EC NUTRITION
Literature Review

Proteins, Catabolism and Sepsis: A Literature Review

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Abstract

Sepsis and, its progression, septic shock are multi-organ failures caused by a complication of an infection. These cases are characterized by an increased in the nutritional requirements and this leads to a catabolic state. This shows a negative nitrogen balance which demonstrate the use of body muscle are metabolic substrate for energy production. This fact leads to a malnourished patient with increased mortality rates. Nutrition in the septic patient is a complicated topic not only for the acute component of the disease but also due to the location and the nutritional misconceptions of the medical team. Investigation in this field is very limited and mainly specific amino acids have been studied but a complete nutritional approach to the patient could lead to a correction in the catabolic state. By correcting the catabolism, we would not only improve the nutritional status of the patient but also improve and/or correct the metabolism. This could lead to appropriate metabolic pathways and better outcomes.

Keywords: *Nutrition; Sepsis; Intensive Care; Protein; Catabolism*

Objectives

The objectives of this systematic review about the nutritional requirements, more specifically the protein requirements, of the septic patient are, not only to examine the last available data, but also to clarify if there is a relationship between a higher protein intake and the patient's recovery.

Nutrition is still one of the least investigated factors. The data review was limited by the small number of articles available which emphasises the need to develop the topic. This paper tries to open new lines of investigation in the nutritional approach to treatment of the septic patient, especially in the intensive care units (ICU) where, sometimes, the nutritional aspect of treatment is secondary to a more pharmacologically-centred approach.

Introduction

Sepsis, with its multi-organ-related complications, is one of the leading causes of death globally and in the most severe cases, requires admission to Intensive Care Units (ICU) or High Dependency Units of hospitals [1]. Clare Reid states that approximately 45% of ICU patients enter a malnourishment state which demonstrates the importance of the nutritional treatment of not only sepsis but all ICU patients [1,2].

The nutritional requirements of these patients are complex and are altered due to the metabolic and physiological changes of the organism [3]. The fundamental objective of a correct nutrition is to maintain lean mass to optimise the different metabolic pathways and to allow the success of the antimicrobial therapy [3]. A low lean mass weight has been proven to increase mortality rates which show that adequate protein intake is essential to prevent the onset of the catabolic state [1,4,5], that is, the process of lean mass destruction due to its use for the production of energy in the metabolic pathways [6].

Nutritional Examination

Although the subject of this paper is the protein requirement analysis of the septic patient's diet, we cannot forget that diet is more than just one type of macronutrient. The nutritional examination of the patient not only allows the healthcare professionals to prescribe the most adequate diet, but also allows them to determine the patient's level of malnourishment. For the acutely unwell or septic patient, a thorough nutritional examination is essential due to the altered metabolism which will cause the infra- or supra- nourishment to affect the prognosis and outcome [7-9]. Different levels of chronic or acute inflammation alter not only the anthropometric values but can also affect the immunological system and muscular functions of these types of patients [10].

There are different tools available to carry out a nutritional examination. However, there are several essential tests that should be carried out on admission of the acutely unwell patient [7]:

- Weight and weight-loss percentage
- Height
- Body Mass Index (BMI): a morbimortality indicator that makes a relationship between height and weight
- Albumin: prognostic test that indicates the visceral protein levels
- Cholesterol: low levels are related to malnourishment and could increase mortality.

Some other diagnostic test could express the evolution of the nutritional aspect of care during the hospital stay. The following methods have been suggested [7,10]:

- Nitrogen balance: good metabolic indicator
- Creatine/height Index: measures the muscular catabolism
- Pre-albumin levels: the most sensitive test to nutritional changes but it is also sensitive to the physiological response of the patient.

The nutritional status of the acutely unwell patient needs to be closely monitored as an altered nutritional state is linked to an increase in the pathology's mortality [10].

A very simple and straightforward tool to carry out this assessment is the MUST (malnutrition universal screening tool) score. This assessment applies points to different items in order to obtain an overall score that will represent the patients' risk of malnutrition. An example of a practical application of this tool is the flowchart created and used at The Royal Bolton Hospital (UK) as seen in appendix 1. When adding up all the scores obtained in the different items, the score obtained will classify the patient's risk in one of the three possible risk levels which will have recommended and regulated actions to follow.

The Nitrogen Balance

The nitrogen balance has been a well-known physiological factor since the 19th century when Voit first measured the difference between the intake of nitrogenous products and the nitrogen excretion as urea [11,12].

The balance can be:

- Equilibrium: when there is no net difference of nitrogen.
- Positive: when the intake is greater than excretion leading to an anabolic state.
- Negative: when excretion is greater than the intake. This is not only due to dietary factors but could be also be related to a physiological process in the body. This nitrogen balance can lead to a catabolic state.

Proteins as Essential Nutrient

Proteins are the most important structural nutrient in dietetics due to their importance in wound healing, immune system support and lean body mass maintenance [4]. The importance of this nutrient has been known since the 19th century when it was observed that animals that were not including proteins in their diets were not able to maintain their body mass and, as a consequence, were using their lean mass as fuel [12].

The normal functioning of protein elements in the body is essential for life as it is understood. Protein monomers, the amino acids, when joined together form a sequence and the order of these amino acids determine the function of the protein as they establish how the amino acid sequence will fold together.

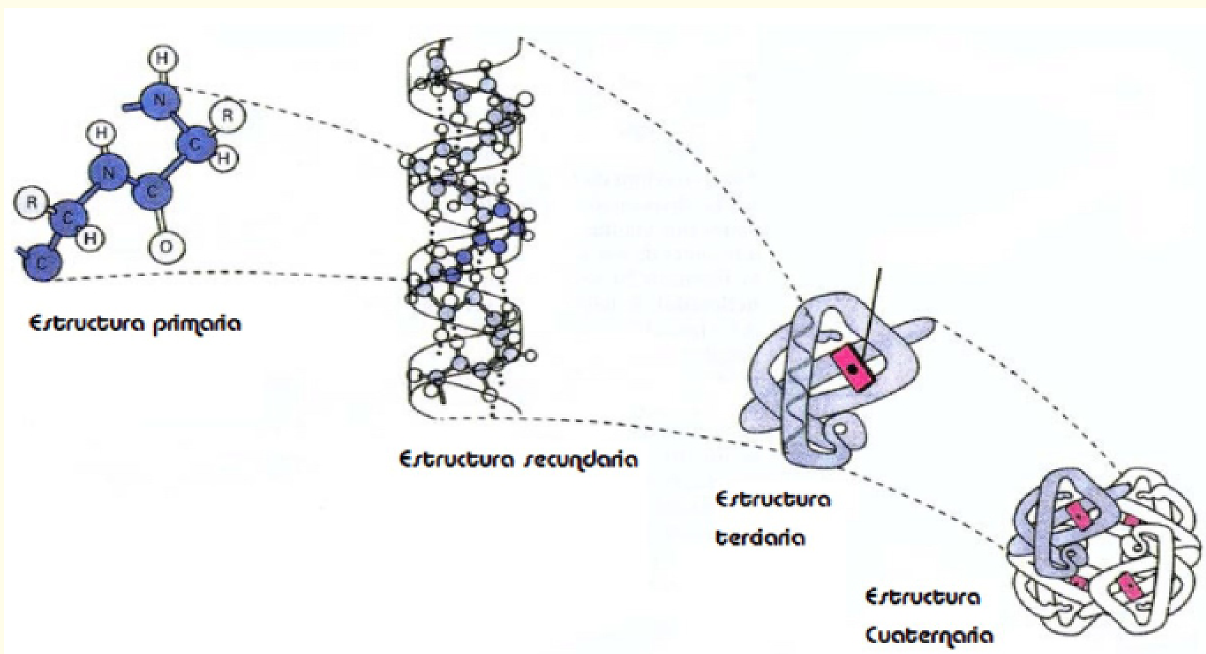

Figure 1: *Protein Structure. Primary structure (amino acid sequence), secondary structure (folding of the amino acid chain), tertiary structure (special folding of amino acids) and quaternary structure (final arrangement of more than one polypeptide chain) [13]. Translated from the picture: (a) primary structure, (b) secondary structure, (c) tertiary structure and (d) quaternary structure.*

Proteins are involved in a constant generation-degeneration cycle which is also referred to as their dynamic state. Each type of protein is degenerated on a specific path and this process of protein degeneration is referred to as protein catabolism [11,12]. The result of this process is the production of amino acids which are nitrogenous in composition and will be excreted through urine.

The nitrogen balance evaluates the relationship between the intake and excretion of nitrogen in the body. A negative balance means that the body is not only unable to form new proteins but it is also using its own as fuel which leads to a decrease in lean body mass. If this process is not stopped, death is the ultimate result.

Inflammation and Sepsis

Cells, one of the basic components of the human body, show a homeostatic system to constant intra and extracellular stimuli. This process allows cells to adapt to any change in the environment. However, there are occasions in which cells need to change as they are not able to adapt. Some of these changes come along the growth process. Other, however, are determined by factors that are not within the physiological limits in the organism, causing pathological changes in the cell [14-16].

The acute inflammatory process takes place in order to neutralise the agents responsible for the change and, if possible, bring the cell back to the homeostatic state. There are four possible outcomes: resolution, scarification, abscessification or cornification [15]. Sometimes, if these alterations occur in more than one system at a time, the inflammatory response becomes erratic, increasing the morbimortality of the pathology [17].

Sepsis, severe sepsis, and sepsis shock are the line evolution of the inflammatory response to a documented infection [16,18]. An infection is an illness caused by a pathogen that when left untreated or when the body is not able to fight it, disseminates through the organism generating a disseminated inflammatory response known as SIRS (systematic inflammatory response syndrome) [19].

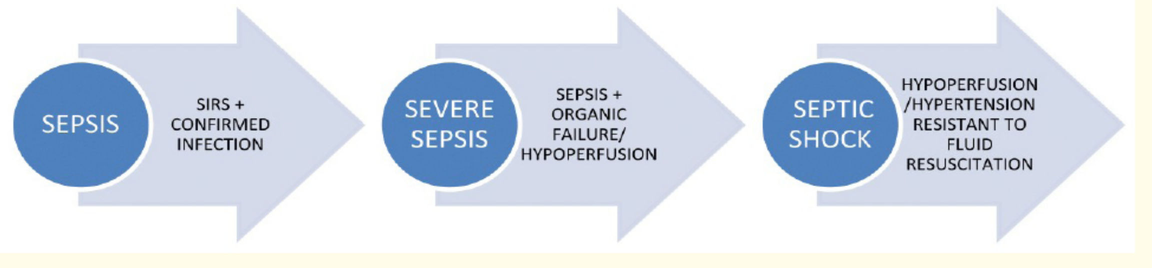

Figure 2: *Evolution from sepsis to septic shock as per NICE clinical guidelines.*

The transition from sepsis to severe sepsis or to septic shock is due to a series of physio-pathological processes. The initial reaction to infection is a neuro-humoral pro-inflammatory and generalised anti-inflammatory response. This process starts with the activation of several cells involved in the immunological response (mainly monocytes, macrophages and neutrophils) that interact with endothelial cells by means of cell surface receptors. The host response also includes the mobilisation of plasma proteins as a result of cellular activation and endothelial modification. This intricated chain of events is further amplified by the complement activation and the coagulation cascade. These interactions occur mainly at the vascular endothelial and therefore, microvascular lesion, thrombosis and loss of vascular continuity (capillary loss) are commonly found leading to tissue necrosis. This diffuse endothelial breach is the reason for the diverse organ dysfunction and the global tissue hypoxia characteristic of sever sepsis and septic shock [15,16,18].

As it can be deduced, infections affect metabolism by incrementing the nutritional requirements to not only carry out the defence mechanisms but also to create the cells required to do so. One of the signs of the altered metabolism is fever or pyrexia. An increase in body temperature causes an increase in the energy requirements which will lead to the usage of glucose and glycogen reserves in the body. Depleting the glycogen reserves from the body leads to it using alternative metabolic routes for energy production, taking not only fats but also proteins forming lean body mass as substrate for these metabolic routes. This process could be aggravated due to a symptom typically manifested by these types of patients: anorexia. Both factors will lead to a negative nitrogen balance, which in physiological terms determines loss of weight in expense of lean body mass, increasing inflammatory markers such as the CRP or lactic acid.

As it has been deducted, infective agents are agents causing organic damage. In 1929, Sir D. Cuthberston started to describe this damage [20,21]. One of the key components of his work was the catabolic phase which involves tissue destruction due to the increased energy requirements of the organism. This is demonstrated in an increased wastage of nitrogen by urine when the patient receives intravenous glucose [21].

After analysing the different physiological aspects mentioned and how they interact with each other, different questions could be proposed. Would a high protein diet prevent muscular catabolism? Should patients' diets be supplemented with specific amino acids? Does protein intake affect the patients' outcome?

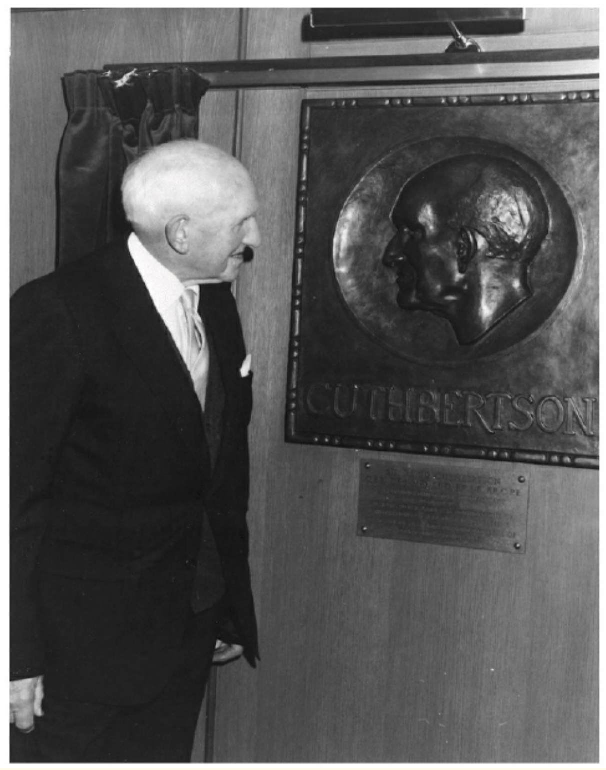

Figure 3: *Sir David Cuthberston (1900-1989) besides a commemorative image at the Glasgow Royal Infirmary, where he worked in the Biochemistry department [20].*

Methodology

In order to carry out the data review, an advanced bibliographic search was performed using MEDLINE, CINAHL, BNI and AMED using the key words PROTEIN, SEPSIS, NUTRITION and PROTEIN REQUIREMENTS linked together with the terms AND. Twenty eight articles were found which were further reduced to ten after excluding articles that took into consideration surgical and paediatric patients.

Another search was carried out in the databases CUIDEN and CUIDEN PLUS to include articles published in Spanish with the terms NUTRICION, SEPSIS, PROTEINAS linked together with the term AND. This search resulted only in fourteen articles. However, only one was analysed further due to the aforementioned excluding factors.

Due to the lack of literature in these last databases, another search was carried out on the database SCIELO with the terms NUTRICION and SEPSIS linked together with the term AND. Twenty-five articles were found and seven were selected for further analysis.

After a critical study of the selected articles, only five were relevant to the Project presented.

Results

Author/year	Sample	Design/ method	Intervention	Data	Findings	Others
Ishibashi N., *et al.* [21] 1992	Patients presenting post-trauma or with severe sepsis	Retrospective study	*In vivo* neutron activation study 3 groups, 3 different daily protein intake (1.1, 1.5, 1.9).	Muscular loss mass of 1.2 +/- 0.7 kg	1.1 → 1.5 = Lean mass loss is halved →1.9 = no further improvement.	Protein requirements were calculated by the lean body mass, hydrated
Sasha CAT., *et al.* [22] 2011	9 adolescent septic patients receiving TPN	Single centred randomised crossover trial	High amino acid profile diets in estándar or high levels. 2 day crossover		High amino acid profile improves protein balance Insulin levels reduce protein synthesis but also protein catabolism	Endogenous glucose formation was not reduced Lipolisis was increased
C Ortiz Leyba., *et al.* [23] 2005		Data review and new guidelines recommendation.	Actual literature		High protein diet Harris –Bennedict equation should be altered on the septic patient.	
TOmoya Hirose., *et al.* [4] 2014	77 ITU patients	Retrospective study	Outcome factors evaluation based on maximum and minimum plasma levels of amino acids.		An altered protein balance increases the mortality	More evidence is needed
Michael J Rennie., *et al.* [24] 2009		Literature review	Evaluation of lean body mass loss due to inability to maintain protein turnover		Lean body mass loss should be prevented Increase of microvascular nutrition is essential.	New guidelines should be presented.

Table 1: *Summary of the results obtained.*

Discussion

We face a topic that has not been deeply researched, but the investigation done shows interesting and valuable conclusions. Generally speaking, metabolic support in intensive care is a topic with little research to reinforce current practices. However, it is a part of the medical treatment that is of great interest among the medical community [26].

In the 80s, diets specifically designed for certain pathologies were starting to be used even though they proved to be of very little difference in patient outcomes [26]. The diet required for the critically-ill patient was, and still is, a common debate topic among intensivists. Not only the nutritional requirements but also the routes of administration are aspects to consider [27]. However, one thing the community seems to have an agreement on is that adequate caloric intake is essential for these patients. Studies show that nitrogen losses in the critically ill patient is elevated and it is something to monitor closely which makes the protein requirements of these patients one of the main concerns in nutritional planning [26]. However, current investigation has switched from considering protein intake as a whole to basing the study on what that protein intake is made of. Dietary aminogram is essential, proving that increasing the intake of some specific amino acids could be more beneficial than just a high protein diet [26,28-30].

Among the studied amino acids, Glutamine, an amino acid discovered in the 1960s, is considered essential in oxidative stress conditions [29]. Glutamine could have beneficial effects in, among others: anti-oxidant effect, nucleotide synthesis, immunological system protector and protective effect of the cellular membranes [26,30]. In addition, Glutamine is a metabolite used for the synthesis of other amino acids including Arginine and Citrulline [30].

Another well-studied amino acid is Arginine. This amino acid, as Glutamine, is essential in metabolic stress status due to its role in the nitric oxide metabolic pathways [28]. Furthermore, it cannot only be synthesised from Glutamine but it can also be supplemented. However, more studies involving Arginine and its effects are needed as its efficacy has not been as studied as Glutamine.

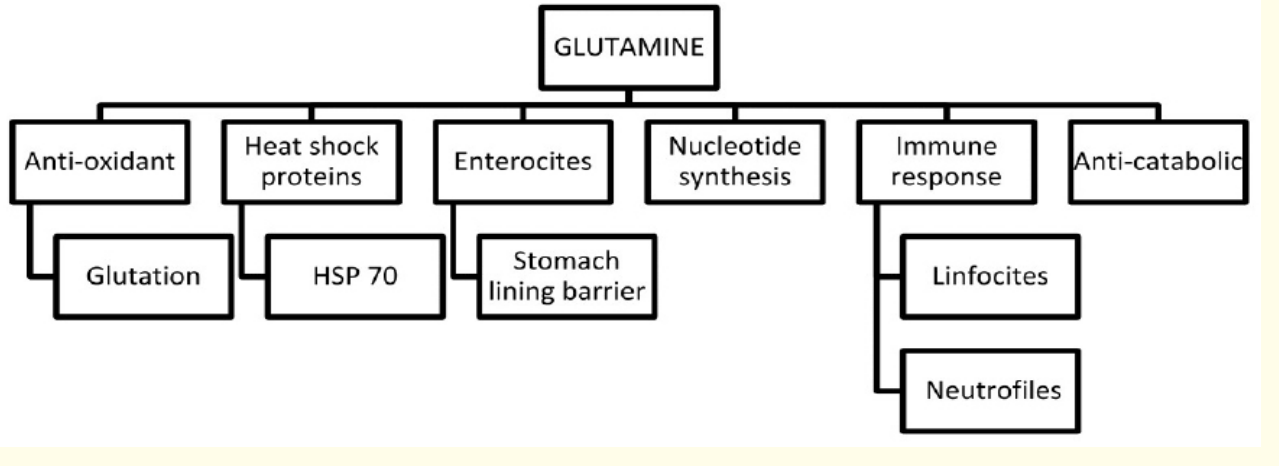

Figure 4: *Glutamine roles [30].*

Leaving aside the amino acids, protein turnover hormonal regulation cannot be neglected. Endocrinological control of these patients is essential in order to correct the catabolic state influenced by muscular fatigue which can be observed in these patients whilst in intensive care [31-33].

One thing that can be observed is the fact that intensive care is a location where recommendations are flexible and not followed in every case [7,34] which increases the risk of malnutrition in the hospitalised patients. On top of this, the micronutrient requirements cannot be forgotten as they are essential in adequate hormonal function [35].

Nutrition in intensive care is, in some countries, not the main focus of patient care as it can be derived from the review done. However, it is a fundamental rock in the patient's treatment.

Although the prescription of a high-protein diet might be the most adequate approach in this case, more research is needed in order to reach a relevant conclusion. Diet planning in the septic patient does not only require macronutrient prescription but also an exhaustive approach, which should be re-analysed including routes of administration, supplementation, and precise time of nutritional intake prescription among others.

Conclusion

The literature review performed lacks an abundance of articles covering the topic studied. However, the data presented are key to understanding the increase in catabolism on the septic patient.

Doctor Nobuya Ishibashe [22] already mentioned in 1998 that the current guidelines on the septic patient are not adequate due to the level of dehydration with which these patients usually present. If preadmission information could not be obtained, protein intake should be prescribed in a 1 gr/kg/day proportion. Another key finding is that further increase after 1.5 gr/kg/day there is no further increase in the maintenance of lean body mass.

Doctor Verbruggen [23] conducted her research in 2011, analysing the effects of high and low amino acid profile diets with teenage patients. She observed that the current recommendations did not take into account the degree of insulin resistance which could develop. When the patients were showings signs of insulin resistance these recommendations would not be beneficial, as even though a high amino acid profile could be beneficial, insulin levels need to be monitored and controlled.

Dr Rennie [25] based his research on the idea that the protein needs of the septic patient are being forgotten in the assessments and care planning. He concluded that catabolism is a problem that should be treated not only in the septic patient but also in the ageing population and when mobility is reduced.

Tomoya Hirose [4] based his research on the fact that protein metabolism is essential for wound healing, immunological response and to maintain lean muscle mass. However, he was not able to find guidelines specifically designed for the septic patient. He concluded that the aminogram was closely related to septic patients' mortality and to an increased stay on the intensive care units.

Ortiz Leyba [24] designed new dietary recommendations to improve outcomes after analysing the artificial nutrition recommendations for septic patients. The recommendations designed involve all the nutritional aspects of the patient's dietary requirements but he makes a special reference to the protein requirements of such patients. He found that increased intake of branch-chain amino acids are linked to lower hospital stays and better outcomes. Among the recommendations, the highlight is on a high protein diet in the septic patient.

The lack of results and their vagueness are evident. However, the need of further investigation is something all of the presented articles agreed on in order to improve the care and outcome of the septic patient in the intensive care unit.

Disclaimer

Project presented as the end of Master's project for the Master's in Nutrition for Health Promotion by the Universidad Complutense de Madrid.

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