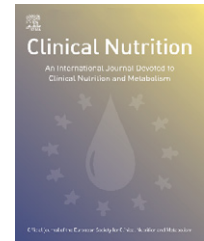




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SHORT REPORT

Perspective: How to evaluate studies on peri-operative nutrition? Considerations about the definition of optimal nutrition for patients and its key role in the comparison of the results of studies on nutritional intervention

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Summary

Different nutritional outcome studies on the same subject can have vast differences in composition of the chosen food without justification, suggesting that the composition of “optimal” nutrition in patients is not known or that optimal nutrition does not exist. The result will be negative studies which reinforces the existing impression that nutritional intervention is of limited value in every day’s patient care. This perspective will put arguments forward that optimal nutrition exists and that the definition of optimal nutrition should be the base of future nutrition intervention studies.

This perspective aims at providing a definition of optimal nutrition and consequently a basis to critically appraise the literature upon nutritional interventions in disease states
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Introduction

In Holland, a working group is busy to prepare guidelines for peri-operative nutrition. In the discussions that are part of the process, it became clear that “just” a critical appraisal

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of the literature would not lead us to an evidence-based guideline for peri-operative nutrition.

Let us share our dilemma with you: a critical appraisal of the literature upon nutrition in disease states cannot be undertaken unless it is clear what the goal of nutritional therapy is. Is it just influencing morbidity or mortality or is it maintaining or improving a certain parameter and via that way influencing morbidity or mortality. The difference is not trivial, as a negative study with a certain nutritional intervention can mean that this intervention is negative because⁽¹⁾ nutrition has no role in it or⁽²⁾ the quantity or the components of the chosen food were inadequate. Most studies on this subject pay attention to equal distribution of calories and nitrogen to the different study arms, but almost never justify the chosen amount of nitrogen and to a lesser degree the amount of calories. The results are that nutritional studies on the same subject can have vast differences in composition of the chosen food without justification.¹ In other words, it seems that the composition of optimal nutrition in patients is not known or that optimal nutrition does not exist. The result will be negative studies and reinforces the existing impression that nutritional intervention is of limited value in every day's patient care.

This perspective will put arguments forward that optimal nutrition exists and that the definition of optimal nutrition should be the base of future nutrition intervention studies.

This perspective aims at providing a definition of optimal nutrition and consequently a basis to critically appraise the literature upon nutritional interventions in disease states. It also guides the way to future interventional nutritional studies.

The basis of this perspective is the multi-step approach: the necessity to take into consideration all the steps necessary before the conclusion is made that an intervention does not influence morbidity and mortality. An example will be taken from the literature on cardiovascular risk factors:

Step 1: Epidemiological studies suggest a relationship between blood pressure height and cardiovascular complications. It is concluded that anti-hypertensive treatment could be useful.

Step 2: In a series of studies, the best drug (or combination of drugs) to normalize blood pressure is determined

Step 3: The effect of treatment with this (combination of) drug(s) on cardiovascular risk is explored. The most important component of step 3 is measurement of blood pressure. This is essential in a negative study. As otherwise no distinction can be made between insufficient treatment (no normalization of blood pressure) and absence of effect (no diminution of the incidence of cardiovascular complications despite normalization of blood pressure).

In outcome studies of nutritional intervention, almost never are parameters measured that verify that the chosen intervention is of optimal quality. This will be explored more in depth in the following paragraphs.

Considerations about the optimal amount of protein in studies of nutritional interventions in ill patients

If a disease is the direct result of inadequate nutrition, the endpoint of an intervention could be survival. An example is

kwashiorkor: from epidemiologic studies, a relationship between poor protein intake and subsequent development of kwashiorkor has been proven. So, augmenting protein intake could be useful to cure kwashiorkor (step 1). However, this association does not prove that existing kwashiorkor is cured by simply providing protein nor does it tell us how much protein should be given. Therefore, the next step should be to quantitate in a limited number of patients the optimal amount of protein that a patient with kwashiorkor can handle (= stimulate protein synthesis maximally). In other words, a series of studies should be done with variable amounts of protein in order to assess the optimal amount for treatment (step 2). Only then follows step 3 in a much larger study which determines that treatment with that optimal amount of protein leads to lesser mortality or morbidity of patients with kwashiorkor.

It can be argued that in diseases just caused by nutritional deficiencies, as in the above-mentioned example, these three steps are not absolutely necessary, but this is definitely not true for nutritional care of patients with complex diseases. In those diseases, the signs of malnutrition are not simply due to lack of food intake, but are also caused by the disease itself. To evaluate the role of nutrition, its potential on reversing the signs of malnutrition in those patients should be studied before outcome studies should start, especially as the role of malnutrition in the course of disease is generally not overwhelming but limited.

Malnutrition and specifically loss of body protein mass have a negative effect on the outcome of disease². A vast body of research has been carried out to assess the effect of nutrition in disease states on morbidity and mortality. In these studies, the nutritional intervention varies. From the methods section of the articles, it is almost never clear why a specific intervention was chosen. Since there is obviously no standard intervention where nutritional therapy is concerned, it seems that it is not known what exactly an optimal nutritional intervention consists of. This means that if we go back to the kwashiorkor example, step 3 is done without knowing what step 2 is. Not surprisingly, these studies are usually disappointing or assessed as not convincing.

The goal of nutrition is to replace losses that have occurred or are taking place. This means that studies should primarily focus on the question whether the intervention works in that respect. In the absence of disease, the minimal requirements of protein and energy are well known. It has also been demonstrated that disease processes alter metabolism in a sense that the requirements of protein and energy intake increase³.

Nutritional therapy under these conditions could be aimed at manipulating metabolism in a way that catabolism is minimized or stopped, thereby allowing time for restoration of the body protein mass. The underlying assumption is that improving the protein mass will lead to neutralizing the disastrous processes that are a consequence of the deficit. This more basic approach is essential. In protein-energy malnutrition, the causative factor for all the problems is thought to be loss of lean body mass, followed by organ dysfunction, including immune deficiency. The goal of nutrition is thus not primarily improvement of immunological functions. Studies on the effects of nutrition on immunity can only be critically assessed if arguments are

provided that the chosen amount and composition of the nutritional therapy are optimal for this specific goal. Although malnutrition and diminished immunological function are linked phenomena, both mediated by a decrease in protein mass and thus also resulting in decreasing organ mass and function, the intervention should be based on a step 2 investigation.

For the purpose of being able to create a guideline, and following the above-mentioned line of reasoning, we took the following goals of nutritional therapy as basis:

1. nutritional therapy is aimed at conservation or restoration of the body protein mass,
2. nutritional therapy includes manipulation of insulin secretion via glucose,
3. nutritional therapy aims at providing adequate amounts of energy, especially when energy stores are depleted.

In the next section, we have tried to make these recommendations more specific for protein and energy requirements.

Considerations about the optimal amount of protein

In this section, attention is only paid to the amount of protein, administered in the standard well-balanced solution of amino acids or peptides. Discussion of its relative amino acid composition is outside the scope of this perspective, especially as studies on this subject should be judged against the amount of standard protein, optimal for patients.

Under normal circumstances in healthy volunteers, the protein breakdown after an overnight fast is greater than protein synthesis, resulting in a negative protein balance. After a meal, the protein synthesis is stimulated and the nitrogen balance becomes positive. This situation will remain for a few hours after a meal. After that period, the balance becomes negative again, until a new meal is taken. The net effect of these fluctuations during the day is a zero-balance.^{4,5}

Although in nutritional terms, the word protein delivery is used, actually the gut breaks down protein into amino acids or very short amino peptides that are absorbed. In the body, these are re-synthesized and become proteins again. The capacity to synthesize protein is limited. The maximum capacity in healthy volunteers, but also in septic patients is 1.5–1.7 g/kg/day.^{6,7} In these studies, the focus was to maximally stimulate the protein synthesis through offering substrate, whilst the real goal of nutrition is to maintain or increase body protein mass for which also protein breakdown should be taken into consideration. Hypothetically stimulation of protein synthesis could also induce stimulation of breakdown, with a resultant lack of effect on the net balance. There are, however, no data showing that stimulation of protein synthesis leads to protein breakdown. The reverse has been shown for certain areas in the human body. It has been shown, that amino acid provision slows down protein breakdown in the splanchnic area, but not in for muscle.⁸ These data indicate that amino acid provision stimulates protein synthesis and lessens protein breakdown

in certain areas. Amino acid provision is therefore an ideal tool to increase whole body protein mass. Furthermore, insulin slows down the rate of protein breakdown and augments the effects of amino acid delivery on the synthesis of protein.⁸ The latter could be an argument to include euglycemia in nutritional studies as a positive factor,⁹ but a thorough discussion of this subject is outside the scope of this perspective.

The maximum capacity of the human body to synthesize protein is reached when 1.5–1.7 g protein/kg/day is administered. In critically assessing articles, these values could be used as surrogate marker for providing adequate nutritional therapy, as *measurement* of protein synthesis can only be done via complicated techniques, not suitable for outcome studies (step 3).

However, before doing that, another part of the step 2 approach is needed by asking the following question: Is 1.5–1.7 g protein/kg/day really the amount, that best maintains whole body protein mass in patients. In such a study, body protein should be determined in a reliable way. The golden standard is the *in vivo* neutron activation analysis. At this moment, we are aware of only two studies that have used this technique. One study was done in surgical patients after major abdominal surgery. The chosen amount of protein was either 0.8 or 1.9 g protein/kg/day.¹⁰ In those patients, provision of 0.8 g protein/kg/day proved to be insufficient to maintain body protein mass, whereas body protein mass was conserved if 1.9 g protein/kg/day was given. The other study was carried out in intensive care patients, given, respectively, 1.1, 1.5 and 1.9 g of protein/kg fat free mass/day during 14 days.¹¹ Provision of 1.5 g proved the optimal amount to preserve protein mass. A higher dosage had no additional value. The amount of 1.5 g/kg FFM equals 1.0 g/kg/day. This suggests that a recommendation of 1.5–1.7 g/kg/day for patients in general might be too high. This is however uncertain, because the latter study was performed in immediate post-trauma patients and severely septic patients in an ICU, probably mechanically ventilated, and fully immobilized. Muscle contractions are essential for sustaining muscular mass. In healthy volunteers, subjected to full immobilization during 4–5 weeks, the nitrogen balance becomes negative despite an intake of 90 g protein and 2700 kcal.¹²

Other studies on the effect of the amount of protein on maintenance of protein mass in ill patients are lacking. The scarcity of data is no reason to ignore them, especially as the data in surgical patients after major surgery and ICU patients point to the same direction. We propose the following statement as guidance in assessing nutrition literature:

In critically assessing articles upon effects of nutrition, protein delivery should be taken into account as a surrogate marker for optimal treatment. Provision of 1.5–1.7 g/kg/day is the optimal amount. Studies where less than 90% of this amount is administered can be assessed as having a not optimal study design and thus categorized as having “uncertain meaning”. For studies done in post-trauma patients or severely septic patients in ICUs, the Ishibashi study¹¹ suggests that 1.2 g/kg pre-illness weight/day is optimal.

Optimal energy delivery

Total energy expenditure (TEE) consists of the components' basal metabolic rate (BMR), specific dynamic action (SDA) or diet-induced thermogenesis, and an activity factor for physical activity (AF). BMR and SDA together are referred to as resting energy expenditure (REE). In circumstances of illness, the energetic requirements of the body to meet the demands inherent of the illness is recalled the "illness factor".

The golden standard for determining TEE is the double-labelled water method. In clinical practice, indirect calorimetry is used. In non-mechanically ventilated patients, a hood technique is used, measuring the BMR. An activity factor, which estimates physical activity and an estimated illness factor, are then added to the BMR. For mobile patients, usually 30–40% is added to the BMR, thereby consisting of a large part of estimated energy in the presumed TEE. As sick people usually cut down in their activity factor, the illness factor can be compensated through a lowering of the AF, so that the TEE for sick people does not need to be increased.³

Another difference between healthy and sick in a metabolic sense is the concept of "energy in the blood-stream". In healthy people in the fasting state, endogenous glucose production and lipolysis become active. When food is ingested, insulin production is stimulated and endogenous glucose production and lipolysis are inhibited proportional to the insulin production. Thus, intake of carbohydrates and fat replaces the endogenous production in an exact quantitative relationship.

Disease states lead to insulin resistance. This disturbs the normal homeostasis. Especially in severe illness, glucose production and fat oxidation will continue at a considerable rate, despite exogenous provision of substrates in an amount that covers the measured energy requirements. This means, that the body will have more energy available than it can use, and thus it will deposit it in its stores. The consequence is a further increase of insulin resistance. This process has not been studied extensively in different disease states, but an extrapolation of findings in obese patients is justified.¹³ Tailoring nutrition towards the measured energy expenditure is therefore hazardous if endogenous liberation of energetic resources is not stopped and can result in overfeeding and insulin resistance. High glucose levels and a high RQ can be used as indicators over overfeeding.

In mechanically ventilated patients, the REE can be measured with indirect calorimetry. Because the measurement is usually done at rest, an estimated activity factor of 10% is added to calculate the TEE. This method, which is easily performed, gives a correct determination of oxygen uptake and CO₂ production thereby allowing for an estimation of REE. In studies where indirect calorimetry was compared with the double-labelled water method, is has proven to be accurate. As over- and underfeeding have negative effects on our patients, it is remarkable that this easy bedside method of determining energy expenditure is so seldom used in intensive care units in Holland. Already in 1998, McClave et al.¹⁴ have shown, in an ICU population of 213 patients, artificially fed according to their doctors orders, that 58.2% was overfed, and 12.2% was underfed.

Only 25% received the amount of calories as determined by indirect calorimetry.¹⁴ As usual, the TEE in this study was defined as REE+10% activity factor. Overfeeding correlated with high mandatory minute volumes on the ventilators and thus an increased work of breathing for the patients, and metabolic acidosis. Our own unpublished data confirm these data for the Dutch population. It is clear that standard treatment with 2000 kcal/day, as is routine practice in many ICUs in the Netherlands, is not optimal nutrition.

In critically assessing articles upon effects of nutrition, energy delivery should be taken into account as a surrogate marker for optimal treatment. Provision of calories should be matched with the measured energy expenditure of patients. Adequate glycemic control is part of an effective and safe nutritional therapy.

Conclusion

In outcome studies of nutritional interventions in ill patients, the value of those studies should be judged against the concept of optimal nutrition. In studies deviating from this concept, the authors should clarify why they did this.

This could be a first step to (1) harmonize studies on this subject, (2) to clarify the role of short-term nutritional therapy in patients and (3) and hopefully diminish the endless series of confusing studies and by that challenge the existing impression that nutritional intervention is of limited value in every day's patient care.

Till new data become available, optimal nutrition for patients can be defined as:

1. Provision of 1.5–1.7 g/kg/day is the optimal amount of protein. Studies where less than 90% of this amount is administered can be assessed as having a non-optimal study design and thus categorized as having "uncertain meaning". For studies done in post-trauma patients or severely septic patients in ICUs, the Ishibashi study suggests that 1.2 g/kg pre-illness weight/day is optimal.
2. Energy delivery should be taken into account as a surrogate marker for optimal treatment. Optimal nutrition is defined as measured REE:+10% in ICU patients or +30% in patients on wards. Adequate glycemic control is part of an effective and safe nutritional therapy.

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