

Advancing from immunonutrition to a pharmaconutrition: a gigantic challenge

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Purpose of review

This review presents some difficulties encountered to develop and translate immunonutrition into clinical practice, and suggests moving forward to a pharmaconutrition approach.

Recent findings

Immunonutrition suffers from inconclusive and contradictory data due to the design of many of experiments and clinical studies conducted so far. The concept of a single immunonutrient formula applicable to various types of patients has also contributed to leave the medical world in a state of uncertainty. We propose to move forward to the concept of pharmaconutrition where a disease-dedicated nutrition therapy is developed following a rigorous step-by-step procedure. Nutrients are selected according to their pharmacological properties and after an in-depth evaluation of their biological interactions when mixed together. The optimum administration schedule (i.e. dose, route, timing and duration) of the new formulae is then determined in well conducted projective clinical trials where it is administered apart from the standard nutrition to ensure full delivery of the expected doses.

Summary

This review suggests moving forward to a pharmaconutrition approach where a rigorous step-by-step procedure would allow overcoming of the difficulties encountered to translate immunonutrition into clinical practice.

Keywords

ω -3 polyunsaturated fatty acids, arginine, dietary nucleotides, folate, glutamine, immunonutrition, pharmaconutrition

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Introduction

Over the last two decades, clinical nutrition has evolved from nutritional support intended only to cover patient's needs to nutrition therapy selected according to patient's disease. This new approach results from growing awareness that patient's health status is closely related not only to quantitative but also to qualitative nutrient intakes. In hospitalized patients, a frequent pattern is the initiation of a vicious circle in which poor food intake facilitates the appearance of infectious and inflammatory complications through alteration of the immune response, which in turn worsens patient's nutritional status. Artificial nutrition, in the form of parenteral or enteral therapy, with specific nutrients in supranormal amounts is expected to overcome insufficient food intake and to stop this vicious circle. Therefore, new formulae enriched with specific nutrients have been developed in order to obtain pharmacological effects on the immune and inflammatory responses. Clinical studies have demonstrated that an immune-enhancing diet also called 'immunonutrition' improves the outcomes of malnourished patients under-

going elective upper gastrointestinal surgery by significantly reducing morbidity, treatment costs and length of hospital stay. In subsequent meta-analyses, the effectiveness of perioperative 'immunonutrition' has been classified as level A evidence, so that it is now recommended in the guidelines of the European Society of Clinical Nutrition and Metabolism (ESPEN) [1]. Unfortunately, the results are less obvious in well nourished gastrointestinal [2] and in critically ill patients [3], and even seem to indicate a trend towards increased risk of mortality in septic patients with pneumonia [4]. These disappointing results can be attributed to the heterogeneity of the population of critically ill patients who probably react differently to the administration of a fixed formula. The poor quality of many of the trials conducted so far hampers the detection of any significant difference in clinical endpoints. Consequently, many clinicians are reluctant to administer 'immunonutrition' as long as its mechanisms of action and assured benefits are not clearly understood and its impact on clinical outcome fully demonstrated. Addressing such concerns is a real challenge that we confront and concentrate on. The proposal

of Jones and Heyland [5**] to move forward from an 'immunonutrition' to a 'pharmaconutrition' approach is a reasonable proposition to boost clinicians' interest in artificial nutrition therapy.

Prerequisite for pharmaconutrition

In theory, a 'pharmaconutrition' approach involves a rigorous step-by-step procedure of development that may appear limited but is the prerequisite for new nutritional therapeutic strategies based on sound scientific principles. To do so, the concept of an immune-enhancing diet applicable to a wide range of pathologies should be progressively replaced by disease-dedicated nutrition therapy [6**]. Nutrients that go into the cocktail should be selected not only empirically but also after an in-depth evaluation of their individual and net effects, because it is likely that the interactions between nutrients may cancel or enhance their individual pharmacological properties. The resulting formula should be then administered apart from standard nutrition via an enteral or parenteral route to ensure full delivery of the expected doses. Finally, the optimum administration schedule (i.e. dose, route, timing and duration) should be determined in well conducted clinical trials with homogeneous population and sufficient number of patients. In our view, such a development procedure would make the acceptance of the 'pharmaconutrition' concept easier for the medical world and health authorities (i.e. level A of recommendation, reimbursement). The downside of such a proposition is the *a priori* determination of the expected beneficial effect of each specific nutrient and then their combined expected effects so as to allow the calculation of a power factor that will determine sample size.

Disease-dedicated strategy

'Pharmaconutrition' could be of beneficial application to a broad spectrum of diseases other than those encountered in surgical and critically ill patients. Among potential pharmaconutrients identified to date, some have demonstrated therapeutic properties in a wide range of metabolic disorders. This is the case for certain amino acids, nucleotides, omega-3 polyunsaturated fatty acids (n-3 PUFAs), vitamins and trace elements. Among amino acids, arginine is well known to improve clinical outcome of patients with burns and heart disease by increasing collagen and mechanical resistance of scar tissues [7] and decreasing hemodynamic pressure and atherosclerosis lesions, respectively [8]. In particular, arginine supplementation may be beneficial for patients with sepsis in which de-novo arginine synthesis and nitric oxide production is severely diminished [9]. Recently, it has been suggested that arginine doses of 0.09 and 0.2 g/kg body weight/day could be tolerated in long-term parenteral and enteral supplementation, respectively [10].

Another example is glutamine, which reduces mucositis, villous atrophy and diarrhea induced by abdominal surgery [11], radiotherapy [12], chemotherapy [13], or following parenteral nutrition or extended period of fasting [14]. Similar to arginine, enteral glutamine supplementation is also used in trauma and burn patients to improve tissue healing. Recently, it has been suggested that 0.5 g/kg body weight/day of glutamine is the minimal therapeutic dose required to obtain a pharmacological effect [15,16].

Regarding n-3 PUFAs, numerous studies have already shown their favorable immunomodulatory effects on a wide range of diseases including rheumatoid arthritis, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), asthma, cystic fibrosis, lupus, diabetes, allergies, psoriasis, multiple sclerosis, atherosclerosis, acute cardiovascular events, neurodegenerative disease, obesity, acute respiratory distress syndrome, and cancer cachexia [17]. Their pharmacological effects have been observed at doses ranging between 1–2 g/kg body weight/day of parenteral lipid emulsion corresponding to 5–15 mg/kg body weight/day n-3 PUFAs. However, infusion of parenteral lipid emulsions should not exceed 2.6 g/kg body weight/day (0.11 g/kg body weight/h) in order to avoid side-effects [18].

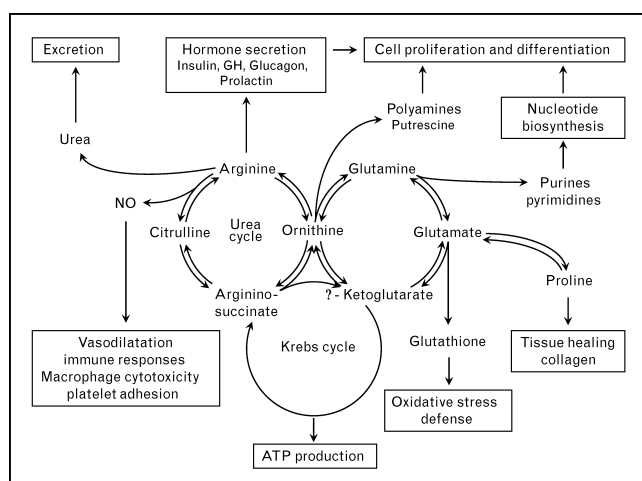
These few examples demonstrate that 'pharmaconutrition' could apply not only to acute inflammatory diseases but also to many chronic diseases. Naturally, the use of a fixed cocktail of nutrients for a wide range of pathologies is certainly unwise. Nutrients should be selected with regard to their pharmacological effects on a specific disease. In addition, 'pharmaconutrition' should be part of an overall therapeutic strategy in which the administration schedule and formula vary according to the different stages of treatment.

Nutrient interactions

The individual effects of several potential pharmaconutrients are now well documented. When mixed together, however, their net effects are much more complex and unpredictable. It is simplistic to think that their individual beneficial effects will be expressed or that their combined effects will be additive in a mixture. Important interactions may occur between them that could cancel or even alter their primary intended effects. Therefore, development of new formulae should take into account and study carefully these interactions. The following examples aim to show the complexity of the nutrient interactions in a formula.

Glutamine/arginine

The metabolic pathways of immunomodulating amino acids are interlinked and bidirectional, so that their

Figure 1 Bidirectional interactions of immunomodulating amino acids on their respective metabolic pathways

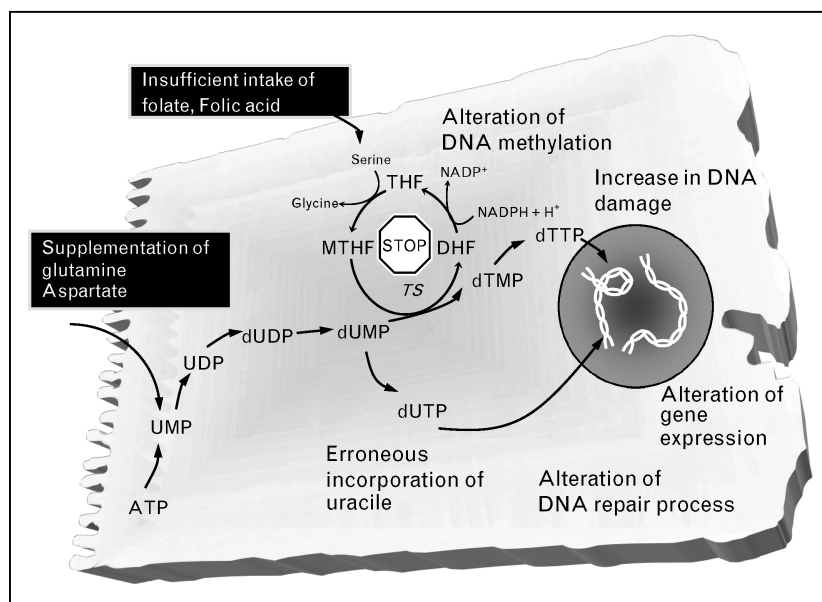
Glutamine and to a lesser extent proline are converted subsequently into glutamate, ornithine, and citrulline in the gut. Citrulline is then released in the blood circulation where it is extracted primarily by the kidney to generate arginine. The reverse reaction can occur through the urea cycle. The action of arginine on the immune response is mediated by nitric oxide and polyamines synthesis and by hormone secretion, whereas glutamine acts mainly on leukocyte and enterocyte proliferation and differentiation by supplying substrates for protein and nucleic acid synthesis and energy through the Krebs cycle. Conversion of glutamine or arginine into glutamate improves oxidative stress and tissue repair by glutathione and collagen regeneration, respectively. GH, growth hormone; NO, nitric oxide.

metabolic fates are dependent on their respective concentrations. For instance, glutamine and to a lesser extent proline are the precursors for the de-novo synthesis of arginine through an intestinal–renal pathway. Glutamine and proline are converted subsequently into glutamate, ornithine, and citrulline in the gut [19]. Citrulline is then released in the blood circulation where it is extracted primarily by the kidney to synthesize arginine. The reverse reaction is also true, as arginine is hydrolyzed in the liver to urea and ornithine by arginase, and then ornithine is converted into citrulline through the urea cycle or into glutamate, proline and glutamine (Fig. 1). Consequently, the question arises if glutamine supplementation has the same biological effects as arginine supplementation on hormonal secretion and polyamine synthesis from ornithine [20]. However, the metabolic relationship between arginine and glutamine are much more complex, because of compartmentalized expression of various enzymes at both organ and subcellular levels and because of changes in enzyme expression in response to diet, disease, hormones and cytokines. As an example, one could suppose that glutamine supplementation enhances nitric oxide synthesis from inducible NOS (iNOS) by increasing plasma levels of arginine. Actually, the effects of these two amino acids are different and sometimes opposing. Glutamine inhibits in a dose-

dependent manner nitric oxide release from endothelial cells and macrophages via a glucosamine-dependent mechanism [21,22]. Nitric oxide is a highly reactive free radical essential for antimicrobial and tumor immunity as well as endothelial function, but high production of nitric oxide can be detrimental by promoting inflammation and by causing mucosal swelling and epithelial damage [23]. Therefore, arginine supplementation together with glutamine may be preferable to arginine alone in septic patients. By lowering the peak of nitric oxide synthesis at the wound site, glutamine may help arginase to convert arginine into ornithine and proline, the latter being necessary for collagen synthesis and tissue recovery from inflammation and injury [24]. In addition, glutamine can act as a metabolic fuel for dividing cells by providing α -ketoglutarate for the Krebs cycle and purine and pyrimidine bases for nucleic acid synthesis [25]. Glutamate synthesis from glutamine by glutaminase may also confer protection against oxidative stress by supplying endogenous glutathione [26]. Thus, arginine supplementation together with glutamine is probably beneficial to support patients' immunity and redox status. Under glutamine-deprived condition, however, arginine supplementation could be harmful in patients with elevated oxidative stress by overproducing nitric oxide and citrulline. According to the patient's condition, an uncontrollable inflammatory process could engage in which stimulation of cytokine (i.e. IL1, IL6, TNF α , IFN γ) production by nitric oxide in turn stimulates nitric oxide production from iNOS. This hypothesis may explain why glutamine has shown to be beneficial for the metabolically stressed patients, whereas the benefits of arginine supplementation is still under debate [27].

Glutamine/nucleotides

Glutamine supplementation does not only interfere with arginine metabolism but also with exogenous nucleotide uptake. Indeed, most of the cells synthesize de-novo nucleotides from simple carbon and nitrogen compounds that are provided by precursors like glutamine, glycine, aspartate, CO₂ and tetrahydrofolate (Fig. 2). Glutamine is required as substrate for three enzymes involved in the de-novo synthesis of purine nucleotides and two enzymes involved in the de-novo synthesis of pyrimidine nucleotides [28]. Most of the time, the de-novo synthesis is preferred to the salvage pathway of preformed nucleotides, but under stress conditions, lymphocytes, macrophages and enterocytes can switch to the latter to spare ATP and lower energy consumption. For instance, in case of metabolic stress or tissue repair where the needs exceed the intrinsic capacity of the de-novo synthesis, cells utilize exogenous purines and pyrimidines from dietary origin or from nucleic acid catabolism. In the pyrimidine salvage pathway, thymidine kinase is the key-enzyme, which phosphorylates exogenous thymidine into

Figure 2 Effect of exogenous glutamine and folate status on the de-novo synthesis and salvage pathway of pyrimidine nucleotides

Glutamine is required for the de-novo synthesis of the key precursor uracil (UMP). Folate provides one carbon unit for the methylation of dUMP into thymidine (dTMP) by thymidylate synthetase. In the presence of sufficient amounts of glutamine and folate, enterocytes and blood cells prefer the de-novo synthesis, but under stress conditions, they can recycle preformed nucleotides from the salvage pathway to spare ATP and lower energy consumption. In case of low folate status, this may induce erroneous DNA-incorporation of dUTP and increase risk of anemia and colorectal cancer. DHF, dihydrofolate; MTHF, methylene-THF; THF, tetrahydrofolate; TS, thymidylate synthetase.

dTMP. Thus, one has to question the logic of additional amounts of nucleotides into formulae that are already amply enriched with glutamine, because glutamine will provide sufficient substrate and ATP from the Krebs cycle to allow leukocytes and enterocytes to continue the de-novo nucleotide synthesis. We have indeed shown in an experimental study that the cell-proliferating effect of nucleotides was masked by the presence of glutamine in an immune-enhancing formula, because of a much more potent stimulatory effect of the latter [29].

Glutamine/folate

Dietary folate intake is essential for the de-novo synthesis of pyrimidine nucleotides, in particular, during DNA replication. All pyrimidine nucleotides are synthesized *de novo* from a key-precursor, uracil (UMP). UMP is converted into dUMP by ribonucleotide reductase and then methylated into thymidine (dTMP) by thymidylate synthetase. One of the crucial roles of folate is to provide one carbon unit for the thymidylate synthetase-mediated methylation of dUMP into dTMP (Fig. 2). Dietary depletion of folate is known to restrict this conversion, resulting in an accumulation of intracellular dUMP, the misincorporation of dUTP into DNA, and subsequently, DNA breakage, alterations of DNA repair and gene expression [30]. This in part explains why low folate status is associated with increased risk of anemia and

colorectal cancer by sensitizing rapidly dividing cells (i.e. erythrocytes and enterocytes). In such a context, it is rational to consider whether glutamine supplementation should accompany folate intake in order to favor pyrimidine synthesis and avoid uracil misincorporation into DNA. It has been suggested that people consuming the highest amounts of folate have 30–40% lower risk of colorectal cancer than those consuming the lowest amounts [31]. However, there is also evidence that high folate intake may favor cancerous lesions in individuals who harbor premalignant lesions [32].

This leaves a number of unanswered questions as to which metabolic factors interfere with glutamine, including other pharmaconutrients, such as arginine, nucleotides, and folate.

Polyunsaturated fatty acids/vitamin E

Pharmacological effects of n-3 PUFAs are mainly explained by their ability to downregulate the synthesis of arachidonic acid-derived eicosanoids. Inhibition of dienic prostaglandin production, such as PGE₂, reduces the expression of antiapoptotic (e.g. Bcl2 and Bcl-X) and proinflammatory (e.g. VEGF and EGFR) proteins. However, cell membrane increase in n-3 PUFAs may promote oxidative stress by triggering autocatalytic chain reactions in the presence of free radicals [33]. Fortunately, fish oil

emulsions usually contain substantial amounts of the antioxidant vitamin E (α -tocopherol) that can stop this deleterious process. Alternatively, the presence of high doses of vitamin E could prevent the formation of lipid peroxidation products, such as malondialdehyde and 4-hydroxy-2-hexenal, which could play an important role in the antitumor action of n-3 PUFAs by increasing oxidative stress and inducing apoptosis preferentially in cancer cells, which are more sensitive to oxidative stress than host cells [34]. Therefore, the mode of administration of n-3 PUFAs cannot be considered in the same way for all types of diseases and the administration of n-3 PUFAs together with vitamin E may be more beneficial to some patients than to others. Clinical relevance of these different metabolic pathways should be well established in further experiments.

Mode of administration

The effectiveness of 'pharmakonutrition' does not depend only on the net physiological effects obtained with a nutrient cocktail but also on the mode of administration (i.e. route, time, and duration). Some 'pharmakonutrients' are particularly unstable *in vivo* with biological half-lives of minutes. For instance, the half-life of some pyrimidine nucleotides is only 5–7 min. Glutamine stability is not much better than nucleotides. This is the reason why glutamine has been coupled with another amino acid (i.e. glycine or alanine) to form a less biodegradable dipeptide. An animal study comparing free glutamine with the dipeptide alanyl-glutamine administration found that splanchnic extraction of hydrolyzed glutamine was higher after dipeptide than after free glutamine administration [35]. The route of administration is also an important factor to target the pharmacological effects on a given tissue. In humans, it has been shown that arterial glutamine concentrations were highest after parenteral administration of alanyl-glutamine [27]. However, with enteral administration the uptake of alanyl-glutamine was better taken up by target tissues, such as gut and gut-associated lymphoid tissues [36]. If the aim of glutamine administration is to affect the immune system and inflammatory process by conversion of glutamine into citrulline in the gut and subsequent generation of arginine, enteral administration is preferred. However, many other approaches may be considered. For instance, 'pharmakonutrition' could be part of the treatment schedule of some cancer patients to radiosensitize or chemosensitize peripheral tumor tissues by supplying protein, nucleic acids, and energy for promotion into cancer cell cycle. In such an approach, parenteral administration of glutamine, as well as other pharmakonutrients, such as nucleotides and n-3 PUFAs, would be preferable.

Thus, there are numerous leads to be explored during the upcoming years with the aim of determining the type of

formula, the dose, and route, as well as the timing and duration suitability for a particular disease and its treatment schedule.

Conclusion

Disease-specific nutrition support has recently received more recognition as preoperative immunonutrition was recommended as the standard of treatment (ESPEN consensus) to optimize the clinical outcome of patients undergoing gastrointestinal surgery. However, these recommendations have as yet not been widely assimilated by the medical community outside of nutrition specialists. Consequently, these recommendations are either not implemented in care units particularly in hospitals without dedicated nutrition therapy teams. Future disease-specific nutrition therapies should be prepared according to rigorous step-by-step procedures systematically applied for drug development, a modality that would give new impetus to the nutrition therapy concept.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 459).

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