

Key Points

- Many diseases are accompanied with a significant and progressive muscle wasting known as cachexia, which is a strong predictor of mortality. The specific underlying mechanisms to muscle wasting in disease are incompletely defined, yet many conditions display inflammation, increased energy expenditure and malnutrition.

- Protein loss occurs through an imbalance between protein synthesis and protein breakdown. Using stable isotope techniques to study protein kinetics, the mechanism of protein loss can be studied and effective therapeutics devised.

- These techniques have revealed altered protein kinetics that favour catabolism and have identified the presence of anabolic resistance in many disease states. Currently, protein high in EAA has shown effectiveness at promoting anabolism.

- There are considerable inconsistencies among the efficacy of nutritional interventions in disease induced muscle wasting. Currently high calorie high protein (EAA) supplementation has shown to be most effective at attenuating muscle loss.

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Figure Legend

Figure 1 an overview of disease induced muscle wasting. Cachexia is a complex syndrome that is associated with many disease states. The development of muscle wasting with disease is multifactorial, with chronic disease often resulting in changes in habitual behavior such as malnutrition and inactivity; along with many adverse effects from drug treatments. These factors are themselves associated with muscle loss and can exacerbate negative disease outcomes. The underlying mechanisms of cachexia across disease states are unclear, although share common characteristics such as inflammation, increased REE and insulin resistance. Loss of muscle mass must occur through an overall imbalance between protein synthesis and protein breakdown. Protein kinetics has shown to be frequently altered, generally favoring a catabolic environment. Further, impaired anabolic responses to nutrition are often present likely contributing to the irreversible nature of cachexia through standard nutritional provision. Many nutritional interventions have been tried to promote anabolism and attenuate muscle wasting. Currently protein high in EAA has shown promising affects, yet many other nutraceutical interventions have shown positive but overall inconsistent results. REE, resting energy expenditure. PS, protein synthesis. PB, protein breakdown. EAA, essential amino acids. HMB, β-hydroxy-β-methylbutyrate. MPS, muscle protein synthesis.

* Engelen et al 2015 - Demonstrated an essential amino acid mixture is more effective at increasing whole body protein synthesis in cancer patients than that of total amino acids. Further this response was equal to healthy controls suggesting EAA may be effective in preventing muscle mass loss

* Mikkelsen et al 2015 - First study in rheumatoid arthritis patients to demonstrate equal responses in muscle protein synthesis and muscle protein breakdown to whey protein. Indicating that in well-treated rheumatoid arthritis patients anabolic sensitivity is maintained

* Faber et al 2017 - Showed increased body weight and performance status in cancer patients using a specially formulated medical food high in EAA, fish oil and vitamins. Previously, deutz et al 2011 demonstrated this medical food was effective at increasing acute MPS in cancer patients. Together these studies show the power of devising anabolic interventions on a acute basis and implementing them on a long term basis.

* Macdonald et al 2015 - The first study to use D_2O to measure long term musle protein synthesis in patients with upper GI cancer. This reveleaed increased muscle protein synthesis in cachetic cancer patients, seemingly contradicting the theory of anabolic resistance in muscle wasting. These techniques are less invasie to atute tracer studies and will undoubtable unravel disease induced alterations in kinetics on a long term 'free living' basis

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