Progress in Nutrition 2018; Vol. 20, N. 3: 447-454 DOI: 10.23751/pn.v20i3.6987

Original article

The role of muscle in disease-related malnutrition. Decalogue of Good Practices

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Summary. *Introduction:* Disease-related malnutrition (DRM) is a major problem in Western societies, and the consequences pose a high economic burden. DRM affects not only muscle mass but also muscle function. However, there are currently few tools and strategies to enable a proper assessment of muscle and estimate muscle loss associated with malnutrition. *Objective:* To highlight the current situation of deficiency in the assessment of muscle mass and function in malnourished patients and to develop recommendations for the inclusion of muscle assessment as an element of measurement in the nutritional recovery of patients with DRM. *Methods:* A multidisciplinary expert panel comprised of twenty-one physicians from Spain was convened to review, refine and summarize current recommendations on the assessment, diagnosis, and nutritional and functional treatment of malnourished patients. *Results:* The experts highlighted the impact of DRM on muscle, as well as the crucial role of this organ in the correct nutritional, metabolic and functional recovery of patients. The lack of strategies for the assessment of muscle in DRM led to a proposed Decalogue of Good Practices for the optimal treatment of these patients. *Conclusion:* The review is intended to guide in the nutritional and functional recovery of patients with DRM, based both on consensus opinions of experts and on the most recent scientific evidence in the field. The proposed Decalogue provides a comprehensive approach to the management of the malnourished patient.

Key words: disease-related malnutrition, nutritional assessment, muscular assessment

Abbreviations

DRM: Disease-related malnutrition;
HMB: β-hydroxy-β-methylbutyrate;
NRM: Nutrition, Recovery and Muscle;
FIM: Functional Independence Measure;
ONS: Oral nutritional supplement.

1. Introduction

Disease-related malnutrition (DRM), can be defined as the "subacute or chronic state in which several degrees of overnutrition or undernutrition are combined with an inflammatory pattern, resulting in changes in body composition and functionality" (1). It is a problem of enormous proportions in Western societies, where the cost exceeds € 120 billion per year in the European Union (2). A high percentage of hospitalized patients suffer from malnutrition, reaching 23% in Spain (37% among patients over 70 years of age), (3) although this is a universal problem recognized by the European Council in the ResAP resolution (4).

DRM affects not only muscle mass, but also its function. The most evident sign of malnutrition is weight loss and since muscle constitutes a significant percentage of body dry weight, it is one of the organs most affected by adaptive changes as a result of DRM. At present there are a scarce number of tools and strategies, both anthropometric and biochemical, that allow an accurate evaluation of both muscle mass and function, to estimate the muscular involvement associated with malnutrition (5).

This guide describes the current situation related to the deficiency in the assessment of muscle mass and function in malnourished patients and proposes the optimal parameters to include, incorporating muscular assessment as an element of measurement in the nutritional recovery of patients with DRM. The guide aims to serve as a reference for health professionals involved in the management of patients with DRM, in order to help improve their clinical situation; as well as providing information to the administrative entities of the hospital sector involved in the care of these patients. It also proposes a Decalogue of Good Practices to guide professionals in the comprehensive treatment of malnourished patients.

2. Methods

A multidisciplinary working group, called "Nutrition, Recovery and Muscle (NRM)" was created, consisting of 21 Spanish physicians (endocrinologists, rehabilitators, geriatricians and sports medicine) with extensive experience in nutritional and functional assessment, diagnosis and treatment of malnourished patients. Basing on the literature review regarding the present status of DRM treatment and the experience in clinical practice, the group reviewed, refined and summarized current recommendations on the assessment, diagnosis, and nutritional and functional treatment of malnourished patients. The consensus document includes a series of recommendations about the role of muscle in DRM and presents a Decalogue of Good Practices, which proposes muscle assessment as an integral part of the patient's treatment.

3. Results

3.1. Implications of malnutrition

In the presence of malnutrition, muscular plasticity acts as a compensatory mechanism of the organism, allowing the metabolic balance to be altered (6). However, sustained protein-calorie malnutrition leads not only to a deterioration of the structural functions of the muscle but also to the metabolic ones, which, if not properly treated, can make it difficult to recover nutritional and functional status.

Correct diagnosis and an appropriate treatment plan play a key role in patient recovery.

3.2. DRM: Methods of screening and nutritional assessment

Nutritional screening is the starting point needed to ensure that all individuals who can benefit from nutritional support are easily identified and that those who cannot benefit are not unnecessarily treated. The nutritional screening tools validated in adults include: Nutritional Risk Screening (NRS), Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA) (5). These tools do not include muscle assessment, with the exception of partial assessment of the MNA scale.

Nutritional assessment aims to characterize the nutritional status of patients with malnutrition or suspected risk of malnutrition, in order to establish a therapeutic plan (7). The procedure is based on a joint use of techniques (clinical and dietary history, physical examination, anthropometry, biochemical parameters and evaluation of interactions between medicines, nutrients and disease) (7). Nutritional assessment scales include some indirect measurement of lean mass. Basic anthropometry does not evaluate lean mass, except for the muscular circumference of the arm; while advanced anthropometry evaluates the muscle indirectly (impedance measurement) or directly (DEXA), with the latter being little used and not standardized in clinical practice. There are also no biochemical parameters that allow an easy evaluation of muscle mass.

As part of the nutritional assessment, hand grip dynamometry is an indirect method that is being introduced to assess muscular functionality. However, reference values are only available for some subpopulations in Spain (8). In geriatric and rehabilitation consultations the *Short Physical Performance Battery* (9) is also used as functional test.

Thus, the assessment of the muscle compartment is scarce in screening and nutritional assessment methods, and there is generally a shortage of anthropometric and biochemical tools that allow a correct evaluation of the muscle mass and function in the malnourished patient.

3.3. The role of muscle in the context of the DRM

Malnutrition affects muscle function even before changes in mass are perceived, so alteration in nutrient intake, digestion or absorption can have a significant impact on muscle health, regardless of changes in muscle mass (10).

The description and redefinition of the muscle as a secretory organ releasing anabolic and catabolic peptides expressed and produced by the muscle fibers, called myokines, has provided a conceptual basis for understanding how skeletal muscle communicates with other organs or tissues to maintain the body homeostasis (11). This shows that in addition to the functions related to movement, power generation and postural maintenance, muscle has a metabolic and even endocrine function (12, 13); as well as an important role in the beneficial effects of exercise on health, and on the pathogenesis of several diseases, such as obesity, sarcopenia and diabetes (11). Therefore, skeletal muscle is increasingly recognized as one of the main regulators of energy and protein metabolism through its communication network with different organs of the body (14).

If the muscle's ability to maintain homeostasis is diminished due to malnutrition, muscle function, including strength or metabolic balance, may be affected. Thus, muscular deterioration or atrophy not only affects the motor function of the muscle, but also the metabolic function, mainly due to the loss of mitochondria and their enzymes and of muscular capillaries (12).

During the hospital stay, important changes occur in the patient due to altered nutrient intake, immobilization and inflammation, which can be included within the concept of metabolic atrophy. Thus, in the absence of contraction, atrophy occurs in both muscle size and function, decreasing not only fiber thickness but also capillary density and muscle metabolic activity (13). DRM is also commonly associated with an onset of chronic or acute disease and the presence of an inflammatory component. To compensate this situation, the organism undergoes an adaptive response. Due to the plasticity capacity of the muscle, this tissue is one of the first to act as a defense against malnutrition.

Muscle plasticity implies a change in the flow and utilization of carbohydrates and proteins as metabolic substrates. Changes related with plasticity include not only the export and use of muscle proteins (as a source of energy to support major functions), but also a decrease in the availability of amino acids throughout the body (mainly glutamine), which affects metabolic functions, oxidative response, protein turnover, muscle mass and strength/contractility. If sustained malnutrition is not adequately treated, the muscle's buffering capacity can be critically overridden. Under these conditions, and as a result of the general body deterioration (e.g. muscular insulin resistance), patients can enter a vicious circle of complications that affect quality of life, prolong hospitalization, and increase risk of readmission, morbidity and healthcare expenses (Figure 1).

3.4. Functional muscle assessment in malnourished patients

There is a strong association between malnutrition and disability that opens the possibility of multiple interrelations between nutritional improvement and motor recovery (14). Several tools are available to determine the patient functional status, which can be grouped into generic and designed for specific conditions. The generic ones assess the functional situation independently of the cause of disability. As generic scales, the following stand out: *Patient Evaluation and Conference System* (PECS), *Katz Activities of Daily Living Scale* (KADLS), *Barthel Index*, Level of Rehabilitation Scale (LRS) and *Functional Independence Measure* (FIM). The Barthel index (15) is widely used in the geriatric setting to assess the patient's functional capacity. This index contains 10 items and its total score varies between 0 (total dependence) and 100 (complete independence).

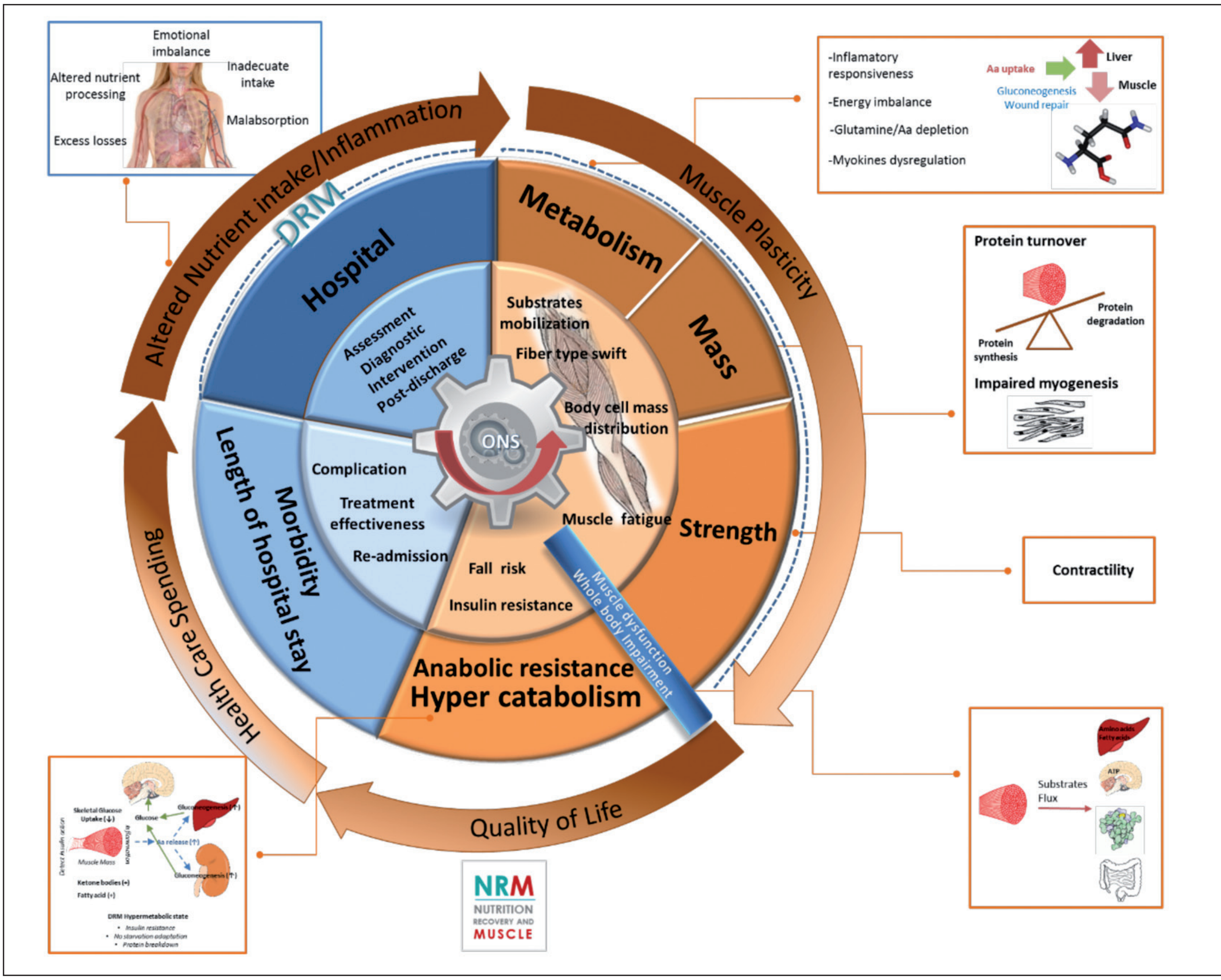

Figure 1. Response cycle in the DRM. If DRM is not properly diagnosed and treated, patients may enter a vicious circle of dysregulation of muscle function that will ultimately affect the nutritional and functional recovery of patients, their quality of life and, at the same time, add to health expenses due to morbidity and increased hospital stays generated by malnutrition. Figure abbreviations: Aa: Amino acids, ATP: Adenosine Triphosphate, DRM: Disease-related Malnutrition, ONS: Oral Nutritional Supplements

In the rehabilitation field, the FIM scale has displaced other generic scales as a global measure of functional disability, having created a benchmark between hospital rehabilitation services in the United States and in other countries. The importance of the FIM scale (16) and Barthel index is that they allow to establish a progression in the acquisition of functional abilities that depend largely on muscular training.

Also, in the assessment of the patient's functional status is important to explore muscle strength, either through measurement of the function of a muscle group (e.g. lower limb while standing or walking), or more analytically by a muscular balance (manual or instrumental).

In outpatients, timed tests, such as the 6-minute walk test (17) and timed up and go (18), among others, allow assessment of muscle mobility and function. It is important to note that these tests have shown a high correlation with important outcome variables, such as survival and quality of life.

3.5. Treatment plan

Optimal nutritional status and energy balance are essential for the rehabilitation of muscle mass and function. Therefore, the integral approach of the malnourished patient should include an adequate nutritional treatment and a physical exercise plan adapted to the individuals' clinical situation, in order to avoid muscle and energy metabolism deterioration, promoting overall health, well-being, and recovery from disease (14).

The main objective of nutritional support is to minimize the protein-calorie imbalance in order to achieve the maximum possible functional independence. Moreover, there is scientific evidence demonstrating the efficacy of nutritional support with specific nutrients to improve certain aspects of DRM, such as the anti-inflammatory (19) or immune-modulatory effects (20) of some nutrients regarding inflammation (1) and impaired immune system function associated with DRM (3).

In the area of muscle recovery, there is still a significant lack of scientific knowledge regarding the pathophysiological mechanisms that relate nutrition and muscle in the disease, as well as clinical studies that demonstrate the joint effect of nutrition and exercise on the main determinants of the disease.

3.5.1 Nutritional and functional support

The broad spectrum of malnutrition in clinical practice makes it necessary to determine the protein, calorie and specific nutrient requirements according to each clinical situation. Furthermore, the nutritional support focused on the muscle implies a whole morphological, metabolic and functional study within the context of malnutrition.

Loss of muscle mass is very important clinically because it leads to decreased strength and exercise capacity. The key to the development of an optimal treatment plan aimed at skeletal muscle recovery and muscle strength as key factors of clinical response lies in clinically distinguishing the causes of muscle loss (21).

Energy requirements

For the calculation of energy requirements, as well as for the selection of the enteral nutrition formula, the classical therapeutic targets should be considered, such as the recovery of lost weight or the improvement of analytical parameters, together with specific targets of muscle recovery, such as lean mass recovery (impedance, arm circumference) and functional recovery (dynamometry/gait test) of the patient.

Protein requirements

There are no specific nutritional recommendations related to the requirements for protein intake in situations of loss of muscle mass or muscle function. The general recommendations of protein intake in adults are around 1.0 -1.2 g of protein/kg of weight/day. Older adults with an acute or chronic pathology need a higher intake of protein (1.2 - 1.5 g/kg body weight/day). This requirement may reach 2.0 g/kg body weight/day in severe malnutrition and severe stress (22).

Specific nutrients

- Amino Acids

The utility of certain supplements, such as glutamine or arginine, in patients with severe acute diseases to improve physical performance and assist in the restoration of lean mass and neuromuscular function, is an area of research that needs more placebo-controlled studies to determine the efficacy and optimal dosing of these (23).

Dietary enrichment with branched-chain amino acids, including leucine, appears to have positive effects on specific signaling pathways for muscle protein synthesis. There are studies in elderly sarcopenic patients with administration of 2.5 and 2.8 g of leucine/day that show an improvement in muscle mass or in physical performance, but not in muscle strength. Also, it has been observed that leucine supplementation in combination with resistance exercise training improves leg muscle mass and muscle strength, but not physical performance (24).

- Omega-3 Fatty Acids

There is extensive literature on the effects of omega-3 fatty acids on muscle parameters in cachexia, with favorable results in certain clinical circumstances, especially in patients with cancer (25). The anti-inflammatory properties of omega-3 fatty acids could improve muscle anabolic resistance in older adults, improving the rate of muscle protein synthesis (26).

- Supplementation with β-hydroxy-β-methylbutyrate (HMB)

HMB is an active metabolite of leucine, present in some foods (avocado, citrus, cauliflower, alfalfa). It is produced naturally in the body, but insufficiently in situations of metabolic stress. HMB acts as a substrate for cholesterol synthesis in the muscle cell and in turn also regulates protein metabolism, inhibiting its degradation and stimulating its synthesis (27).

HMB has shown positive effects on lean body mass and strength following exercise, and in disease-related muscle wasting. In clinical trials, the administration of HMB is able to attenuate the decrease of muscle mass in patients submitted to 10 days of absolute rest and 8 weeks of later recovery, which emphasizes its potential effect regardless of the physical activity, aspect of special interest in the field of hospital malnutrition, since it frequently involves prolonged periods of rest (28). A growing body of evidence suggests HMB may help slow the muscle loss experienced in sarcopenia and improve measures of muscle strength (29). Moreover, in elderly malnourished patients, the use of a high-protein oral nutritional supplement (ONS) containing HMB is associated with a 50% significant reduction in mortality risk at hospital discharge (4.8% vs 9.7%; p = 0.018), compared with placebo (30).

In those clinical circumstances that involve a nutritional and muscular deterioration, the use of specific ONS to target muscular recovery can support improvements in nutritional, metabolic and muscular parameters; especially when associated with a therapeutic exercise plan.

3.5.2 Therapeutic exercise

The treatment plan should always include therapeutic exercises, even in patients with a poor nutritional and functional status. Muscle contraction, even when small, contributes to improved muscle protein synthesis and decreased atrophy.

Three types of exercise can be used to increase muscle strength: isometric, isotonic and isokinetic. In isometric exercise, the muscle maintains a constant length when a resistance is applied, without changes in the joint position. With aging, the isometric contraction decreases (31). Isotonic exercise is performed at constant power and is the best known and practiced. These contractions occur along with amplitude of movements against resistance, the velocity is not stationary and is divided into two phases: a) concentric or positive phase: contraction with shortening of the muscle and b) eccentric or negative phase: contraction with elongation of the involved muscle. Isotonic training is effective for improving strength and should be considered as a key part of increasing muscle strength. To do this, there is a great variety of methods and equipment: weights, fixed resistors, cables and pulleys, machines of constant and variable resistance, as well as devices with elastic, hydraulic or robotic resistance; all having as a common goal achieve a voluntary contraction during training, according to the patient's situation (32). For its part, the isokinetic exercise tries to mobilize the maximum force-generating capacity of a muscle along a complete joint path at constant speed, for which specific machinery is needed.

A training program should include (in patients whose condition allows): warm-up, aerobic exercise, strength training and a cooling period. In very impaired patients, only the act of contracting the muscles and trying to "force", will serve to enhance muscular trophism and its beneficial effects. Aerobic training will include low-impact activities: walking, pedaling, swimming, or climbing stairs. Strength training should target the large muscle groups, which are important for the activities of daily living: legs, trunk, shoulders, triceps, biceps, leg triceps, abdominals and waist. Strength training can be done at low, medium or high intensity. This intensity is defined by maximum repetition (MR). To achieve muscular enhancement, it is recommended to train at 60 to 80% of 1 MR, in three sets of 8 to 12 repetitions, three times a week (33).

It is important to remember that only strength training, that is, muscular contraction against resistance, is the one that can stop or reverse sarcopenia. There is a loss of muscle strength of 5-10% per week if muscle specific strength training is ceased (34).

4. Conclusion

The achievement of an adequate nutritional status and energy balance is fundamental for the recovery of mass and muscle function in the malnourished patient. Appropriate nutritional supplementation should, in those cases where it is possible, be accompanied by an exercise plan to maintain trophism and muscle protein synthesis. There is evidence of the benefit of this combined intervention. All this shows the need to implement strategies and methods for measuring muscle mass and function that allow documentation of the impact caused by DRM on these parameters, as well as the evolution of their recovery.

Decalogue of Good Practices:

1. The diagnosis of malnutrition and muscular deficit is basic to improve the nutritional management of patients, since both worsen prognosis.
2. Nutritional screening, through any of the available validated tools, should provide an estimate of the risks associated with malnutrition. The 'MUST' tool is useful in ambulatory and hospitalized patients, both in hospitals and the home setting.
3. Muscle evaluation should be integrated in the nutritional assessment process, including body composition data (impedance measurement), function (dynamometry), or any other tool that assesses muscle function.
4. Complete muscular functional assessment should include evaluation of muscle strength through measurement of a muscle, or muscle group, by muscle balance (manual or instrumental) and timed tests in outpatients.
5. The integrated approach that supports the nutritional and functional recovery of the patient must be based on an intervention that includes nutritional treatment and an adequate exercise plan. For correct protein synthesis, the muscle needs the stimulation via muscular contraction, as well as proper nutrition.
6. The objective of the intervention is to achieve an overall improvement of the disease in out-patients, as well as to improve muscle composition and functionality during hospital admission.
7. The provision of nutritional support should meet the patients' macro- and micronutrient requirements, and should be adapted to each clinical situation.
8. The recommendation for the administration of other specific nutrients should be based on relevant health outcomes with proven scientific evidence.
9. An exercise training program must adapt, in its different phases, to the characteristics and clinical situation of patients, including aerobic and strength training exercises, combined with nutritional supplementation.
10. Clinical follow-up of patients should include anthropometric, biochemical and muscular functionality parameters to monitor adequacy of nutritional and functional recovery.

Funding:
This study is sponsored by Abbott Nutrition.

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