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Defining malnutrition: a plea to rethink

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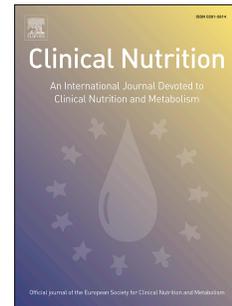
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1 Defining malnutrition: a plea to rethink.

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14 1 Introduction

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

21 Two alternative ways to diagnose malnutrition were formulated.

22 1. BMI < 18.5 kg/m²

23 2. Unintentional weight loss > 10% of initial body weight irrespective of time or > 5% in the last
24 3 months combined with either

25 a. BMI < 20 kg/m² if < 70 years of age, or BMI < 22 kg/m² if older than 70 years or

26 b. FFMI < 15 and 17 kg/m² in women and men respectively.

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

36 2 Definition of Malnutrition

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

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

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

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

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

71

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

74

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

83

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

87
88 A crucial problem with this definition is that there is no linear relationship between deficiency or
89 excess of nutrients and body composition and function. This is because the state of malnutrition in
90 clinical practice and in areas with endemic malnutrition is not often exclusively the result of a
91 deficiency of nutrients. It is also substantially influenced by the presence of disease, chronic infection
92 and other stressful factors leading to inflammation, which influences body composition, function,
93 longevity and clinical outcome.(12, 16, 17) It is equally important that the catabolic effects of non-
94 infectious or infectious inflammation cannot be overcome by nutritional support alone. (18) At best a
95 beneficial healing response may be supported when inflammatory activity is long standing and
96 cannot be rapidly treated.

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

105
106 3. *Malnutrition is a subacute or chronic state of nutrition, in which a combination of varying*
107 *degrees of under- or overnutrition and inflammatory activity has led to changes in body*
108 *composition and diminished function.*

109
110 Essentially inflammation has been added, but the other aspects might be adapted according to
111 definition 2. for instance by adding “clinical outcome”. The definition was included in the ESPEN LLL
112 module on malnutrition, is included in the fourth edition of the blue book (20), and is consistent with
113 consensus statements published in JPEN and Clinical Nutrition, endorsed by ASPEN and ESPEN. (2, 3)

114 3 Diagnosis of Malnutrition

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

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

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

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

145

146 **4 Questions regarding the Consensus Statement.**

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

152 **4.1 How to arrive at consensus?**

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

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

169 want to know whether the individual is failing to ingest or absorb enough, we must realize that we
170 will establish only one of the two major factors leading to diminished functional capacity in most of
171 the people we treat, without establishing the often overriding influence of inflammation. What is
172 worse is that we will not be able to set priorities for treatment, and that we will not know what
173 benefit will be likely to result from nutritional support. The earlier consensus guidelines endorsed by
174 ASPEN and ESPEN rightly underline that the benefit of nutritional support is blunted in the presence
175 of severe inflammation, and that this knowledge should lead to prioritizing treatment of
176 inflammatory causes, notwithstanding instituting nutritional support. Precise assessment, for
177 instance of inflammatory markers like CRP, orosomucoid (α_1 -glycoprotein acid) and albumin in a
178 composite approach with (negative) nutrient balance, fat free mass and clinical signs of inflammation
179 will also permit the determination of whether a patient is improving or deteriorating (28, 29). It is
180 therefore important to assess the two major elements leading to malnutrition.

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

188

189 **4.2 How to detect nutritional risk and how to diagnose malnutrition?**

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

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

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

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

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

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

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

253

254 **5 Consequences of the chosen approach to diagnose malnutrition.**

255

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

260 published in nutrition and general journals and is included in the ESPEN blue book (fourth
261 edition)(20). Similarly, the consensus statement significantly deviates from views present in other
262 parts of the world and developed in collaboration with ESPEN, and could cause confusion. Even more,
263 countries and nutrition societies have in recent years come close to agreement on how to define
264 malnutrition, underlining the role of nutrition and inflammation. This led in 2010 to the two parallel
265 papers with authors from 5 continents that were published in the JPEN and Clinical Nutrition and
266 endorsed by ASPEN and ESPEN (2, 3). In these papers an identical statement was given regarding the
267 definition/pathophysiology of malnutrition as given in italics in the third definition in section “**2.**
268 **Definition of Malnutrition**”. The present ESPEN Consensus Statement deviates significantly from the
269 papers and the other ESPEN endorsed activities mentioned. Finally, in a recent consensus meeting in
270 ASPEN, the views expressed by ESPEN representatives as described in the Cederholm et al paper (1)
271 were qualified as a controversy with views expressed by representatives of ASPEN, PENSA and
272 FELANPE.(Jensen GL. Global Leadership Conversation: Addressing Malnutrition. JPEN 2016 Mar 18)
273 We must also realize that ESPEN has changed its name from reflecting artificial nutrition alone, to
274 ‘Clinical Nutrition and Metabolism’. Malnutrition is our main “disease” of interest and our practice
275 will be handicapped when rejecting clinical and metabolic effects to be considered when diagnosing
276 malnutrition. Only when we can adequately diagnose the cause and degree of malnutrition,
277 quantitate the risk it carries for adequate host response, tissue function, growth and long term
278 survival, establish priorities for treatment and offer adequate treatment, will we have more impact
279 on clinical practice.

280 **6 Conclusions and Recommendations**

281

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

286 The essence of our argument is that malnutrition is a condition involving a nutritional status
287 which is “mal”, that is bad for the patient in terms of impairing function and hence clinical outcome.
288 It is therefore entirely appropriate, and indeed essential, that the diagnosis of malnutrition must
289 include some aspect of function/clinical outcome. Cederholm has noted in his reply to a letter to the
290 Editor (Mokaddem F. Clin Nutr.2016;35(1):237) that the consensus group required objective criteria
291 for a diagnosis of malnutrition and that functional criteria are too non-specific. (Clin Nutr. 2016;
292 35(1):237) The objective criteria we propose include an assessment of nutritional state and
293 inflammation (by plasma CRP and albumin), which if present will impair function more than poor
294 nutritional state alone. By linking inflammation only to cachexia, Cederholm et al have ignored the
295 importance of inflammation in the vast majority of malnourished patients, who require to have their
296 inflammation controlled before nutritional support can be fully effective.

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

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

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

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

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

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

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

324

325 **Authors’ contributions**

326 All authors contributed equally to the manuscript.

327

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330

331 **Conflict of interest**

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

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334

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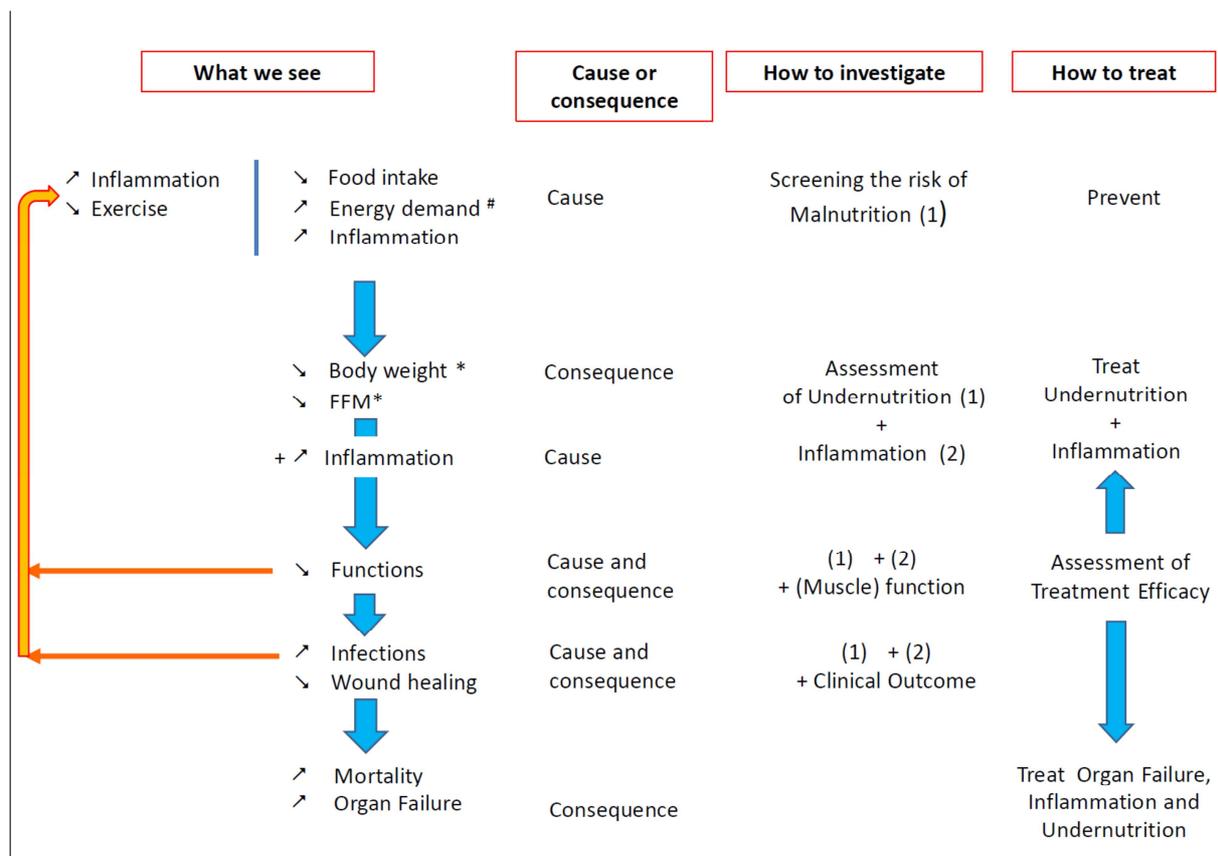


Figure 1. Schematic representation of the diagnosis and treatment of malnutrition

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.