Review Article

Autophagy, critical illness and nutrition therapy: a narrative review for non-specialists

Autofagia, doença crítica e terapia nutricional: uma revisão narrativa para não especialistas

DOI: 10.37111/braspenj.2021.36.4.13

Haroldo Falcão Ramos da Cunha[1]

Keywords:
Autophagy. Macroautophagy. Nutrition Therapy. Critical care.

Unitermos:
Autofagia. Macroautofagia. Terapia Nutricional. Cuidados Críticos.

Address for correspondence
Haroldo Falcão Ramos da Cunha
Rua Barata Ribeiro, 533 – casa 8 – Rio de Janeiro, RJ, Brazil – CEP: 22040-001
E-mail: haroldofalcao@gmail.com

Submission:
September 28th, 2021

Accepted for publication:
December 2nd, 2021

ABSTRACT

Introduction: In recent years, the concept of autophagy has been incorporated on the lexicon of intensive care unit (ICU) nutrition therapy. Macroautophagy, or simply, autophagy, is a continuous homeostatic process, through which degradation of cytoplasmic components (i.e., damaged organelles, toxic, senescent, or defective protein aggregates) occurs. **Methods:** Narrative review. **Results:** The article presents an overview of the topic focusing the interplay among autophagy, nutrition therapy and critical care illness. **Conclusions:** Although further studies on the interface between autophagy and nutrient supply are needed, nutritional therapy professionals can now reinforce their understanding of their own specialty, considering that their intervention is not limited to the mere supply of fuel for the metabolism, but extends for the induction of biochemical stimuli and signals capable of interfering with critical cellular processes in health and disease.

RESUMO

Introdução: Nos últimos anos, o conceito de autofagia foi incorporado ao léxico da terapia nutricional em unidade de terapia intensiva (UTI). Macroautofagia, ou simplesmente autofagia, é um processo homeostático contínuo, através do qual ocorre a degradação dos componentes citoplasmáticos (isto é, organelas danificadas, agregados de proteína tóxicos, senescentes ou defeituosos). **Método:** Revisão narrativa. **Resultados:** O artigo apresenta uma visão geral do tópico, enfocando a interação entre autofagia, terapia nutricional e doenças em cuidados intensivos. **Conclusões:** Embora mais estudos sobre a interface entre autofagia e aporte de nutrientes sejam necessários, os profissionais da terapia nutricional podem agora reforçar o entendimento de sua especialidade, visto que sua intervenção não se limita ao mero fornecimento de combustível para o metabolismo, mas se estende para a indução de estímulos e sinais bioquímicos capazes de interferir em processos celulares críticos na saúde e na doença.

1. Médico graduado pela Faculdade de Medicina da Universidade Federal do Rio de Janeiro (FM/UFRJ), Especialista em Medicina Intensiva pela Associação de Medicina Intensiva Brasileira (AMIB), Área de Atuação em Terapia Nutricional Parenteral e Enteral, Especialista em Nutrologia pela Associação Brasileira de Nutrologia (ABRAN), Rio de Janeiro, RJ, Brazil.

INTRODUCTION

In recent years, the concept of autophagy has been incorporated into the vocabulary of nutrition therapy in intensive care medicine. Autophagy is the intracellular process of degradation and reuse of cellular structures and organelles, capable not only of maintaining the tissue's physiological condition, but also providing substrates or components for energetic, functional, and structural purposes. It is ubiquitous among animal species and in humans, was initially studied in rare conditions such as mitochondrial diseases.

Recently, autophagy was recognized as a relevant process in other clinical scenarios as sepsis, and some authors postulates an important role in critical care patient. Since many stimuli can modulate autophagy, nutritional therapy emerges as a modulator of this process to the point of affecting the clinical outcome. In this non-systematic review, we will present key publications in nutrition therapy that supported these arguments, adding perspective to the intensive care physician and nutrition therapy specialists.

WHAT IS AUTOPHAGY AND WHY IS IT IMPORTANT?

Macroautophagy, which we will simply call autophagy, is a continuously functioning homeostatic process, through which the degradation of cytoplasmic components such as damaged organelles, toxic, senescent, or defective protein aggregates occurs. By preventing this accumulation, the formation of deposits and consequent impairment of function is avoided, as is the case, for example, of senescent mitochondria that can become sources of free radical generators. So far, autophagy is the only known mechanism for cytoplasmic removal of this type of residue[1-3].

HOW AUTOPHAGIC PATHWAYS ARE REGULATED?

As a continuous process, autophagy is modulated by several microenvironmental signals that trigger coordinated subcellular responses, varying according to cell type[4]. In skeletal muscle, it occurs by activation of two proteolytic systems, triggered by environmental, epigenetic or pathological stimuli: the ubiquitin-proteasome pathway and the lysosomal pathway. Several genes participate in this process, and some seem to have special relevance as great 'orchestrators' of autophagy, such as the FoxO gene. Reviews on autophagic pathways were publishes elsewhere and will not be explored on this review[5-8].

Although occurs physiologically, the process is susceptible to different microambiental stimulus, such as food deprivation and cellular and organic stress, resulting in disbalancing in favor to stimulation or inhibition. The promotion of autophagy may have specific effects on muscle tissue, resulting in cellular loss or, in the other extreme, its inhibition may result in accumulation of intracellular debris, inclusion bodies and dysfunctional mitochondria, with loss of function[6]. These altered processes can be noticeable under light microscopy and in functional tests: in the liver, for example, accumulation of dysfunctional mitochondria is observed in a pattern like that observed in mitochondrial diseases[5,8,9].

In chronic critically ill patients, hallmarks of insufficient autophagy activation such as accumulation of autophagic substrate and scarcity of autophagic vacuoles are present in liver and muscle tissue biopsies[6,10]. Although molecular mechanisms remain under investigation, the plausible hypothesis that itself determines lean mass loss through direct consumption of muscle fiber rests unrefuted. According to this reasoning, the sarcopenia of severe disease may be a direct result of an excess of autophagy.

New insights, however, have suggested that autophagy may have a protective role, where inhibition of autophagy would be harmful to the stress response. In this sense, the autophagic flow would be necessary in the acute phase to recycle senescent material, contributing to better cell functioning in the scenario of severe disease. A possible analogy is to compare autophagy to the sharpening of a knife: for the tool to keep it sharp and useful, it is necessary to lose a certain amount of its substance.

HOW CAN NUTRITIONAL THERAPY INTERFERE WITH AUTOPHAGY?

Micro ambiental stimulus may interfere with autophagy, promoting inhibition or intensification. A key modulating factor is nutrient availability of nutrients, a potent suppressor of autophagy, especially amino acids, insulin and other grows factors[11]. Its inhibitory role provided basis for the hypothesis explaining why full nutrition therapy in an early phase of acute critical illness may not result in better outcomes. The conundrum about the better strategy in acute phase rests unsolved, since recent trials involving more than 15000 patients could not uncontroversial show benefit in favor of early nutrition of not[12].

Although much of the discussion goes around methodologic issues, such as type of disease, gravity scores, route of nutrition therapy, recent evidence of autophagy inhibition associated mainly in the recovery phase of a life-threatening insult shed light over a potential role of the process[13].

Autophagy has been studied from a mechanistic standpoint by some groups in the context of nutrition therapy in intensive care since EPaNIC study[14]. In the study, the use of early parenteral nutrition was not associated with better prognosis compared to a more conservative strategy. At the time, the mechanisms that explained these findings were not

fully clarified. In the year following its publication, Derde et al.[15] studied a model of severe disease in rabbits, submitted to fasting and a load of isocaloric parenteral nutrition containing different proportions of glucose, amino acids and lipids. The effects of these interventions on biochemical and histological markers of autophagy failure (mitochondrial dysfunction and tissue damage) were evaluated. The offer of lipids and above all amino acids was able to suppress autophagy, causing changes in liver and muscle tissue.

The results in animal model were studied in the clinical field. In 2013, Hermans et al.[16] published a randomized and controlled trial using muscle biopsy technique and biomarker dosage to understand how the timing of total parenteral nutrition (TPN) onset affected muscle strength and the quality of myocyte autophagy. Patients with late TPN had a lower incidence of weakness than the early group (34% vs. 43%), in addition to larger cross-sectional area of the muscle fiber. Biomarkers related to the formation of the autophagosome (intracellular organ that performs autophagy) and the staining for ubiquitin were higher in the late group, showing that the autophagy pathway was enhanced. In patients with prolonged critical illness, muscular autophagy was inversely correlated with ICU-acquires weakness.

Considering this new knowledge, the EPaNIC group revisited the work to dispel some confounding elements present in the original study design. It was necessary, for example, to assess whether the deleterious effects of early parenteral nutrition were related to the severity of the disease or to the dose and type of macronutrients used, since EPaNIC trial gathered a large number of patients of the most varied types, many who even spent a short time in the intensive care unit or even with TPN. To solve this bias, post hoc analyses were made, taking in account groups stratified according to severity[17]. Two main analyses were made. In the first one, all patients were included to study the effect of the original randomization on the selection of groups that received early nutrition or not. In the second, the existence of an association between the amount and type of macronutrients in the recovery of patients was studied in the cohorts who remained in the ICU after days 3, 5, 7, 10 and 14. The primary outcome in both assessments was time to discharge from the ICU alive. For the first part of the investigation, an additional outcome was considered: the occurrence of new infections. After rebalancing according to disease severity and type, there was no interference of allocation in the outcomes found. However, it was possible to identify that a lower dose of macronutrients, especially amino acids, was associated with a faster recovery and that incremental doses were associated with a delay in recovery. The glucose supply, although high, was below the lipogenesis threshold and was not related to major deleterious effects. Consonant results were observed years later, in PEPaNIC[18], which tested EPaNIC hypothesis in the pediatric population. With no difference in mortality, the late TPN group had fewer infections than the early TPN group (10.7% vs. 18.5%; OR 0.48 and 95% CI 0.35 to 0.66). The length of stay was also shorter (6.5±0.4 days vs. 9.2±0.8 days), as well as the time on MV (p=0.001), need for dialysis (p=0.04), and time on a laboratory panel compatible with inflammation (p=0.001). Delayed parenteral nutrition was also associated with lower levels of γ-GT, bilirubin, and C-reactive protein. All these conclusions reinforced the thesis that autophagy may interplay as a relevant process in severe disease, sensible to modulation by nutritional therapy.

Another domain that rests relatively unknown are the relations between timing and route for nutritional stimulus, type of disease and autophagy. In 2014, Weijs et al.[19] found in a retrospective study that a protein intake of 1.2 g/kg/d until the fourth day was related to better survival in non-septic patients without overfeeding, and in contrast, septic or overfeed patients did not benefit of protein intake over 1.0 g/kg/d. Although at the time of publication, the theme of autophagy was not usually addressed in the nutritional therapy literature in the context of severe disease, the study suggests that the relationships between these three domains are not linear. Bendavid et al.[20], in 2019, studied the outcome of patients under nutrition therapy in two levels of protein intake, lower and higher than 0.7g ptn/kg/d, and observed that higher protein levels were related to better outcomes.

The PROTINVENT trial[21] added some insights over Bendavid' study. It was a single-center retrospective study, carried out between January 2011 and December 2015, with the objective of comparing clinical outcomes in patients with different protein intakes in the first seven days of severe disease: mortality within 6 months, length of stay in the ICU, time of hospital admission, hospital mortality, duration of mechanical ventilation and need for hemodialysis. Three groups were formed for this comparison: a) <0.8 g ptn/kg/d, b) 0.8 – 1.2 g ptn/kg/d and c) >1.2 g ptn/kg/d. In all, 455 critically ill patients with a minimum mechanical ventilation time of 7 days were included in the analysis. The researchers found a time-dependent relationship between protein offer and mortality: low offers (<0.8 g/kg/d) before D3 and high offers (>0.8 g/kg/d) after D3 were related to lower mortality in 6 months. The 6-month mortality reduction was observed when the supply was even more staggered or asymmetric, in steps of <0.8 g/kg/d in D1-D2, 0.8–1.2 g/kg/d in D3-D5 and finally >1.2 g/kg/d after D5.

It is necessary to bear in mind that the mechanisms and pathways of autophagy are not fully known. The concept that has gained ground in the field of intensive care requires further study. Clinical studies until were not able to distinguish between important domains that compose the background where nutrition time, route and targets, and model of critical disease take place. Evidence suggests that more layers of

complexity must be added to the conundrum. Tardif et al.[22], in an in vitro study using cultures of myocytes and human plasma, measured the autophagic flow, one of the ways to quantify this dynamic process. Plasma and myocytes from volunteers and critically ill patients were studied in the absence and presence of chloroquine, a known autophagy blocker. Critically ill patients responded in 3 possible ways: indifferent, with increased autophagic flow or with its blockage. An increase in autophagic flux was observed when the plasma level of essential amino acids was lower. When this level was higher, however, no autophagy blockade was observed. Thus, the authors concluded that early enteral nutrition in severe disease, although not able to completely block autophagy, may contribute to a certain attenuation of the beneficial effect. In vitro studies, although not reflecting the complexity of critically ill patients, have the virtue of denying the null hypothesis that autophagy happens in a simple way, without admitting nuances of the most diverse types. In other words, autophagy may present with different phenotypes depending on host response.

CLINICAL APPLICATIONS OF AUTOPHAGY

Until this moment, clinical management should be guided by bedside judgement and high quality randomized controlled trials and guidelines that does not support early full nutrition support in critically ill patients. Autophagy rests as an interesting but to be evolved concept, not feasible to be measured in clinical setting due to extensive laboratory testing and biopsies[23].

Pharmacological manipulation by autophagy inducers or inhibitors may be in the future an important tool[24]. Drugs as rapamycin has shown effect in overcome feeding-induced suppression of autophagy and reduce morbidity in an animal model[25]. Potential immunosuppressive or diffuse effects may preclude its widespread use in critically ill patients.

THE BENEFIT OF THE DOUBT

Although several authors have advocated a protective role of autophagy in critical illness[26,27], others keep skeptical about its role as a main driver[28,29]. From preclinical studies to the randomized trials, there are evidence of benefit early, but no full, enteral nutrition in critical care patients.

Catabolism of protein and oxidation of amino acids is related to disease severity or the degree of oxidative stress. Neither starvation nor feeding imposes as relevant factor in reducing protein degradation and amino acids usage. By the other hand, both result in reduced protein synthesis[30]. How these mechanisms may influence the clinical course of the critically ill patient is unknown and more aspects with added complexity must be taken in account. Each patient may present himself with unique needs for its own cellular substrates to be recycled in autophagic process, far from the idea of an all or nothing process. These individual demands may be also modified by insulin supplementation or nutrition therapy strategy. It is worth considering that although autophagy operates as an active life-long process even during physiological crisis, it may have different relevance depending on critically ill disease phase, such as chronic critically ill patients.

Although the interactions between autophagy and critical illness have been studied, it is worth not do replace significative amount of evidence on the benefits of enteral nutrition therapy.

A balanced autophagy response is therefore probably ideal for optimal outcome. Neither nutrient excess (or overfeeding/hyperglycemia) leading to impaired autophagy nor starvation leading to massive breakdown of lean body mass for inefficient energy generation by amino acid stores (or too much autophagy). This is probably best achieved by adequate and balanced nutrition application in critical illness, including sufficient protein to minimize cellular and lean body mass losses. The ideal dose of each macronutrient needed to optimize this balance is unknown and is a basic question needing further research.

CONCLUSION

The discovery of autophagy and, above all, the power of nutritional stimulation in modulating the autophagic flow opens new perspectives for understanding how nutritional therapy can be even more fully related to the recovery of critically ill patients. However, this new pathway must be viewed as another piece in the puzzle, rather than a new mechanism replacing others. Autophagy, as a physiological process, must be viewed not statically, but dynamically, as an adaptive response that admits different grades, with modes of operation depending on tissues and organs[23].

In this sense, autophagy emerges as a potentially important therapeutic target in critical illness, that must be taken in account as part of managing nutrition under uncertainty. In the scarcity of lab tests to monitor autophagy, the decision making will pendulate between withholding autophagic stimulus, e.g., withholding nutrition, or coping with increasing risks for starvation. In the future, research may identify novel agents suitable ICU patients.

In an epistemological perspective, as new physiological pathway, researchers and clinicians must exercise the prudence and judicious clinical reasoning in order to accommodate new evidence, with its positivity, without immediate replacement of the actual knowledge basis.While we await further studies on the interface between autophagy and nutrient supply, nutritional therapy professionals can now reinforce their understanding of their own specialty, considering that their

intervention is not limited to the mere supply of fuel for the metabolism, but extends for the induction of biochemical stimuli and signals capable of interfering with critical cellular processes in health and disease.

REFERENCES

1. Saha S, Panigrahi DP, Patil S, Bhutia SK. Autophagy in health and disease: a comprehensive review. Biomed Pharmacother. 2018;104:485-95.
2. Parzych KR, Klionsky DJ. An overview of autophagy: morphology, mechanism, and regulation. Antioxid Redox Signal. 2014;20(3):460-73.
3. Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature. 2008;451(7182):1069-75.
4. Masiero E, Agatea L, Mammucari C, Blaauw B, Loro E, Komatsu M, et al. Autophagy is required to maintain muscle mass. Cell Metab. 2009;10(6):507-15.
5. Lecker SH, Goldberg AL, Mitch WE. Protein degradation by the ubiquitin-proteasome pathway in normal and disease states. J Am Soc Nephrol. 2006;17(7):1807-19.
6. Sandri M. Signaling in muscle atrophy and hypertrophy. Physiology (Bethesda). 2008;23:160-70.
7. Mammucari C, Milan G, Romanello V, Masiero E, Rudolf R, Del Piccolo P, et al. FoxO3 controls autophagy in skeletal muscle in vivo. Cell Metab. 2007;6(6):458-71.
8. Zhao J, Brault JJ, Schild A, Cao P, Sandri M, Schiaffino S, et al. FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. Cell Metab. 2007;6(6):472-83.
9. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell. 2008;132(1):27-42.
10. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Güiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. 2011;96(4):E633-45.
11. Cuervo AM, Macian F. Autophagy, nutrition and immunology. Mol Aspects Med. 2012;33(1):2-13.
12. Gunst J. Recovery from critical illness-induced organ failure: the role of autophagy. Crit Care. 2017;21(1):209.
13. Van Dyck L, Casaer MP, Gunst J. Autophagy and its implications against early full nutrition support in critical illness. Nutr Clin Pract. 2018;33(3):339-47.
14. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506-17.
15. Derde S, Vanhorebeek I, Güiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology. 2012;153(5):2267-76.
16. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1(8):621-9.
17. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Resp Crit Care Med. 2016;187(3):247-55.
18. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med. 2016;374(12):1111-22.
19. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014;18(6):701.
20. Bendavid I, Zusman O, Kagan I, Theilla M, Cohen J, Singer P. Early administration of protein in critically ill patients: a retrospective cohort study. Nutrients. 2019;11(1):106.
21. Koekkoek WACK, van Setten CHC, Olthof LE, Kars JCNH, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: the PROTINVENT retrospective study. Clin Nutr. 2019;38(2):883-90.
22. Tardif N, Polia F, Tjäder I, Gustafsson T, Rooyackers O. Autophagy flux in critical illness, a translational approach. Sci Rep. 2019;9(1):10762.
23. Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016;12(1):1-222.
24. Levine B, Packer M, Codogno P. Development of autophagy inducers in clinical medicine. J Clin Invest. 2015;125(1):14-24.
25. Gunst J, Derese I, Aertgeerts A, Ververs EJ, Wauters A, Van den Berghe G, et al. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. Crit Care Med. 2013;41(1):182-94.
26. Owen HC, Vanhees I, Gunst J, Van Cromphaut S, Van den Berghe G. Critical illness-induced bone loss is related to deficient autophagy and histone hypomethylation. Intensive Care Med Exp. 2015;3(1):52.
27. Rosenthal MD, Carrott P, Moore FA. Autophagy: should it play a role in ICU management? Curr Opin Crit Care. 2018;24(2):112-7.
28. McClave SA, Weijs PJ. Preservation of autophagy should not direct nutritional therapy. Curr Opin Clin Nutr Metab Care. 2015;18(2):155-61.
29. Heyland DK, Wischmeyer PE. Does artificial nutrition improve outcome of critical illness? An alternative viewpoint! Crit Care. 2013;17(4):324.
30. Berg A, Rooyackers O, Bellander BM, Wernerman J. Whole body protein kinetics during hypocaloric and normocaloric feeding in critically ill patients. Crit Care. 2013;17(4):R158.

Institution where the study was conducted: Clínica São Vicente, Rio de Janeiro, RJ, Brasil.

Conflict of interest: The author declares none.