Ethical aspects, public policies and new paradigms in clinical nutrition and metabolism: challenges for research

Aspectos éticos, políticas públicas y nuevos paradigmas en nutrición clínica y metabolismo: desafíos para la investigación

Diana Cárdenas[1*], Charles Bermúdez[2]

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Research in clinical nutrition aims, on the one hand, to study the causal relationship between the administration of artificial nutrients and clinical outcomes and, on the other, to determine the levels of supplementation required to achieve specific results. The ultimate goal is to modulate certain immunological and metabolic processes to prevent or treat malnutrition associated with disease and related comorbidities(1). Like any science, it is based on scientific facts. A scientific fact is a hypothesis that has been corroborated once confronted with reality in a specific experiment or experience. The scientific method is not speculative and is based on real and verified facts(2). Therefore, we ask ourselves: How are artificial nutrients studied? How is their clinical benefit demonstrated?

Clinical nutrition has used the scientific method through clinical efficacy trials. The starting point is the fundamental studies (mechanistic studies or basic research) where the mechanisms and the role that artificial nutrients play in metabolic processes during health and disease are evaluated, with different methodologies (metabolomic, isotope, etc.) and at different levels (cellular, tissue, animal organisms or people). Subsequently through randomised controlled trials (RCTs) it is possible to assess the effects of artificial nutrient interventions on specific outcomes. According to evidence-based medicine (EBM) the study should be randomised, double-blind and placebo-controlled.

In recent decades, great advances have been made in clinical nutrition. However, doubts and uncertainties persist regarding certain crucial issues such as the dose of protein required by the critically ill patient, the use of pharmaconutrients, and the diagnostics criteria of sarcopenia and malnutrition, among others. These doubts are even more profound in Latin America since the clinical practice recommendations or certain parameters are mostly based on European or North American references and guidelines that do not take into account the characteristics of the population or the most relevant problems of our clinical practice.

Dr. Isabel Correia in the guest editorial "Lack of science or bad science" from this issue questions the reasons for these doubts and puts on the table very important aspects such as the methodological quality of the studies, the misuse of meta-analyses and commercial interest or marketing effect (and accurately raises the need for another editorial on the subject) of some current issues in clinical nutrition. For my part, I question the specific difficulties of research in clinical nutrition. Can we explain the dubious or poor quality of some studies as a result of the particular characteristics and specific difficulties of clinical nutrition?

Before mentioning three difficulties that I consider relevant and that stand out in the articles in this issue of the journal, it must be noted that most of the recommendations in the clinical practice guidelines are based on low levels of evidence. For example, the ESPEN

1 Medical Surgeon, Universidad El Bosque. University Diploma in Dietetics, Clinical Nutrition and Therapeutics, Bichat Hospital, Denis Diderot University, Paris, France. Master of Science, René Descartes University, Paris, France. Magister in Metabolism and Nutrition, University Paris Diderot, France. Magister in International Relations, International Politics, University of Lyon, France. Doctorate in Philosophy, University of Franche-Comté, Besançon, France.
*editor-rmnc@nutriclinicacolombia.org
2 Surgeon, Clínica La Colina and Clinica del Country, Bogotá., D.C, Colombia.

Guidelines for Nutrition in Critically ill Patients published in 2018 present a total of 57 recommendations[3]; 41% are recommendations based on the clinical experience of the participants in the guidelines (GGP, Good practice points); 33 % are type B, that is, based on studies classified as 2 ++ (high quality systematic reviews, case studies and control or cohort studies, see guide for further details); 19% type 0 recommendations, that is, non-analytical studies, case series and expert opinion. Only 7% of recommendations are based on solid evidence with a low bias risk RCT, quality meta-analyses and systematic reviews. This means that decisions are still made based on intuition, opinion and individual experience, in other words, in a speculative manner.

Opinions could arise from fundamental research where basic knowledge of the physiological aspects of the nutrient is inferred in a possible beneficial effect in a pathological state. That is to say, starting from the knowledge of the physiopathology of the disease and the pharmacological or metabolic actions of the nutrient it is possible to elaborate a theoretical rationing of a "mechanistic" type that allows predicting or suggesting a therapeutic benefit. However, these assertions can be erroneous and often not beneficial, and also have serious side effects. For example, studies evaluating the antioxidant properties and actions on the lipid metabolism of vitamin E suggest that a diet enriched in this vitamin could be associated with lower cardiovascular mortality. Even observational studies in populations with a diet rich in vitamin E show lower cardiovascular mortality.

While this fundamental knowledge is important, it is also fragmented and the theoretical reasoning behind it is speculative. This means that deductions at this level cannot guarantee the accuracy of the reasoning and its conclusions, in our case, the efficacy of the nutrient or the nutritional intervention. Therefore, RCTs become indispensable, as long as they are performed correctly, they are able to demonstrate a real benefit. In the case of vitamin E, despite well-done RCTs with a significant number of patients it has not been possible to show clinical benefit from the administration of vitamin E[4]. Let us look at the case of the fashionable immunonutrient glutamine (Gln) in the 1990s and 2000s. Animal studies have shown that it improves intestinal barrier function and has an effect on oxidative stress and inhibition of inflammatory processes such as activation of NF-κB and production of TNF-α. The cascade of signal regulation induced by Gln is described by Dr. Manzanarez and Dr. Hardy in the brilliant article published in this issue. They describe how the administration of Gln results in the suppression of many important inflammatory mediators including reactive oxygen species. Therefore, it could be induced that this nutrient administered in pharmacological doses would have a beneficial effect in septic patients or patients with severe degree of inflammation in intensive care units (ICU). However, the ESPEN guidelines, with grade A evidence, recommend not to administer Gln in the form of di-peptide in patients in unstable or difficult ICU and with hepatic or renal failure. The authors of the article emphasize the need to know the plasma levels of the immunonutrients of the patients before their supplementation and to adopt a more pharmaceutical approach classifying the immunonutrients as drugs, that is, to study them under the paradigm of pharmaconutrition.

This is an example that makes clear the need to perform RCT under appropriate conditions and taking into account some particularities of clinical nutrition.

IT IS NECESSARY TO CONSIDER NUTRIENTS AS REAL DRUGS

Intake history and basal plasma levels of the nutrient or immunonutrient of interest may influence the response being studied.

In drug studies, researchers make sure that research participants do not have plasma levels of the drug being studied. In contrast, most nutrition studies do not consider basal levels of nutrients, and sometimes intake is not assessed either. It is known that these levels may influence the expected response. Many nutrients have thresholds, i.e. they are limited by enzyme saturation, transporter or receptor. In addition, the metabolism of many nutrients is different in hypercatabolic states compared to the healthy person, which can lead to specific deficiencies or increased basal levels. The requirements are not the same and in the hypercatabolic patient it is not only a question of making up for a deficit or covering a requirement of nutrients but also of modulating a metabolic response.

In clinical studies, if the nutrient reference level is adequate, should the result be expected to be minimal? If a "supra-physiological" effect is desired, how can we know when these levels are reached if the baseline level is not known? Conducting the studies under the paradigm of pharmaconutrition could provide an answer to this point as well as a better knowledge of the adaptive metabolic response to stress.

THE ETHICAL PROBLEM OF CONTROL GROUPS IN CLINICAL NUTRITION

A control group is a group of individuals who will not receive or will not be affected by the treatment studied and is indispensable for evaluating the effect of the treatment or intervention. Some individuals may be selected to be part of this group, which has ethical implications. For example: is it ethical to study a group of people with sarcopenia or malnutrition knowing that receiving placebo does not correct this condition? Is it ethical to study the administration of high doses of protein in the critically ill patient (≥ 2.2 g/kg/d) as proposed in the EFFORT clinical study by the authors Ortiz and Heyland in the article published in this issue? In both cases, the answer is yes. In other words, it is ethical as long as the principle of clinical equipoise (i.e. clinical indetermination or therapeutic uncertainty exist) is applied. Individuals with sarcopenia/undernutrition and patients who will receive high doses of protein may be part of these studies because there is doubt or uncertainty about the best option or which should be the standard treatment. This concept implies that there is real uncertainty about the benefit of the treatment, which is fulfilled in the case of the EFFORT study. The ESPEN guidelines confirm this doubt and with a level of evidence 3 and 4 (expert opinion) recommend 1.3 g/kg/day and state that it is possible that just as with calorie targets, optimal protein targets in the ICU change over time, and that a high protein intake is only beneficial if it is not associated with overfeeding (excess calories). I believe that these latter aspects should be addressed by the EFFORT study and other RCT that seek to elucidate this point.

Latin America needs to improve clinical nutrition research and conduct good quality RCT to build its own evidence and recommendations. Although we could say that the lack of resources and education in this field are the main reasons why the region does not build its own knowledge, the lack of public policy is the real starting point of the problem. In this sense, the Cartagena Declaration on the Right to Nutritional Care and the Fight against Malnutrition, which will be signed at FELANPE's extraordinary assembly in May, will be able to contribute to the construction of public policies based on its fundamental principles. Dr. Humberto Arenas, former president of FELANPE 2016-2018, reflects on the 2008 Cancun Declaration on the Right to Food in Hospitals, an important precursor to the Cartagena Declaration[5]. In addition, we applaud the efforts of the ACNC to hold the Colombian consensus meeting on immunonutrition in surgical patients, which we publish in this issue of the Journal of Clinical Nutrition and Metabolism.

Here, evidence-based medicine is not being questioned, but some challenges and difficulties of clinical nutrition research and the need to build better scientific evidence are proposed. This could be done taking into account the need to consider nutrients as true drugs, the ethical aspects of the definition of control groups and the lack of recommendations and own scientific evidence in Latin America.

We hope that the Journal of Clinical Nutrition and Metabolism will be a publication that favors communication and the construction of knowledge in clinical nutrition in the region; and therefore, improves the quality of care for patients who require artificial nutrition, which must be based on the best possible evidence.

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