Accepted Manuscript

Defining malnutrition: a plea to rethink

P. Soeters, F. Bozzetti, L. Cynober, A. Forbes, A. Shenkin, L. Sobotka

PII: S0261-5614(16)31272-9

DOI: 10.1016/j.clnu.2016.09.032

Reference: YCLNU 2941

To appear in: *Clinical Nutrition*

Received Date: 9 February 2016

Revised Date: 19 August 2016

Accepted Date: 30 September 2016

Please cite this article as: Soeters P, Bozzetti F, Cynober L, Forbes A, Shenkin A, Sobotka L, Defining malnutrition: a plea to rethink, *Clinical Nutrition* (2016), doi: 10.1016/j.clnu.2016.09.032.

Defining malnutrition: a plea to rethink.

Authors: Soeters P.[1], Bozzetti F.[2], Cynober L.[3], Forbes A.[4], Shenkin A.[5], Sobotka L.[6]

[1] Faculty of Medicine and Life Sciences, Maastricht University Medical Centre, Maastricht, the Netherlands
[2] Faculty of Medicine, University of Milan, 20100 Milan, Italy
[3] Service de Biochimie, Hôpital Cochin, AP-HP, Hôpitaux Universitaires Paris Centre, and Biological Nutrition laboratory, EA 4466, Faculty of Pharmacy, Paris Descartes University, Paris, France.
[4] Norwich Medical School, University of East Anglia, Norwich, UK
[5] Department of Clinical Chemistry, University of Liverpool, Liverpool, United Kingdom
[6] Third Department of Medicine, Medical Faculty Hospital Hradec Králové, Charles University, Prague, Czech Republic.

1 Introduction

In a recent issue of Clinical Nutrition (1) a sizeable group of knowledgeable ESPEN members published a consensus report on Diagnostic Criteria for Malnutrition in both clinical and population setting. To arrive at this report, clinical scientists were chosen to represent the clinical fields of medicine, surgery, intensive care, oncology and geriatrics. Communication occurred in several ways and after each step in the procedure confirmation was sought from the participants. Ultimately a ballot was organized among the members of ESPEN to seek approval of the statements in the report.

Two alternative ways to diagnose malnutrition were formulated.

1. BMI < 18.5 kg/m^2
2. Unintentional weight loss > 10% of initial body weight irrespective of time or > 5% in the last 3 months combined with either
   a. BMI < 20 kg/m^2 if < 70 years of age, or BMI < 22 kg/m^2 if older than 70 years or
   b. FFMI < 15 and 17 kg/m^2 in women and men respectively.

Despite these efforts we have serious concerns regarding the conclusions drawn because they might add to the confusion rather than bringing clarity. In this commentary we will try to point out the shortcomings of the present "consensus" in this regard, and propose to stick to the earlier consensus statements published in 2010, endorsed by ESPEN (2) and ASPEN (3), which included a rational approach to the definition and assessment of malnutrition. In our opinion this can be achieved only when etiological factors such as inflammation and under- or overnutrition are considered. We will restrict this commentary to the undernourished state and its relationship to malnutrition states. In our opinion, it is not possible to dissociate the ways to diagnose malnutrition from its definition.

2 Definition of Malnutrition

Part of the confusion in the nutritional world arises from the interpretation of the term "Definition". *A definition is a precise statement of the nature of a thing or condition.* In the nutritional and metabolic world we specifically want to define nutrition related disorders. Several efforts have been made in the past to formulate a definition to describe precisely the pathophysiology of

undernutrition/malnutrition as it is encountered in the majority of individuals considered malnourished, both in areas with endemic malnutrition and in clinical settings.

A century ago two forms of undernutrition were distinguished in children in areas with endemic malnutrition. Marasmus was considered to result from lack of both energy and protein, and typically is characterized by loss of fat free mass and fat mass, without oedema and with relatively normal visceral proteins including albumin. Kwashiorkor was considered to result specifically from lack of intake of protein, and its phenomenology included oedema, disturbances in growth and colour of hair, skin lesions,fatty liver and hypoalbuminemia. The kwashiorkor children showed less growth retardation suggesting that their malnutrition was of more recent onset.(4) Later research revealed that this phenomenology was not restricted to children but also occurred in adults.(5) It has been suggested that the difference in symptomatology in endemic malnutrition resulted from the development of infectious diarrhoea: chronic in marasmus, acute in kwashiorkor and often occurring after suffering from measles or malaria (6, 7). More recently, some evidence has been published from a study of identical twins in Malawi, that differences in the gut microbiome were responsible for kwashiorkor type malnutrition occurring in one child of a pair of identical twins and marasmic malnutrition in the other. (8) Importantly the design of the study helps to confirm that it is unlikely that differences in diet were responsible for the differences in phenotype. Waterlow also questioned the postulated role of differing diets. (4)

In the 1960s and 1970s it became increasingly clear that the features of kwashiorkor type malnutrition in our hospitals were predominantly related to infectious or non-infectious inflammation (5). In addition, as long ago as the early 1930s Cuthbertson (9) had already pointed out that the inflammatory effects of trauma included net nitrogen losses. Although the concepts were correct and accepted by many clinicians in ESPEN, the nomenclature was not widely applied in clinical nutrition.

When observing severely malnourished individuals in the developed world as well as those in areas with endemic malnutrition, it is clear that their functions are impaired in every imaginable respect.(10-12) Indeed, insufficient food intake can only be considered to be significant when this has led to functional disturbances. Therefore in the 1980s the concept that diminished function is an essential element of malnutrition was developed within the ESPEN community (13). The following definition was presented in courses and congresses:

1. *Malnutrition is a subacute or chronic state of nutrition, in which undernutrition has led to a change in body composition and diminished function.*

In the remainder of this manuscript the term “function” encompasses muscle function, cognitive function and immune function, supporting a host response leading to successful clinical outcome, appropriate growth in children, regeneration, restored quality of life and long term survival. The concept was strongly promoted by the BAPEN community (14), who added “clinical outcome” as a consequence of biological functioning to the definition. This was included in the ESPEN basic and advanced courses and in the third edition of the so-called “blue book” (12). In addition both undernutrition and overnutrition were considered to be part of the malnutrition spectrum, leading to the following definition: (15)

2. *Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size, composition), body function and clinical outcome.*

A crucial problem with this definition is that there is no linear relationship between deficiency or excess of nutrients and body composition and function. This is because the state of malnutrition in clinical practice and in areas with endemic malnutrition is not often exclusively the result of a deficiency of nutrients. It is also substantially influenced by the presence of disease, chronic infection and other stressful factors leading to inflammation, which influences body composition, function, longevity and clinical outcome.(12, 16, 17) It is equally important that the catabolic effects of non-infectious or infectious inflammation cannot be overcome by nutritional support alone. (18) At best a beneficial healing response may be supported when inflammatory activity is long standing and cannot be rapidly treated.

If the nutritional world therefore wants to assess not only whether the individual does not eat or absorb enough or overfeeds, but also to assess the changes in body composition and functions to which this has led, then inflammatory status should be taken into account. In this way nutritional assessment identifies the pathophysiological state of the individual, and also includes assessment of the risk not to recover well from trauma and disease, and to have a low life expectancy. This is more relevant in clinical practice. These considerations have been the underlying reasons to attribute the "mal" in malnutrition to be more than under- or overnutrition but to view it as a syndrome consisting of inadequate nutrition and inflammation. This led to the following definition (19):

3. *Malnutrition is a subacute or chronic state of nutrition, in which a combination of varying degrees of under- or overnutrition and inflammatory activity has led to changes in body composition and diminished function.*

Essentially inflammation has been added, but the other aspects might be adapted according to definition 2. for instance by adding "clinical outcome". The definition was included in the ESPEN LLL module on malnutrition, is included in the fourth edition of the blue book (20), and is consistent with consensus statements published in JPEN and Clinical Nutrition, endorsed by ASPEN and ESPEN. (2, 3)

3 Diagnosis of Malnutrition

In the Shorter Oxford English Dictionary "diagnosis" is defined as "*Determination of a diseased condition by investigation of its symptoms*". In medicine diagnosing a specific disease or condition requires identifying the causative micro-organism or other non-infectious causes and the typical symptoms and sequelae. Along similar lines, diagnosing malnutrition requires identifying the causative factors, their consequences for body composition and the resulting functional disturbances. Although in general more severe disease roughly corresponds with more severe inflammation, the inflammatory activity itself should be assessed specifically because some disease entities, considered "severe" and which have a major impact on nutritional intake are not associated with severe inflammation but are largely caused by (semi-)starvation alone. Examples include intestinal pseudo-obstruction, anorexia nervosa, swallowing disorders due to cerebrovascular events or dementia, all of which can produce a major reduction in nutritional intake, but with variable and sometimes only

minor systemic inflammation. In these situations nutritional support is far more effective in preserving muscle mass and body weight than when severe inflammation is present.

Inflammation is a universal reaction to disease, trauma or surgery and, when substantial and persisting, leads to substantial loss of fat free mass; moreover, it is connected with fluid retention. Even when fat free mass solids are not yet markedly decreased, pre-existing inflammation negatively influences host response, healing and survival.(21, 22) This is even truer when dealing with infectious inflammation. Consequently, it appears mandatory to assess "disease severity" not (only) on the basis of a formal diagnosis but also on the basis of the consequences of this disease entity for appetite and food intake, ability to ingest and absorb nutrients, and the inflammatory activity itself, which may be assessed for instance by general laboratory parameters like haemoglobin, negative acute phase proteins like albumin and transthyretin (prealbumin), and positive acute phase proteins such as C-reactive protein (CRP) (13, 23-26). It is noteworthy that disease severity is a component of almost all scores aiming to screen patients at risk of malnutrition, malnourished patients and those who will benefit from nutritional support.

Following from these views we have proposed to make this definition more practicable by weighting the different factors (inflammation, undernutrition) and their effects on outcome in defined populations, which would then allow assessment of the degree of malnutrition as a risk factor for outcome of surgical or medical treatment, growth and regeneration or quality of life and longevity (19).

4 Questions regarding the Consensus Statement.

The recent consensus statement (1) lacks most of the criteria outlined in the preceding paragraphs and therefore in our opinion does not meet the requirements for a definition and a diagnosis. It is rather an *agreement* as to when to call an individual malnourished, without taking into consideration its precise nature, causes and consequences. Importantly questions to answer are still how to define and diagnose malnutrition and how to arrive at consensus.

4.1 How to arrive at consensus?

When we set out to diagnose malnutrition we should first define what it actually is. Intuitively most of us consider patients in our hospitals, while we also have a vague impression of little children with swollen bellies and oedematous arms, and especially legs with very little muscle, in areas of the world with endemic malnutrition. Most of us also know that in both situations this state of malnutrition is associated with two major characteristics: undernutrition, implying a negative nutrient balance, and disease. Defining malnutrition in our view is synonymous with defining its pathophysiology. To this effect we must take the influence of both undernutrition and infectious/non-infectious inflammation into account, because only a minority of patients is exclusively undernourished. This is exactly what is claimed in the previous consensus statement endorsed by ASPEN and ESPEN (2, 3). It should also be emphasized that there is a progressive negative impact on survival depending on the degree of undernutrition and inflammation, and that therefore the thresholds which separate well-nourished and malnourished people may be in some way artificial (27).

The next step is to agree whether we only want to diagnose undernutrition, implying weight loss due to inadequate intake or digestion and intestinal absorption of food, or if we truly want assess the state patients/individuals are in with its consequences for body composition and function. If we only

want to know whether the individual is failing to ingest or absorb enough, we must realize that we will establish only one of the two major factors leading to diminished functional capacity in most of the people we treat, without establishing the often overriding influence of inflammation. What is worse is that we will not be able to set priorities for treatment, and that we will not know what benefit will be likely to result from nutritional support. The earlier consensus guidelines endorsed by ASPEN and ESPEN rightly underline that the benefit of nutritional support is blunted in the presence of severe inflammation, and that this knowledge should lead to prioritizing treatment of inflammatory causes, notwithstanding instituting nutritional support. Precise assessment, for instance of inflammatory markers like CRP, orosomucoïd (α1 –glycoprotein acid) and albumin in a composite approach with (negative) nutrient balance, fat free mass and clinical signs of inflammation will also permit the determination of whether a patient is improving or deteriorating (28, 29). It is therefore important to assess the two major elements leading to malnutrition.

A pitfall of the chosen approach described in the new consensus document (1) is that consensus conferences and voting sessions threaten not to arrive at the truth. If at the time of Galileo a vote had established whether the sun turns around the earth or vice versa, the consensus would have been that the earth is the centre of the universe.(30) When talking about science, the experts should have a decisive influence on the foundations on which an ultimate decision must be based. The participants in the voting sessions are obviously experts in several fields, but these do not always include pathophysiology and/or nutritional assessment methods.

4.2 How to detect nutritional risk and how to diagnose malnutrition?

Several screening methods have been devised, and within ESPEN the Nutritional Risk Screening (NRS 2002) method has been developed and has become popular (31, 32). It includes weight loss, diminished nutritional intake, BMI and disease severity. The equally popular MUST score includes similar elements and is also adequate (33). Of note, abnormalities in these factors are graded according to their severity. The numbers acquired add up to a score reflecting the risk of malnourishment. Patient cohorts with a high risk score have been shown to benefit more often from nutritional support than patient cohorts with a low risk (34). It is a concern that these scores and others mix causes (diminished food intake, disease severity) and consequences (weight loss, low BMI). If we wanted to know only whether an individual can generate an optimal immune and healing response, assessment of muscle, cognitive and immune function would suffice. When we also want to know what causes a decrease in these functions we must assess the two major causes: nutritional intake/digestion and/or the presence of inflammation. These last factors give guidance on how to treat. (Figure 1)

The accuracy of the screening methods and proposed diagnostic methods may also vary depending on whether we want to predict the outcome of surgery, chemotherapy or other types of non-nutritional treatment, the effect of nutritional treatment itself, growth and regeneration, long term survival or to assess quality of life. Consequently, the term “nutritional risk” is confusing because it is unclear which risks (i.e. risk of malnutrition or risk of nutrition-related complications) are assessed in the screening methods.

The diagnosis of malnutrition proposed on the basis of the new consensus procedure does contain BMI and weight loss, and, in principle, fat free mass index (fat free mass corrected for body size: FFMI). However, in most institutions this index will not be assessed routinely, although anthropometry and impedance measurements would be feasible. More sophisticated measures like CT scanning, MRI or DEXA are costly but may be adapted to a simpler and less costly application in nutritional assessment. Also PET-scanning will become increasingly available. At present these

methods to assess body composition are not used routinely anywhere, except in research (35). It should be pointed out however that most cancer patients undergo routine CT scanning to establish the stage of cancer before treatment and it would only require an adaptation in the software to obtain a similarly routine measure of fat free mass versus fat mass. Such methods might therefore in the future be validated and routinely employed in cancer patients, including establishment of normal values using large cohorts of healthy subjects.

The remaining items to diagnose malnutrition (or its risk) proposed in the consensus statement do not include food intake, inflammation or function. Measuring only BMI and weight loss will be far less discriminative than the NRS 2002 or the MUST (32). **It seems to be highly illogical first to use a risk screening tool that contains a number of crucial elements and subsequently to make the more precise diagnosis of malnutrition by assessing only a few of the same elements.**

On a population basis, body weight increases in the course of life until approximately 5-7 years before death due to an increase in fat mass, while fat free mass starts to decrease after approximately 30 years of age, leading to a gradual decrease of functional capacity.(36, 37) The decrease in fat free mass will develop unnoticed when only weight or BMI is taken into account. It is the result of comorbidity, inadequate composition of the diet, low physical activity, and very likely also due to the aging process itself and is therefore not completely preventable. Nevertheless, there are indications that exercise and increased protein intake may be beneficial (38). In the phase of increasing body weight the proposed diagnostic approach in the consensus statement, assessing only weight loss and BMI will not detect (the development of) low fat free mass and the resulting loss of functional abilities.

In another clinical scenario many individuals in younger age groups with sub-acute or chronic disease lose weight due to the catabolic influence of disease-related inflammation. This leads to shrinkage of fat free mass, even when nutritional intake is energetically adequate.(39) The Cederholm's et al consensus statement (1) on how to diagnose malnutrition will in this situation mistakenly lead to the conclusion that the individual is malnourished due to inadequate intake. This situation is even more complex, because weight loss with shrinkage of fat free mass solids may be obscured by oedema maintaining body weight. This phenomenon will not necessarily be detected by DEXA, CT scanning, MRI or impedance measurements. Only sophisticated methods like total potassium or nitrogen measurements would be adequate, but they cannot be performed routinely. This oedema results from increased capillary leakage caused by disease or trauma related inflammation and leads to an increase in extravascular interstitial space, and the distribution volume of albumin.(40) Albumin dilutes in this volume, leading to hypalbuminaemia, which therefore largely reflects inflammation and also indicates that the concentration of solids in this volume is decreased compared with healthy states.(25) Further research may establish the validity of hypalbuminaemia as a correction factor to compute fat free mass solids from morphometric fat free mass as, for example, measured by CT scanning. Management of such patients requires full understanding of the pathophysiology leading to the changes in body composition.

5 Consequences of the chosen approach to diagnose malnutrition.

Several problems may arise from the published consensus on "diagnostic criteria for malnutrition" (24). The consensus deviates from views expressed for decades in ESPEN (see **2. Definition of Malnutrition**). In clinical practice the presence of inflammation is known to influence symptoms and function significantly. This has been taught in the ESPEN advanced and basic courses, has been

published in nutrition and general journals and is included in the ESPEN blue book (fourth edition)(20). Similarly, the consensus statement significantly deviates from views present in other parts of the world and developed in collaboration with ESPEN, and could cause confusion. Even more, countries and nutrition societies have in recent years come close to agreement on how to define malnutrition, underlining the role of nutrition and inflammation. This led in 2010 to the two parallel papers with authors from 5 continents that were published in the JPEN and Clinical Nutrition and endorsed by ASPEN and ESPEN (2, 3). In these papers an identical statement was given regarding the definition/pathophysiology of malnutrition as given in italics in the third definition in section "**2. Definition of Malnutrition"**. The present ESPEN Consensus Statement deviates significantly from the papers and the other ESPEN endorsed activities mentioned. Finally, in a recent consensus meeting in ASPEN, the views expressed by ESPEN representatives as described in the Cederholm et al paper (1) were qualified as a controversy with views expressed by representatives of ASPEN, PENSA and FELANPE.(Jensen GL. Global Leadership Conversation: Addressing Malnutrition. JPEN 2016 Mar 18)

We must also realize that ESPEN has changed its name from reflecting artificial nutrition alone, to 'Clinical Nutrition and Metabolism'. Malnutrition is our main "disease" of interest and our practice will be handicapped when rejecting clinical and metabolic effects to be considered when diagnosing malnutrition. Only when we can adequately diagnose the cause and degree of malnutrition, quantitate the risk it carries for adequate host response, tissue function, growth and long term survival, establish priorities for treatment and offer adequate treatment, will we have more impact on clinical practice.

6 Conclusions and Recommendations

We suggest that the ESPEN community rethinks its views on how to define malnutrition and how to diagnose it. (see ways to diagnose malnutrition in Introduction; ref 1) The new statement may confuse the nutrition world. It is unsuitable to define treatment priorities and to predict effects of nutritional support.

The essence of our argument is that malnutrition is a condition involving a nutritional status which is "mal", that is bad for the patient in terms of impairing function and hence clinical outcome. It is therefore entirely appropriate, and indeed essential, that the diagnosis of malnutrition must include some aspect of function/clinical outcome. Cederholm has noted in his reply to a letter to the Editor (Mokaddem F. Clin Nutr.2016;35(1):237) that the consensus group required objective criteria for a diagnosis of malnutrition and that functional criteria are too non-specific. (Clin Nutr. 2016; 35(1):237) The objective criteria we propose include an assessment of nutritional state and inflammation (by plasma CRP and albumin), which if present will impair function more than poor nutritional state alone. By linking inflammation only to cachexia, Cederholm et al have ignored the importance of inflammation in the vast majority of malnourished patients, who require to have their inflammation controlled before nutritional support can be fully effective.

The participants of the consensus conference have not produced a set of criteria to diagnose malnutrition. They have produced a limited set of criteria to screen for malnutrition. Despite their stated intention, they note themselves that individuals identified by their criteria will require more detailed investigation to identify the subset with a true diagnosis of malnutrition, and with an understanding of the causes to ensure that appropriate treatment is commenced. They recommend first using a well-established screening tool such as NRS 2002, and then following this up with their diagnostic tool. Nowhere else in medicine when a disease is screened for using a number of tests, is the diagnosis confirmed by using only two of the same tests already included in the screening

procedure. To reach a diagnosis, more specific tests are needed than the screening criteria so that the screening data can be correctly interpreted.

For this purpose consensus should be reached which techniques to use to diagnose malnutrition and to assess function, to predict the capacity to overcome the metabolic and nutritional burden of disease treatment and define priorities for treatment.

A final recommendation regards nomenclature. In the consensus statement apparently no agreement was reached to use "undernutrition" or "malnutrition" to describe the malnourished state of our patients. In definition 3 in the subsection "**3 Definition of Malnutrition"** the term "malnutrition" is used for the state of nutrition of all our patients. The term "undernutrition" may then be used exclusively to indicate that the individual is or has been in a negative nutrient balance. We can opt to call such an individual "malnourished" but should specify that there is no or little accompanying inflammatory activity.

In summary, we propose that ESPEN reconfirms its earlier position that the definition of malnutrition should contain the following elements:

"Malnutrition is a state of disordered nutrition, in which a combination of varying degrees of over- or undernutrition and inflammatory activity has led to a change in body composition, diminished function and outcome."

Having agreed this definition, we recommend that tools be suggested and validated in different populations to make the diagnosis, based on the elements included in the definition.

Authors' contributions

All authors contributed equally to the manuscript.

Funding

This opinion paper was not funded in anyway.

Conflict of interest

The authors have no conflict of interest related to this opinion paper.

7 References

1. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015;34(3):335-40.
2. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. Clin Nutr. 2010;29(2):151-3.
3. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr. 2010;34(2):156-9.
4. Waterlow JC. Classification and definition of protein-calorie malnutrition. British medical journal. 1972;3(5826):566-9.
5. Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, Smith MF. Nutritional and metabolic assessment of the hospitalized patient. JPEN J Parenter Enteral Nutr. 1977;1(1):11-22.
6. Laditan AA, Reeds PJ. A study of the age of onset, diet and the importance of infection in the pattern of severe protein-energy malnutrition in Ibadan, Nigeria. Br J Nutr. 1976;36(3):411-9.
7. Whitehead RG. Infection and the development of kwashiorkor and marasmus in Africa. The American Journal of Clinical Nutrition. 1977;30(8):1281-4.

8. Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, Cheng J, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. Science. 2013;339(6119):548-54.
9. Cuthbertson DP. The distribution of nitrogen and sulphur in the urine during conditions of increased catabolism. Biochem J. 1931;25(1):236-44.
10. Bruce AC, Erik LP, Louise HB, Carol AP. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004;43(1):61-6.
11. Sullivan DH, Roberson PK, Johnson LE, Mendiratta P, Bopp MM, Bishara O. Association between Inflammation-Associated Cytokines, Serum Albumins, and Mortality in the Elderly. Journal of the American Medical Directors Association. 2007;8(7):458-63.
12. Iwata M, Kuzuya M, Kitagawa Y, Iguchi A. Prognostic value of serum albumin combined with serum C-reactive protein levels in older hospitalized patients: continuing importance of serum albumin. Aging Clin Exp Res. 2006;18(4):307-11.
13. de Jong PC, Wesdorp RI, Volovics A, Roufflart M, Greep JM, Soeters PB. The value of objective measurements to select patients who are malnourished. Clin Nutr. 1985;4(2):61-6.
14. Stratton RJ, Elia M, Green CJ. Scientific Criteria for Defining Malnutrition. Disease-related Malnutrition: an evidence-based approach to treatment: CABI Publishing, CAB International, Wallingford, Oxon OX10 8DE, UK; 2003. p. 1-34.
15. Meier R, Stratton RJ. Epidemiology of malnutrition. In: Sobotka L, editor. Basics in Clinical Nutrition. Third Edition ed. Prague, Czech Republic: Publishing House Galén; 2004. p. 31-7.
16. Potapov EV, Loebe M, Anker S, Stein J, Bondy S, Nasseri BA, et al. Impact of body mass index on outcome in patients after coronary artery bypass grafting with and without valve surgery. European heart journal. 2003;24(21):1933-41.
17. Arshad A, Rashid R, Benjamin K. The effect of disease activity on fat-free mass and resting energy expenditure in patients with rheumatoid arthritis versus noninflammatory arthropathies/soft tissue rheumatism. Modern Rheumatology. 2007;17(6):470-5.
18. Remels AH, Gosker HR, van der Velden J, Langen RC, Schols AM. Systemic Inflammation and Skeletal Muscle Dysfunction in Chronic Obstructive Pulmonary Disease: State of the Art and Novel Insights in Regulation of Muscle Plasticity. Clinics in Chest Medicine. 2007;28(3):537-52.
19. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren MA, Schols JM, Halfens RJ, Meijers JM, et al. A rational approach to nutritional assessment. Clin Nutr. 2008;27(5):706-16.
20. van Bokhorst-de van der Schueren MA, Soeters PB, Reijven PL, Allison SP, Kondrup J. Diagnosis of malnutrition-Screening and assessment. In: Sobotka L, editor. Basics in Clinical Nutrition. Fourth Edition ed. Prague, Czech Republic: Publishing House Galén; 2011. p. 21-32.
21. Volk HD, Reinke P, Docke WD. Clinical aspects: from systemic inflammation to 'immunoparalysis'. Chemical immunology. 2000;74:162-77.
22. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. Am J Respir Crit Care Med. 2001;163(2):316-21.
23. Soeters PB. Serum albumin and mortality. Lancet. 1990;6(3):267.
24. Ingenbleek Y, Bernstein L. The stressful condition as a nutritionally dependent adaptive dichotomy. Nutrition. 1999;15(4):305-20.
25. Soeters PB. Rationale for albumin infusions. Curr Opin Clin Nutr Metab Care. 2009;12(3):258-64.
26. Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, et al. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. Journal of Parenteral and Enteral Nutrition. 2003;27(1):1-9.
27. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-9.
28. Ingenbleek Y, Bernstein LH. Plasma Transthyretin as a Biomarker of Lean Body Mass and Catabolic States. Advances in nutrition (Bethesda, Md). 2015;6(5):572-80.
29. Ingenbleek Y, Young V. Transthyretin (prealbumin) in health and disease: nutritional implications. Annu Rev Nutr. 1994;14:495-533.

30. Soeters P, Bozzetti F, Cynober L, Elia M, Shenkin A, Sobotka L. Meta-analysis is not enough: The critical role of pathophysiology in determining optimal care in clinical nutrition. Clin Nutr. 2015.
31. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22(4):415-21.
32. da Silva Fink J, Daniel de Mello P, Daniel de Mello E. Subjective global assessment of nutritional status - A systematic review of the literature. Clin Nutr. 2015;34(5):785-92.
33. Elia M, Stratton RJ. Considerations for screening tool selection and role of predictive and concurrent validity. Curr Opin Clin Nutr Metab Care. 2011;14(5):425-33.
34. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-36.
35. Lodewick TM, van Nijnatten TJ, van Dam RM, van Mierlo K, Dello SA, Neumann UP, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? HPB : the official journal of the International Hepato Pancreato Biliary Association. 2015;17(5):438-46.
36. Dey DK, Rothenberg E, Sundh V, Bosaeus I, Steen B. Height and body weight in the elderly. I. A 25-year longitudinal study of a population aged 70 to 95 years. Eur J Clin Nutr. 1999;53(12):905-14.
37. Shatenstein B, Kergoat MJ, Nadon S. Anthropometric changes over 5 years in elderly Canadians by age, gender, and cognitive status. J Gerontol A Biol Sci Med Sci. 2001;56(8):M483-8.
38. Arentson-Lantz E, Clairmont S, Paddon-Jones D, Tremblay A, Elango R. Protein: A nutrient in focus. Appl Physiol Nutr Metab. 2015;40(8):755-61.
39. Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(3 Pt 1):745-52.
40. Fleck A, Raines G, Hawker F, Trotter J, Wallace PI, Ledingham IM, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet. 1985;1(8432):781-4.

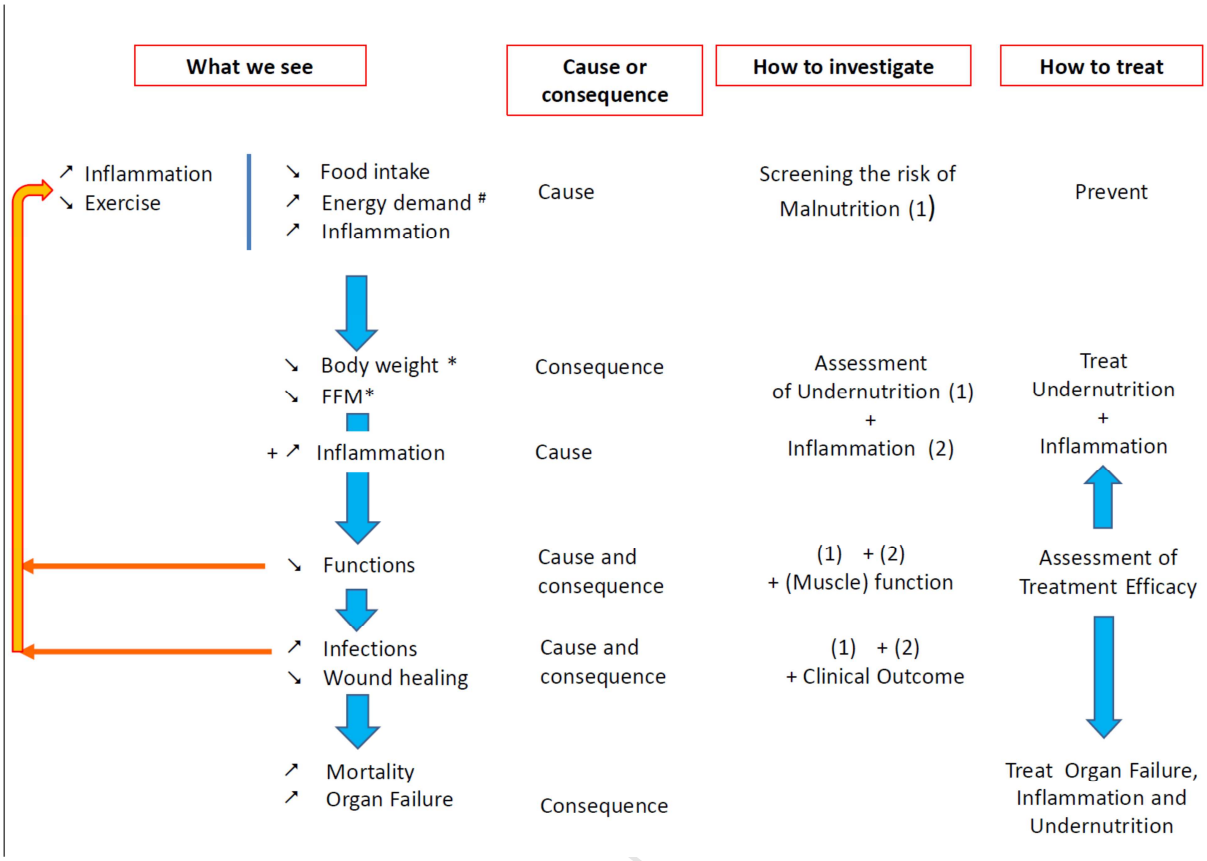

Figure 1. Schematic representation of the diagnosis and treatment of malnutrition

In the first column the chain of events is depicted leading from undernutrition/inflammation, to changes in body weight and composition along with functional disturbances. These elements jointly contribute to the risk of infection, inadequate wound healing, and increased mortality. In the second column cause/consequence relationships are listed. The art of investigation and clinical outcomes are described in the third column. The final column addresses treatment efficacy and adaptation to be employed in the case of initial failure.

* Inflammation and undernutrition both lead to loss of fat free mass, but in subacute and severe inflammation, although body weight/ fat free mass may increase with nutritional treatment, fat free mass solids will not.

Energy demand decreases when physical activity decreases and generally increases in diseased and other inflammatory conditions.