Nutrition 65 (2019) 179–184

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review article

Anabolic competence: Assessment and integration of the multimodality interventional approach in disease-related malnutrition

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ARTICLE INFO

Article History:
Received 10 November 2018
Received in revised form 6 February 2019
Accepted 20 March 2019

Keywords:
Anabolic competence
Disease-related malnutrition
Nutrition
Physical activity
Internal milieu
Proteins

ABSTRACT

Disease-related malnutrition (DRM) is a frequent clinical problem, characterized by loss of lean body mass and decreased function, including muscle function and immunocompetence. In DRM, nutritional intervention is necessary, but it has not consistently been shown to be sufficient. Other factors, for example, physical activity and hormonal or metabolic influencers of the internal milieu, are also important in the treatment of DRM. A prerequisite for successful treatment of DRM is the positive balance between anabolism and catabolism. The aim of this review was to approach DRM using this paradigm of anabolic competence, for conceptual and practical reasons. *Anabolic competence* is defined as "that state which optimally supports protein synthesis and lean body mass, global aspects of muscle and organ function, and immune response." Anabolic competence and interdisciplinary, multimodality interventions create a practical foundation to approach DRM in a proactive comprehensive way. Here, we describe the paradigm of anabolic competence, and its operationalization by measuring factors related to anabolic competence and suited for clinical management of patients with DRM.

Introduction

Disease-related malnutrition (DRM) is common in clinical settings [1,2]. *Malnutrition* is defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" [3]. DRM can lead to increased risk for complications (e.g., impaired wound healing, increased hospital length of stay, and higher mortality) [1,4]. Utilization and efficacy of nutrients is affected by several factors including physical (in)activity and hormonal/metabolic influences of patient internal milieu, which includes inflammation. Treatment of DRM, therefore, must not only optimize nutritional intake, but also address broad anabolic or anticatabolic factors [5].

To this purpose, it would be useful to consider DRM from the perspective of anabolic competence. *Anabolic competence* has been defined as "that state which optimally supports protein synthesis and lean body mass, global aspects of muscle and organ function, and immune response" [6]. The paradigm of anabolic competence was developed to facilitate a comprehensive and practical interdisciplinary multimodality approach that could be used to address malnutrition and lean body mass/function deficit. Within this paradigm, factors identified as being involved in anabolic competence were categorized into three domains: nutritional milieu, exercise, and hormonal milieu [6]. We used a revised model (Fig. 1), which includes the broader term *physical activity*, which addresses both exercise and daily activity, as all forms of activity contribute to support of anabolic competence. Moreover, instead of hormonal milieu, the term *internal milieu* is used and includes hormones in addition to other neuroendocrine regulators, inflammatory factors, and the adverse effects of disease treatment (e.g., chemotherapy, radiation, corticosteroids), which can affect anabolic competence.

AGN and GN received unconditional grants from Nutricia. FO is copyright holder of the Patient-Generated Subjective Global Assessment (PG-SGA) and PG-SGA-based Pt-Global app/web tool, and co-founder of the PG-SGA/Pt-Global Platform. HJW was co-developer of the PG-SGA-based Pt-Global app and was co-founder of the PG-SGA/Pt-Global Platform. The authors have no further conflicts of interest of interest to declare.

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https://doi.org/10.1016/j.nut.2019.03.010
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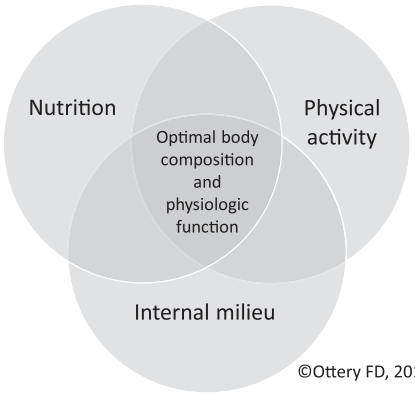

Fig. 1. The three domains of anabolic competence. Adapted from Langer et al. [6].

Standardized, reliable, and proactive assessment and monitoring are required to determine the degree of anabolic (in)competence. Moreover, within the paradigm of anabolic competence, the patient's nutritional status is evaluated from a dynamic perspective, whereas DRM is usually considered as a static state, which ignores the possibility of anabolism despite absolute muscle mass/function deficit. For example, a patient may have lost 15% weight in the previous 6 mo, but may have regained 2% weight in the past month, indicating anabolism rather than ongoing catabolism, despite the 13% net weight loss. Therefore, the shape of the weight curve and the rate of weight change are critical in understanding the progression of reversal of DRM. The Patient-Generated Subjective Global Assessment (PG-SGA), widely used to screen or assess nutritional risk or deficit, captures the underlying dynamic processes and core components of intervention supporting anabolic competence [7].

In this review, we describe the modifiable factors contributing to support of anabolic competence, and how these factors can be assessed and monitored to better match with clinical intervention practice.

Nutrition

Optimal intake of macro- and micronutrients is essential for maintenance of metabolic equilibrium. Hence, nutritional interventions form the core of treatment strategies aimed at promoting anabolism and/or counteracting catabolism. Protein is critical for anabolism as substrate for tissue synthesis. To meet metabolic demands necessary to maintain normal body composition in a healthy individual, the World Health Organization (WHO) recommends a daily protein intake of 0.8 g/kg body weight (BW) [8]. Higher daily protein intake of ≥1 g/kg BW is recommended for individuals >65 y of age, to account for age-related muscle tissue degradation [9]. In patients with DRM, nutrient requirements are even higher due to effects of the disease, generally indicated as the inflammatory milieu. This may increase resting energy expenditure and nitrogen excretion, indicating higher protein requirements [10]. Daily protein intake of 1.2 to 1.5 g/kg BW, as recommended for patients with cancer, is generally recommended in malnourished patients [11,12]. Daily protein requirements of critically ill patients are considered to be as high as 1.2 to 2 g/kg BW, and potentially higher for patients with burn injuries or multitraumas [13]. Additionally, some studies suggest that in older adults the distribution of protein intake throughout the day may be important in promotion of maximal protein synthesis response per meal [14].

There is evidence that specific nutrients can elicit anabolic responses directly. Certain branched-chain amino acids, in particular leucine, may directly trigger an anabolic response through the mechanistic target of rapamycin (mTOR) pathway [15]. Nevertheless, sufficient bioavailability of all other amino acid precursors for protein synthesis remains imperative to obtain a relevant increase in protein synthesis [16]. Furthermore, increasing evidence supports the positive role of ω-3 polyunsaturated fatty acids (PUFAs) in the anabolic response. Particularly in older adults, ω-3 PUFA supplementation has demonstrated an increase in post-exercise and post-absorptive protein synthesis and an improvement in muscle strength [17–19]. The exact mechanisms for this beneficial effect on protein synthesis remain to be determined. The effect seems to occur independently of the anti-inflammatory properties of ω-3 PUFAs, considering that inflammatory markers remained unchanged after ω-3 PUFA supplementation in presence of significantly increased protein synthesis [17].

Sufficient protein intake does not independently determine the utilization of proteins. Importantly, nutritional intake does not equal nutrient bioavailability. Digestion and absorption of protein relies on several factors, including the composition and digestibility of the proteins, other dietary constituents, gastric motility, gastric pH, small intestinal transit time, and most importantly the pancreatic protease secretion and activity. These factors can be negatively influenced by both the disease itself and by adverse effects of medication (e.g., corticosteroids, antianabolic agents such as megesterol acetate) or other therapy (e.g., radiotherapy). Both proteins and malnutrition itself [20] can modulate gastric emptying rate and thereupon modify the postprandial metabolic response. Proteins classified as "fast" could promote a higher anabolic response compared with "slow" proteins [21]. For example, when ingested separately, whey protein is considered fast as it remains soluble in the stomach, and casein is considered slow as the clotting of casein reduces the rate of stomach emptying [22]. However, the gastric emptying rate of protein depends on total meal composition [21]. Disturbances in pancreatic enzyme secretion and/or activity can impair protein digestion. Furthermore, reductions of the intestinal absorptive surface, and gastrointestinal diseases that impair intestinal absorption (e.g., inflammatory bowel disease, gastroenteritis, and bowel ischemia) can severely reduce protein absorption [23,24]. Additionally, protein utilization is strongly interrelated with energy balance. Protein synthesis not only requires energy, but protein itself can be used as an energy source. Nitrogen balance studies showed that nitrogen retention in humans improved with increasing or adequate energy intake [25,26].

Finally, the complex effects of disease can greatly impair protein utilization in both acute and chronic settings. Impaired utilization is apparent from the incomplete therapeutic effect of nutritional support in DRM, as opposed to the complete therapeutic effect in malnutrition without disease, for example, starvation (Fig. 2) [10]. Impaired protein utilization in DRM indicates the need for a multimodality interventional strategy over a "protein-energy–only" strategy, also taking into account the other components contributing to anabolic competence. The specific effects of different disease states on nutrient intake, uptake. and utilization can differ between and within patients, and vary with disease severity. Therefore, the management of DRM requires a personalized and dynamic approach.

The reduced effectiveness of nutritional interventions alone in DRM versus malnutrition without disease indicates that further insight into the metabolic derangements, and their effect on protein utilization, may allow improvement in the management of DRM. To facilitate further improvement, a bedside tool quantifying

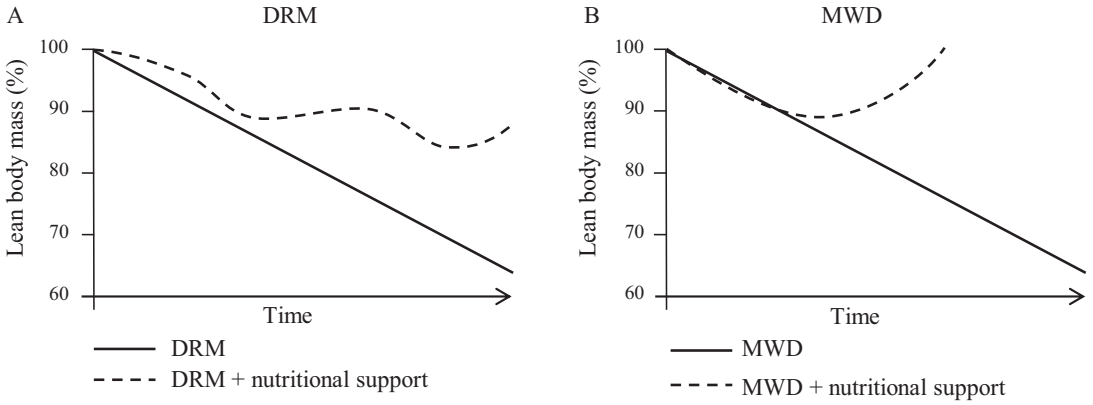

Fig. 2. Hypothetical relationship of the effect of nutritional support on lean body mass in the treatment of DRM compared with MWD. Nutritional intervention alone in DRM is insufficient to maintain or recover lean body mass as protein utilization is impaired (**A**), whereas nutritional support in MWD may be sufficient to recover lean body mass (**B**). DRM, disease-related malnutrition; MWD, malnutrition without disease. Adapted from Jensen et al. [10].

protein utilization would be useful. Although the nitrogen balance method (i.e., the difference between nitrogen intake and loss, which reflects the gain or loss of total body protein), is a good indicator of either anabolism or catabolism, this method is not able to provide insight in changes in protein synthesis and breakdown [27]. As amino acids are used either for protein synthesis or are oxidized [28], a breath test that measures amino acid oxidation might serve as a non-invasive clinical tool to collect information on protein utilization by the body [29,30].

Physical activity

Physical activity (i.e., daily activity and exercise) is a crucial anabolic trigger as it increases the utilization of ingested protein for protein synthesis in the body and is, therefore, a highly relevant modifiable factor in treatment of DRM. Although exercise was incorporated into the paradigm of anabolic competence almost two decades ago, it is just in the past decade that exercise and daily activity are fully being recognized as important anabolic triggers for the prevention [31] and treatment of disease [32]. A recent review compiled the beneficial effect of physical activity on clinical outcomes of 26 diseases (e.g., metabolic diseases) and cancer [32].

Muscle-strengthening exercise (e.g., resistance and aerobic physical exercise) conveys specific benefits contributing to anabolic competence [33]. Resistance exercise stimulates muscle hypertrophy and increases muscle strength [34]. Aerobic physical exercise improves maximal oxygen consumption [35], insulin sensitivity [36], and decreases oxidative stress [37]. Improved aerobic fitness increases the capacity to perform muscle-strengthening exercise and daily activities. This positive feedback loop further enhances anabolic competence, as demonstrated in women over 70 years of age [38].

Data on levels of physical activity in patients with DRM are lacking. In various patient populations, low levels of physical activity are associated with higher mortality and worse disease outcomes [39], probably related to, among others, loss of muscle mass, inflammation, and deranged metabolism [39,40]. Increasing the physical activity level in certain patient populations may be beneficial. For example, a 12-wk randomized controlled trial (RCT) with 130 sarcopenic geriatric patients, in which regular controlled exercise was given with or without supplementation of 22 g of whey protein and 2.5 μg vitamin D, resulted in a decreased risk for malnutrition with both interventions, with the largest decrease found in those with supplementation [41]. These results demonstrate the synergistic effect of nutrition and physical activity on reducing malnutrition risk in sarcopenic geriatric patients. Yet, RCTs that take into account all aspects of anabolic competence are limited.

WHO guidelines have guided the target amount of physical activity in patient populations such as those with cancer [11]. Whether the WHO guidelines are an attainable and a realistic goal for patients with DRM is questionable because the guidelines are intended for disease prevention rather than for restoring muscle mass in patients with DRM.

As physical activity can contribute to anabolic competence, physical *in*activity has the opposite effect. Disuse muscle atrophy (e.g., bed rest) has detrimental effects on muscle mass and strength [42,43]. Moreover, bed rest with inadequate protein ingestion can lead to a loss of muscle mass of ~95 g/d in healthy older adults [44]. For patients with DRM, any increase in physical activity, combined with nutrition, can contribute to their anabolic competence [12]. Avoidance of *in*activity, as a more feasible goal in patients with DRM, is relevant and meaningful.

Several instruments have been developed to assess physical activity for research applications and may not be suited for clinical purposes. Common instruments to quantify physical activity and intensity are self-reported physical activity questionnaires (SPRAQs) [45]. Although SPRAQs are easy to administer, the shortfall of many SPRAQs is that they are less sensitive in detecting light- to moderate-intensity physical activity, and inquire information on average habitual physical activity, rather than measuring actual or recent day-to-day physical activity [46], which is indispensable information for the acutely ill.

Considering DRM, objective day-to-day measurements of physical activity and physical function would provide more clinically relevant information, which can be useful for monitoring a patient's condition and to assess adherence to physical activity interventions. The need for such monitoring is most apparent in hospitalized patients with acute (or acute-on-chronic) disease, where disease state, activity, and nutritional status evolve from day to day.

Influencers of internal milieu

In patients with DRM, the effect of ingested nutrition combined with physical activity on subsequent protein processing is influenced by hormonal and metabolic influencers of the internal milieu, including neuroendocrine regulation, inflammation activity, and disease treatment. Inflammation, lack of physical activity, and disturbed internal milieu hinder an anabolic response, with synergistic detrimental effects on muscle mass and overall anabolic competence, reinforcing the need for a multimodality approach.

The major molecular pathway responsible for the regulation of protein synthesis is mTOR and subsequent activation of the mTORC1 pathway. The mTOR pathway is activated by insulin, testosterone, leucine, a leucine metabolite β-hydroxy β-methylbutyric acid, and physical activity [47–50]. For protein degradation, the lysosomal pathway, the calcium-regulated calpains pathway, and the ubiquitin-proteasome pathway have been identified. The latter is the main contributor to loss of muscle mass in acute and chronic disease, as many anabolic and catabolic signaling pathways are involved in the regulation of the ubiquitin-proteasome pathway genes [51]. The molecular mechanisms of protein synthesis and degradation are described elsewhere [47–49,51].

Net protein breakdown (i.e., loss of muscle mass) in DRM is mostly related to increased inflammation owing to the disease itself, or its treatment, as seen in patients with sepsis, cancer, and renal failure [52]. Inflammation leads to loss of muscle mass by both promoting catabolism and impairing anabolism in muscle. Furthermore, inflammation increases energy and protein requirements [10]. Although inflammation-related muscle degradation is not fully clarified, the proinflammatory cytokine tumor necrosis factor-α is a significant mediator. Tumor necrosis factor-α stimulates production of various catabolic cytokines, and is associated with muscle mass loss in, for example, patients with cancer [53]. C-reactive protein, a well-established marker for acute and chronic inflammation, impairs the proliferation of muscle cells [54] and has been associated with lower muscle mass in for example women aged 65-70 years and patients on dialysis [54,55]. This suggests that inflammation reducing treatment could reduce the loss of muscle mass. However, RCTs are needed to confirm causality and effect size.

Furthermore, because hormones play an important role in physiologic homeostasis, disturbances in the hormonal milieu can negatively influence anabolic competence. Leptin is produced by both adipose tissue and skeletal muscle and is an important regulator in whole body energy homeostasis [56,57]. Leptin functions as a "satiety hormone," whereas ghrelin is considered a "hunger hormone" [58]. Ghrelin promotes weight gain and lowers the uptake of glucose by reducing insulin secretion [58]. A major anabolic regulator is insulin, by regulating the uptake of amino acids and blood glucose into muscle, and regulating metabolism [59]. By indirectly activating the mTORC1 pathway, insulin growth factor (IGF)-1 induces hypertrophy [60]. Together with insulin, IGF-1 and growth hormone form a regulatory axis, which regulates cell apoptosis versus growth [61]. Sex steroid hormones promote anabolism. Exercise increases sex steroid hormone levels [62]. Low levels of sex steroid hormones can be increased with, for example, testosterone replacement therapy, but leads to increased risk for prostate cancer, stroke, and myocardial infarction [63]. Medical treatment of disease can disturb the internal milieu. For example, radiation therapy in the head and neck region, including the thyroid gland, may lead to hypothyroidism [64]. Exogenous systemic corticosteroids or antianabolic agents may cause decreased anabolic competence as well [65].

Thus, as the hormonal/metabolic derangements in DRM, caused by the disease itself or by adverse effects of treatment, are complex and dynamic, monitoring is difficult. Despite associations between possible blood markers and risk for DRM, no simple measures have emerged that reliably reflect the metabolic derangements and can guide clinical management.

Practical and comprehensive assessment of anabolic competence and DRM

As DRM is characterized by loss of lean body mass and function. Effective treatment of DRM must result in measurable outcomes, such as improved lean body mass, muscle function, and immune function. To proactively improve a patient's nutritional status, an easy and practical assessment and monitoring tool is essential. Assessment and monitoring requires inclusion of the domains of anabolic competence, as well as outcome measures for the clinical setting to acquire information on the current state of DRM, the progression of DRM, and the effect of intervention on DRM.

Despite improvements in the understanding and recognition of the importance of anabolic and catabolic stimuli in the development and reversal of DRM, the PG-SGA was specifically developed in the context of and operationalizes the paradigm of anabolic competence [7,66]. The PG-SGA has demonstrated good validity and is a bedside instrument that can screen, assess, and monitor nutritional status and risk factors, and can be used to triage for multimodality interventions and to monitor the effect of these interventions [67]. The PG-SGA uses a patient-centric approach to address patient concerns and improve patient and health care professional (HCP) interaction. The domains assessed and monitored by the PG-SGA are as follows:

- changes in body weight;
- changes in nutritional intake;
- symptoms that negatively influence intake, absorption, and utilization of nutrients.;
- level of activities and function;
- conditions that increase nutritional risk or requirements;
- metabolic stress; and
- physical examination [66].

The PG-SGA captures and provides an overview of information, generated by both the patient and HCP, from different domains into one document that provides actionable information for, among others, the physician, the nurse, the dietitian, and physiotherapist, respectively. As such, it facilitates and enhances an interdisciplinary, multimodality treatment [66]. The studies available on reliability of the PG-SGA suggest good interrater reliability (90% agreement in PG-SGA categories between physician and dietitian) [68] and good agreement (intraclass correlation coefficient = 0.901) between dietitians [69], sufficient internal consistency (Cronbach's $\alpha = 0.722$) [70], and good reproducibility (test–retest: $r = 0.866$) [70]. A detailed explanation of the PG-SGA including its scoring, content validity, and good predictive value have been described elsewhere [66,71]. One of the potential barriers is that PG-SGA–naive HCPs may find the physical examination difficult, although comprehensible. Therefore, training is recommended, as 1 day of PG-SGA training improves perceived difficulty and comprehensibility [72]. However, perceived difficulty of the physical examination part of the PG-SGA remained below the acceptable level after 1 day of training despite clear improvements, and therefore requires additional training, more information, or both [74]. Another potential barrier is the perceived lack of time for applying the PG-SGA. However, the time needed to complete the patient and the professional components of the PG-SGA is <5 minutes, for both patients and professionals, respectively [71].

Discussion

Anabolic competence is vital for patients with DRM, whereby adequate nutrition alone does not resolve catabolism or increase anabolism. Net catabolism, as represented by decreasing lean body mass, leads to significantly compromised outcomes and will remain ongoing if other complementary conditions needed for anabolic competence are not met. The paradigm of anabolic competence serves as a theoretical base, from which clinical implications can be made for each of the domains of anabolic competence.

The clinical implications are, among others, establishing a daily protein intake of 1.2 to 1.5 g/kg BW, the encouragement of patients to stay out of bed or chair when possible to avoid physical inactivity, and to monitor influencers of the internal milieu (e.g., inflammatory activity by measuring change in C-reactive protein levels as a reflection of anti-inflammatory treatment effectiveness and adequacy of relevant hormone levels). In this narrative review, we emphasized that, rather than solely concentrating on nutritional intake, other factors that determine anabolic competence, that is, physical activity and influencers of internal milieu, are imperative for achieving and maintaining a good nutritional status and thus must be integrated into the assessment, monitoring, and treatment of DRM.

Ultimately, integration of clinically relevant and practical measurements to assess modifiable factors contributing to anabolic competence could serve as the foundation for decision making and intervention to optimize an interdisciplinary multimodality approach, and could contribute to both the prevention and treatment of DRM.

Current knowledge about the separate domains involved in patients with DRM implicates that further research is needed toward monitoring the effectiveness of treatment in DRM patients aimed at optimizing all three domains of anabolic competence. Therefore, at least changes in lean body mass, muscle function, and inflammatory and hormonal status must be monitored.

Conclusion

We consider the paradigm of “anabolic competence” and its practical application as highly valuable to daily clinical practice. Therefore, we propose to implement the concept of anabolic competence in clinical practice for the treatment of DRM. Standardized, reliable, and practical instruments that incorporate the domains of anabolic competence, such as the PG-SGA, could help to improve the prevention, treatment, and monitoring of DRM.

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