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Clinical Science of Nutrition (Cli Sci Nutr) is the peer-reviewed, not-for-profit, open access, scholarly, online only publication of the Society of Clinical Enteral Parenteral Nutrition - Turkey. The journal is published tri-annually in April, August, and December and its publication language is English.

The journal aims to contribute to the literature by publishing high impact content and become one of the leading publications of the field while functioning as an open discussion forum on significant issues of current interest. Clinical Science of Nutrition also aims to have significant input in emphasizing the increasing importance of clinical nutrition in Turkey and the region, identifying the effects of differences between societies on study results in a clearer way and converting clinical applications into scientific publications as well as forming a bridge between West and East.

The scope of Clinical Science of Nutrition includes original research articles, review articles, case reports, conference reports, and letters to the editor as well as editorials, abstracts from international and national congresses, panel meetings, conferences and symposia. As an online-only publication, in addition to traditional manuscript submissions, Clinical Science of Nutrition is also able to process video, audio and interactive software submissions. Authors, are encouraged to submit their content in the most appropriate medium to best convey their findings to the audience of Clinical Science of Nutrition.

The journal covers all aspects of nutrition and dietetics including prevalence of malnutrition and its effects on clinical results; nutritional support and delivery methods and their advantages and disadvantages; nutritional support products and their side effects; immune system and nutritional support; ERAS protocol and nutritional support; home parenteral and enteral nutrition; nutrition support teams and their necessity, challenges and potential solutions of nutritional support.

The journal's target audience includes academicians, practitioners, specialists and students interested in nutrition and dietetics.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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CLINICAL SCIENCE OF NUTRITION

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2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, and Discussion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Ar-

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Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 15% in the journal. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with ISO 4 standards. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	300 (Structured)	50	6	7 or total of 15 images
Review Article	6000	300	60	6	10 or total of 20 images
Case Report	2500	250	20	No tables	10 or total of 20 images
Letter to the Editor	1000	No abstract	5	No tables	No media
Editorial	1000	No abstract	5	No tables	No media

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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CONTENTS

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Invited Review

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Malnutrition, apoptosis, and autophagy triangle in critically ill patients

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ABSTRACT

Malnutrition is an important cause of mortality and morbidity in critically ill patients. Moreover, malnutrition leads to increased apoptosis leading to secondary immune deficiency. Nutritional support is therefore an important aspect of patient care in critically ill patients. Although total parenteral nutrition (TPN) provides sufficient energy and protein requirement to critically ill patients, it increases the risk of infection by inducing apoptosis in the intestinal epithelial cells resulting in the loss of mucosal epithelial barrier function. However, early parenteral nutritional support inhibits autophagy in critically ill patients, leading to suppression of natural immunity, infection development, and increased organ dysfunction. Autophagy is an important repair process in the recovery of organ dysfunction caused by critical disease. Therefore, the absence of parenteral nutritional support in the acute phase of critical disease stimulates autophagy and accelerates recovery. Even though it is thought that fasting-activated autophagy may have positive effects on critical illness, early trophic/hypocaloric enteral nutrition support should be initiated in patients at high risk of malnutrition.

Keywords: Apoptosis, autophagy, enteral nutrition, inflammation, malnutrition

There is a rapid catabolic process caused by systemic inflammatory response in critically ill patients treated in intensive care units. This catabolic process leads to malnutrition by causing imbalances in protein and energy metabolisms (1).

Approximately 10%-70% of hospitalized patients have signs of malnutrition. More importantly, malnutrition remains undiagnosed in 70% of the patients, and 70%-80% of the patients do not receive any nutritional support in the hospital. Malnutrition occurs more rapidly due to the underlying inflammatory response and catabolic stress in critically ill patients monitored in intensive care units (2).

On the other hand, malnutrition is still an important cause of secondary immune deficiency with unclear mechanisms. Malnutrition changes the immune response by reducing cell-mediated immunity, phagocytosis function, secretory antibody response, and antibody affinity, and influencing the complement system and cytokine production. Thus, especially in critically ill patients, the malnutrition-induced immune dysfunction often presents with an infection that becomes an important risk factor for sepsis and mortality (3). Malnutrition in critically ill patients leads to the development of complications such as decreased respiratory muscle strength, consequently leading to low ventilation capacity, prolonged mechanical ventilation time, delayed wound healing, prolonged intensive care stay, and increased morbidity and mortality (1, 2, 4, 5).

Some studies have reported that the provision of caloric requirements by early enteral nutrition in critically ill patients reduces the hypermetabolic response (6, 7). In addition, early initiation of enteral nutrition has been shown to help promote intestinal mucosal integrity, motility, and intestinal blood flow (8). In addition, enteral nutrition has been shown to provide significant improvement in organ dysfunction score, reduce the incidence of infection, shorten the length of hospital stay, and accelerate wound healing (9).

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Apoptosis

Apoptosis is a type of cell death called programmable cell death (Type I), in which cells destroy themselves without inflammation, and is regulated by genes, requires protein synthesis and energy, and promotes homeostasis in an organism. It was first described in 1972 by Kerr et al. (10) with the term "physiological cell death." Although apoptosis appears as a physiological mechanism for homeostasis during development and aging, it can also occur as a defense mechanism against pathological stimuli, like when cells are damaged by disease or harmful agents (Figure 1).

Many genes in an organism mediate the mechanism of apoptosis (11). Inhibition or overexpression of genes controlling apoptosis has an important role in the pathogenesis of diseases in humans. In this context, apoptosis appears to be a very important mechanism in the pathophysiology of sepsis. Increased apoptosis of lymphocytes from immune cells in patients with sepsis is accompanied by decreased apoptosis of leukocytes (12). While one is the main determinant of immune dysfunction, the other is a sign of persistent infectious inflammation observed in sepsis (11). In sepsis, gastrointestinal and pulmonary epithelial cells undergo intense apoptosis, which is one of the main reasons for organ dysfunction. All of these have been reported to contribute to the development of impaired immune response during sepsis and sepsis-induced organ dysfunction (10, 13).

Relationship Between Nutrition and Apoptosis

Malnutrition is an important cause of apoptosis in critically ill patients. In studies examining the relationship

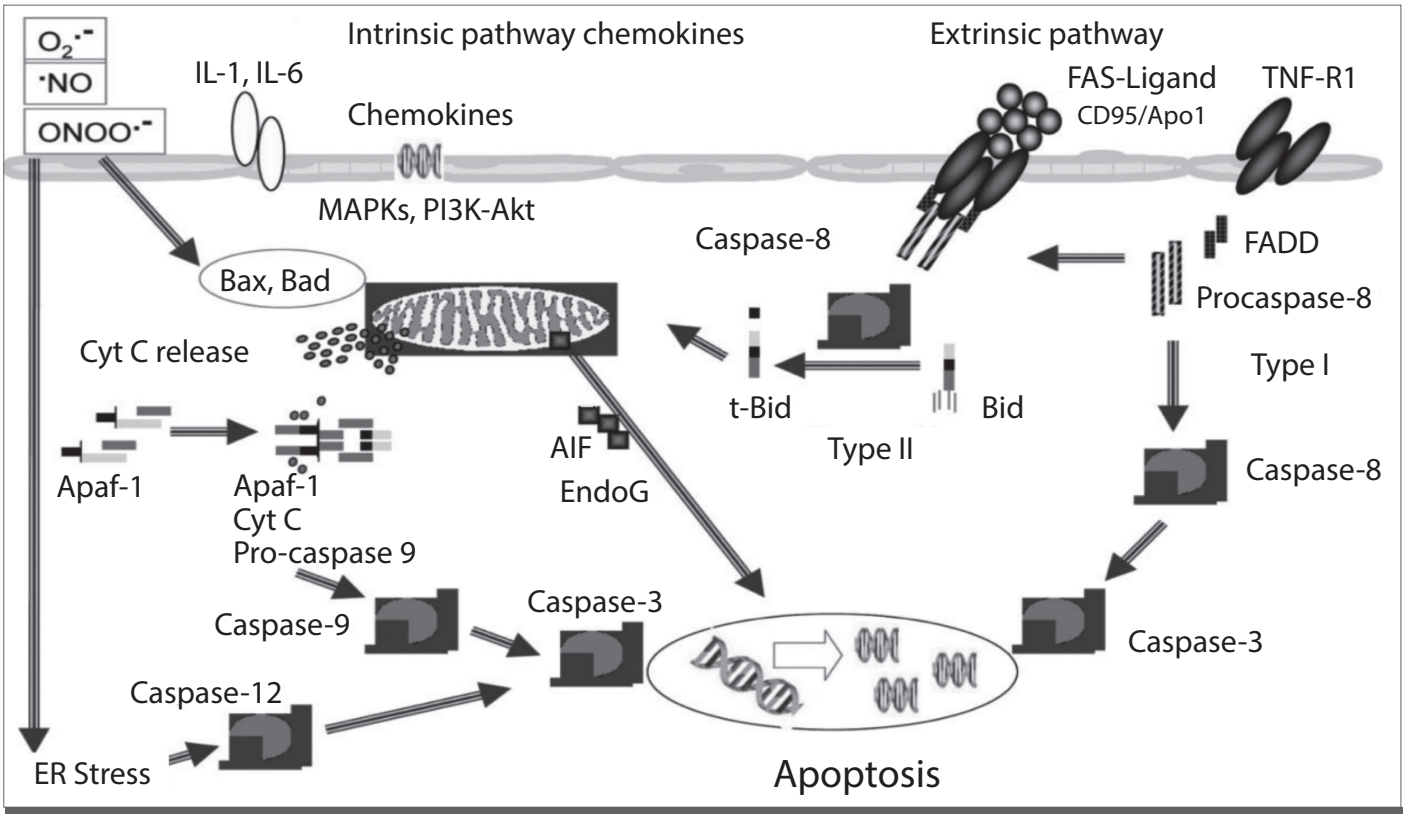

Figure 1. Summary of the extrinsic pathway (death receptor pathway) that initiates apoptosis by transmembrane receptor-mediated interactions and the intrinsic pathway that causes changes in the inner membrane of the mitochondria initiated by intracellular signals. Intracellular signals are DNA damage, increased intracellular calcium levels, decreased pH, metabolic and/or cell cycle disorders, and hypoxia. Extracellular signals are inadequate growth and reproduction factors, activation of death receptors (Fas-FasL or TNF mediated), cytotoxic T lymphocytes and ischemia, toxins, UV, chemotherapeutic drugs, and external factors such as radiation. In both signal paths, caspases are employed

MAPK: mitogen-activated protein kinase; PI3K-Akt: phosphoinositide 3-kinase/Akt; APAF-1: apoptosis protease activating factor-1; ER: endoplasmic reticulum; IL: interleukin; Cyc C: cytochrome C; Endo G: endonuclease G; TNF: tumor necrosis factor

Table 1. Effects of total parenteral nutrition on the intestinal system
Mucosal atrophy as a result of decrease in intestinal epithelial cell proliferation and increased apoptosis
Decrease in mucosal epithelial barrier function as a result of reduction in crypt/villus complex number
Reduction of intraepithelial lymphocyte and lamina propria lymphocyte counts
Increased bacterial translocation as a result of impaired intestinal barrier function

between malnutrition and apoptosis, malnutrition has been shown to reduce the expression of Bcl-2 gene family proteins, which have been shown to have anti-apoptotic activity, and consequently increase apoptosis in peritoneal macrophages (14). Similarly, severe malnutrition developed in experimental animals has been shown to cause increased apoptosis in thymus and spleen cells. On the other hand, malnutrition can delay the apoptotic functions of neutrophils and mononuclear cells (3, 14-17). It has been proposed that malnutrition in critically ill patients causes increased apoptosis, changes defense mechanisms, leads to dysfunction of lymphohematopoietic organs, and changes immune response, and is an important risk factor for the development of sepsis. Although the effects of malnutrition on the hematopoietic system are still unclear, they appear to be responsible for inadequate hematopoiesis, which is irreversible in the short term.

Inadequate activation of neutrophils has an important role in acute respiratory distress syndrome (ARDS) and the pathogenesis of sepsis. Apoptosis is necessary for the removal of neutrophils from the tissue that has developed inflammation and for timely resolution of inflammation. Resolvins and protectins endogenously produced from eicosapentaenoic acid (immunomodulatory effective nutrition) substrates have been shown to increase phagocytic clearance of bacteria, reduce inflammation severity, modulate neutrophil chemotaxis, and provide neutrophil apoptosis (16, 18, 19). However, resolvins, which increase inflammation by increasing the apoptosis of neutrophils in ARDS, have also been shown to have a protective effect against reperfusion damage and heart failure in cardiomyocytes after myocardial infarction (20, 21).

Although total parenteral nutrition (TPN) provides sufficient energy and protein requirements to critically ill patients, it may lead to sudden malnutrition of the intestinal system (22). Numerous studies have shown that TPN causes significant physical changes in the intestinal mucosa and significant changes in the intestinal mucosal immunity. It has been reported that TPN application increases intestinal permeability, induces apoptosis of intestinal epithelial cells, reduces intraepithelial lymphocyte and lamina propria lymphocyte counts, and causes mucosal imbalance of intestinal cytokines (22-24). However, it has been shown that administration of TPN instead of enteral nutrition leads to changes in the expression of intestinal Toll-like receptors and cytokine by inducing apoptosis in interferon-g mediated intestinal cells, resulting in the development of bacterial translocation and sepsis (Table 1) (23).

Relationship Between Nutrition and Autophagy

Autophagy or programmable cell death (Typ II), literally meaning "self-eating of the cell," is an important biological mechanism leading to the breakdown of intracellular proteins and organelles in lysosomes by being enclosed in vesicles (25, 26). Autophagy has been shown to assist in the maintenance of homeostasis by providing recycling of intracellular molecules in the event of short-term starvation or cellular stress (27). While fasting, glucagon, oxidative stress, and glutamine provide stimulation of autophagy, nutrition, insulin, and hyperglycemia cause inhibition of autophagy (28). The protection of homeostasis in cellular stress in critical disease depends on the interaction between autophagy and inflammasome, while autophagy stimulation has also been shown to be protective against organ dysfunction and mortality (Figure 2) (29).

The relatively new concept of autophagy has just entered the field of nutrition. In pathophysiological studies, which report that early full nutrition has no effect on mortality in critically ill patients, negative results are shown; early full nutrition has been shown to inhibit autophagy and fail to suppress endogenous catabolism (30). However, studies have shown that inhibition of autophagy of the liver and skeletal muscle develops after parenteral nutritional support in critical illness and consequently increases muscle weakness and muscle loss (31-33). Moreover, it is thought that autophagy suppressed by early parenteral nutritional support in critically ill patients may lead to suppression of natural immunity and may contribute to an increase in infection rate and organ dysfunction (34, 35).

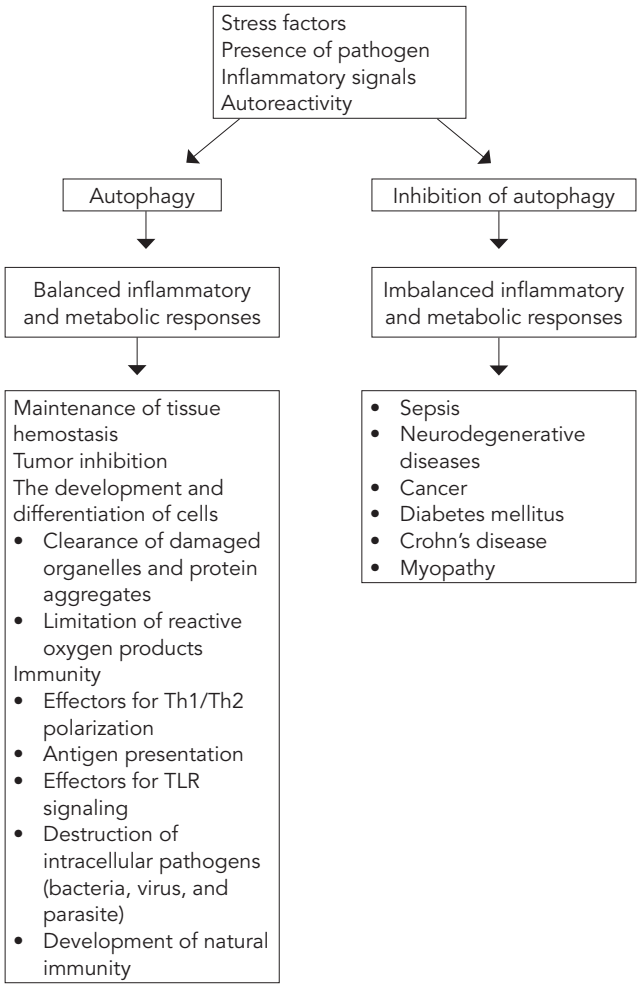

Figure 2. Physiological and pathological roles of autophagy. The main role of physiological autophagy is to ensure the maintenance of homeostasis by clearing the damaged organelles and protein aggregates from the cytoplasm. Autophagy contributes to both natural and adaptive immunity. Inhibition of autophagy is the basis of many diseases

In experimental studies in which the effect of macronutrient composition on autophagy was examined, inhibition of autophagy and organ damage caused by nutrition have been shown to be more serious for nutrients containing high amino acid contents than nutrients containing high lipid and carbohydrate contents (31, 36). These findings have been confirmed in studies conducted in critically ill patients. In the subgroup analysis of the EPaNIC study, muscle biopsies performed in patients receiving early parenteral nutritional support have shown that autophagy is less activated and consequently more muscle weakness and a longer recovery period are observed (32, 35).

In summary, although fasting in acute critical disease is thought to be an adaptive response and may be beneficial in activating autophagy in the acute phase, the risk of malnutrition should be screened within 48 hours of admission, given the adverse effects of malnutrition. Intensive care patients with high risk of malnutrition should be evaluated in detail. Considering the fact that enteral nutrition prevents the development of infection, decreases the length of stay in the ICU and mechanical ventilator, and has positive effects on mortality and preservation of gastrointestinal system mucosal integrity in critically ill patients with high risk of malnutrition, it is valuable. Consequently, considering the reduction of bacterial translocation and, more importantly, the effects of early complete enteral nutritional support on autophagy inhibition, early trophic enteral nutritional support should be initiated within the first 24-48 hours.

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References

1. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review [Formula: see text]. JPEN J Parenter Enteral Nutr 2017; 41: 744-58. [CrossRef]
2. Maday KR. The importance of nutrition in critically ill patients. JAAPA 2017; 30: 32-7. [CrossRef]
3. Cakir FB, Berrak SG, Aydogan G, Tulunay A, Timur C, Canpolat C, et al. Effects of Malnutrition on Neutrophil/Mononuclear Cell Apoptotic Functions in Children with Acute Lymphoblastic Leukemia. Nutr Cancer 2017; 69: 402-7. [CrossRef]
4. Allen K, Hoffman L. Enteral Nutrition in the Mechanically Ventilated Patient. Nutr Clin Pract 2019; 34: 540-57. [CrossRef]

5. Mogensen KM, Horkan CM, Purtle SW, Moromizato T, Rawn JD, Robinson MK, et al. Malnutrition, Critical Illness Survivors, and Postdischarge Outcomes: A Cohort Study. JPEN J Parenter Enteral Nutr 2018; 42: 557-65. [CrossRef]
6. Mochizuki H, Trocki O, Dominioni L, Alexander JW. Reduction of postburn hypermetabolism by early enteral feeding. Curr Surg 1985; 42: 121-5.
7. McDonald WS, Sharp CW, Jr., Deitch EA. Immediate enteral feeding in burn patients is safe and effective. Ann Surg 1991; 213: 177-83. [CrossRef]
8. Dominioni L, Trocki O, Fang CH, Mochizuki H, Ray MB, Ogle CK, et al. Enteral feeding in burn hypermetabolism: nutritional and metabolic effects of different levels of calorie and protein intake. JPEN J Parenter Enteral Nutr 1985; 9: 269-79. [CrossRef]
9. Ostadrahimi A, Nagili B, Asghari-Jafarabadi M, Beigzali S, Zalouli H, Lak S. A Proper Enteral Nutrition Support Improves Sequential Organ Failure Score and Decreases Length of Stay in Hospital in Burned Patients. Iran Red Crescent Med J 2016; 18: e21775. [CrossRef]
10. Kerr JF. History of the events leading to the formulation of the apoptosis concept. Toxicology 2002; 181-182: 471-4. [CrossRef]
11. Cinel I, Opal SM. Molecular biology of inflammation and sepsis: a primer. Crit Care Med 2009; 37: 291-304. [CrossRef]
12. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. Nat Rev Immunol 2006; 6: 813-22. [CrossRef]
13. Spapen HD, Jacobs R, Honoré PM. Sepsis-induced multi-organ dysfunction syndrome-a mechanistic approach. J Emerg Crit Care Med 2017; 1. [CrossRef]
14. Rivadeneira DE, Grobmyer SR, Naama HA, Mackrell PJ, Mestre JR, Stapleton PP, et al. Malnutrition-induced macrophage apoptosis. Surgery 2001; 129: 617-25. [CrossRef]
15. França T, Ishikawa L, Zorzella-Pezavento S, Chiuso-Minicucci F, da Cunha M, Sartori A. Impact of malnutrition on immunity and infection. J Venom Anim Toxins Incl Trop Dis 2009; 15: 374-90. [CrossRef]
16. Ortiz R, Cortes L, Cortes E, Medina H. Malnutrition alters the rates of apoptosis in splenocytes and thymocyte subpopulations of rats. Clin Exp Immunol 2009; 155: 96-106. [CrossRef]
17. Cortes-Barberena E, Gonzalez-Marquez H, Gomez-Olivares JL, Ortiz-Muniz R. Effects of moderate and severe malnutrition in rats on splenic T lymphocyte subsets and activation assessed by flow cytometry. Clin Exp Immunol 2008; 152: 585-92. [CrossRef]
18. Weylandt KH, Chiu CY, Gomolka B, Waechter SF, Wiedenmann B. Omega-3 fatty acids and their lipid mediators: towards an understanding of resolvin and protectin formation. Prostaglandins Other Lipid Mediat 2012; 97: 73-82. [CrossRef]
19. El Kebir D, Gjorstrup P, Filep JG. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci U S A 2012; 109: 14983-8. [CrossRef]
20. Keyes KT, Ye Y, Lin Y, Zhang C, Perez-Polo JR, Gjorstrup P, et al. Resolvin E1 protects the rat heart against reperfusion injury. Am J Physiol Heart Circ Physiol 2010; 299: H153-64. [CrossRef]
21. Halade GV, Kain V, Serhan CN. Immune responsive resolvin D1 programs myocardial infarction-induced cardiorenal syndrome in heart failure. FASEB J 2018; 32: 3717-29. [CrossRef]
22. Ralls MW, Demehri FR, Feng Y, Woods Ignatoski KM, Teitelbaum DH. Enteral nutrient deprivation in patients leads to a loss of intestinal epithelial barrier function. Surgery 2015; 157: 732-42. [CrossRef]
23. Ikeda T, Hiromatsu K, Hotokezaka M, Chijiiwa K. Up-regulation of intestinal Toll-Like receptors and cytokines expressions change after TPN administration and a lack of enteral feeding. J Surg Res 2010; 160: 244-52. [CrossRef]
24. Freeman JJ, Feng Y, Demehri FR, Dempsey PJ, Teitelbaum DH. TPN-associated intestinal epithelial cell atrophy is modulated by TLR4/EGF signaling pathways. FASEB J 2015; 29: 2943-58. [CrossRef]
25. Cuervo AM, Macian F. Autophagy, nutrition and immunology. Mol Aspects Med 2012; 33: 2-13. [CrossRef]
26. Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature 2008; 451: 1069-75. [CrossRef]
27. He L, Zhang J, Zhao J, Ma N, Kim SW, Qiao S, et al. Autophagy: The Last Defense against Cellular Nutritional Stress. Adv Nutr 2018; 9: 493-504. [CrossRef]
28. Stuever MF, Kidner RF, Chae FE, Evans DC. Full Nutrition or Not? Nutr Clin Pract 2018; 33: 333-8. [CrossRef]
29. Christopher KB. Nutritional metabolomics in critical illness. Curr Opin Clin Nutr Metab Care 2018; 21: 121-5. [CrossRef]
30. Van Dyck L, Casaer MP, Gunst J. Autophagy and Its Implications Against Early Full Nutrition Support in Critical Illness. Nutr Clin Pract 2018; 33: 339-47. [CrossRef]
31. Derde S, Vanhorebeek I, Guiza 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: 2267-76. [CrossRef]
32. Hermans G, Casaer MP, Clerckx B, Guiza 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: 621-9. [CrossRef]
33. Preiser JC, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of

critically ill patients: consensus and controversies. Crit Care 2015; 19: 35. [CrossRef]
34. Yuk JM, Yoshimori T, Jo EK. Autophagy and bacterial infectious diseases. Exp Mol Med 2012; 44: 99-108. [CrossRef]
35. 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: 506-17. [CrossRef]
36. Belghit I, Panserat S, Sadoul B, Dias K, Skiba-Cassy S, Seiliez I. Macronutrient composition of the diet affects the feeding-mediated down regulation of autophagy in muscle of rainbow trout (O. mykiss). PLoS One 2013; 8: e74308. [CrossRef]

CLINICAL SCIENCE OF NUTRITION

Original Article

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Effects of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine supplementation on the body composition and muscle strength in the elderly

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ABSTRACT

Objective: Oral amino-acid-combination supplements have become a common intervention to maintain or potentially increase the lean body mass (LBM) in the elderly. Our aim was to determine the tolerance and efficacy of the 8-week beta-hydroxy beta-methylbutyrate/arginine/glutamine (HMB/Arg/Gln) supplementation on anthropometrics, LBM, muscle strength, and gait speed in elderly patients.

Methods: In this longitudinal observational study, a total of 131 elderly patients were evaluated at two consecutive visits, including baseline (Week 0) and single follow-up (Week 8). The use of HMB/Arg/Gln was evaluated in terms of patient compliance, the efficacy on anthropometrics, LBM (kg, measured with bioelectrical impedance analysis-BIA), muscle strength (kg), gait speed, and safety.

Results: The mean (standard deviation, SD) age was 74.7 (6.8) years (57.3% of participants were males). Of the patients were diagnosed with malnutrition (according to the Subjective Global Assessment test). The main indications for the HMB/Arg/Gln supplementation were sarcopenia (45.8%) and cancer cachexia (42.0%). Only two patients stopped supplementation because of taste problem (1.5%). Overall, 79.4% of patients were still on HMB/Arg/Gln at the follow-up. The mid-upper-arm circumference (MUAC, 25.3–27.0 cm, p=0.017), mid-upper-arm muscle circumference (MUAMC, 21.7–22.2 cm, p=0.006), hand grip strength (16.0–19.0 kg, p=0.0001), and gait speed (0.5–0.7 m/sec, p=0.008) were increased after the HMB/Arg/Gln supplementation. The adverse events were reported in 14 (10.7%) patients. No serious adverse events were reported in association with HMB/Arg/Gln.

Conclusion: Our findings showed that 8 weeks of the HMB/Arg/Gln supplementation applied twice daily were well tolerated and safe in the elderly. The supplementation seems to improve the MUAC, MUAMC, muscle strength, and gait speed.

Keywords: Beta-hydroxy-beta-methylbutyrate, elderly, gait speed, muscle mass, strength, tolerability

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Introduction

Reaching up to 15% per decade by the age of 70, muscle loss is common throughout the aging process, while sarcopenia or the loss of muscle mass and/or function has been considered to be associated with the functional status, which is directly linked to the health status in the elderly (1, 2). A decline in the lean body mass (LBM) has been associated with decreased physical function, impaired quality of life, poor treatment response, and increased mortality (3).

Based on their capability to increase the protein synthesis in skeletal muscles, the use of amino-acid-combination oral nutritional supplements has become one of the interventions to maintain or potentially increase the LBM in the elderly (3, 4). Beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of leucine, has been shown to stimulate protein synthesis and inhibit proteolysis, while arginine (Arg) and glutamine (Gln) increase collagen and protein synthesis (5-7). Accordingly, the use of the HMB, Arg, and Gln combination in a dietary supplement (HMB/Arg/Gln) has become increasingly studied in terms of its muscle-sparing properties and safety. It seems that HMB/Arg/Gln was more effective in replenishing fat-free mass and reversing weight loss compared to placebo in different populations with various clinical disorders (3, 8, 9).

This non-interventional, prospective, observational multi-center study was designed to evaluate the elderly patients who were applied HMB/Arg/Gln therapy to determine the efficacy of 8-week HMB/Arg/Gln therapy on anthropometrics, LBM, muscle strength, and gait speed.

Patients and Study population

This was a non-interventional, prospective, observational multi-center study. There were 20 centers participating with sufficient experience on adult nutritional supplement therapy across Turkey (already registered at ClinicalTrials.gov; identifier NCT02146612). During the study period, all the patients with HMB/Arg/Gln (2.6 g HMB, 14.8 g Arg, and 14.8 g Gln per sachet) therapy were screened. The exclusion criteria were age <65 years, no indications for the usage of HMB/Arg/Gln, acute medical problem, trauma or severe cognitive impairment (mini-mental state examination score <10), and a history of allergy or hypersensitivity reaction to the HMB/Arg/Gln combination. Patients gave their written informed consent prior to study-specific procedures with the understanding that they had the right to withdraw from the study at any time.

The study was conducted at two consecutive visits, including baseline (Week 0) and single follow-up (recommended at Week 8) visits. A total of 131 patients aged ≥65 years were enrolled into the study.

Data collection

Data on patient demographics (age, gender), primary diagnosis, Subjective Global Assessment (SGA) (10), taste evaluation, and concomitant diseases were collected at the baseline visit. Data on the HMB/Arg/Gln usage patterns (duration [day], amount [package/day], patient compliance [regular use], and persistence [continuation, discontinuation, and reasons for discontinuation]) were collected at the follow-up visit. Data on anthropometrics (height [cm], weight [kg], triceps skin fold [TSF], mid-upper-arm-circumference [MUAC, cm] and calf circumference [CC, cm]), LBM (kg) measured with bioelectrical impedance analysis (BIA), muscle strength measured with a hand dynamometer (kg), and gait speed (m/sec) were collected at both visits.

Study parameters

The HMB/Arg/Gln supplementation tolerance and its effects on anthropometrics, LBM, muscle strength, and gait speed from baseline to follow-up were evaluated. Safety was also evaluated based on the reports of adverse events (frequency, system–organ classification, severity, relation to study medication, and outcome).

Anthropometric measurements

Body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). Measurements of MUAC were made in accordance with the National Kidney Foundation's guideline on nutrition in patients with CKD. MUAC was based on the circumference of the left upper arm, measured at the mid-point between the tip of the shoulder and the tip of the elbow between the olecranon process and the acromium. TSF was measured with a Harpenden skin fold caliper (ASSIST Creative Resources Ltd, LL13 9UG, UK). The calculation of MUAMC (cm) was done using the formula MUAC-(3.14 x TSF) (11). The CC (calf circumference) was measured from the largest diameter of the left calf with a flexible tape.

Bioelectrical impedance analysis

LBM (kg) was determined via BIA using the Tanita MC-980MA Multi-Frequency Segmental Body Composition Monitor (Tanita, Tokyo, Japan). For the BIA measurements, the subject stood in an upright position with the bare feet on the analyzer footpads. The impedance between the two feet was measured while an alternating current (50 kHz and ~200 μA) passed through the lower body. Measurement was computed with this impedance value.

Muscle strength and gait speed

The dominant hand grip strength was determined using a Jamar Plus Digital Hand Dynamometer, which is model 2A, hydraulic, analog dynamometer having the anatomical grip with five-position options. This instrument is the recommended and preferred tool, considered to be the gold standard for documenting the grip strength (12). A 4-meter gait speed with ≤0.8 m/sec was associated with low physical activity (2).

Serum prealbumin measurement

Serum prealbumin (PAB) concentrations of the patients (g/dL) were measured by the Cobas Integra 800 Autoanalyser (Roche, Mannheim).

HMB/Arg/Gln regimen

Consistent with manufacturer's instructions, an oral nutritional supplement with a combination of HMB, Arg, and Gln (Abound), and the sachet containing 1.3 g HMB, 7.4 g Arg, and 7.4 g Gln, was recommended to be consumed with 250 mL of water, two times a day.

Statistical analysis

Categorical variables are summarized as n (%), whereas continuous ones are summarized as median (minimum–maximum). The change over time for continuous variable was tested using the Wilcoxon test due to non-normal distribution patterns of continuous variables. Type 1 error was accepted as 0.05. Analyses were performed on the IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethical Committee of Istanbul University, Istanbul School of Medicine (1038/2012). Informed consent was obtained from all individual participants included in the study.

Results

Patient characteristics

Baseline data of the patients were evaluated at Visit 1 (mean [standard deviation, SD] age, 74.7 [6.8] years; 57.3% were males). All patients were diagnosed with malnutrition according to SGA. In those with insufficient oral intake, an energy-/protein-rich diet and/or enteral nutrition supplement was given according to daily needs. Out of 131 patients, 122 (93.1%) attended Visit 2, which was performed for a median 62.0 days after the enrollment (Nine patients were died during the study). Diabetes mellitus (17.6%) and chronic kidney disease (3.1%) were the two most common concomitant diseases encountered in our cohort (Table 1). The main indications for the HMB/Arg/Gln regimen were sarcopenia in 60 (45.8%), cancer in 55 (42.0%) patients, and wounds in 27 (20.6%) (Table 1).

HMB/Arg/Gln use

The HMB/Arg/Gln supplement was used for a median 30.5 days (36 days in cancer patients) at an amount of median 2.0 package/day (58.2% of the cancer patients were still using two packages/day at Visit 2). The taste of HMB/Arg/Gln was identified as very good, good, or neutral by 91.5% of patients. Only two patients (1.5%, one cancer, one sarcopenia) discontinued the supplement because of they had a problem with taste. Overall, 79.4% of patients used HMB/Arg/Gln on a regular basis.

Changes in anthropometrics, LBM, muscle strength, gait speed, and laboratory findings

Although the weight, BMI, and LBM values improved or were maintained in 60.9%, 63.9%, and 65.3% of patients at the follow-up visit, respectively, they did not reach statistical significance (weight, 64.6 to 65.0 kg, p=0.25; BMI, 23.7 to 24.2 kg/m^2, p=0.203; LBM, 35.3 to 37.7 kg, p=0.09) (Table 2), which is similar in patients with cancer (LBM, 38.7 to 39.0 kg, p=0.20, 65.5% of the patients with cancer had improved or maintained LBM); sarcopenia (LBM, 38.5 to 39.4 kg, p=0.09); and in the wound group (LBM, 49.7 to 50.2 kg, p=0.40).

A significant increase was noted in the median MUAC (25.3 to 27.0 cm, p=0.017); MUAMC (21.7 to 22.2 cm, p=0.006); and CC (36.5 to 37.7 cm, p=0.001), which were improved or maintained at the follow-up visit in 62.8%, 62.2%, and 73.3% of patients, respectively (Table 2). When cancer patients were taken into consideration, although MUAC (25.5 to 25.9 cm, p=0.124) and MUAMC (21.9 to 21.8 cm, p=0.70) did not change significantly, CC (40.2 to 42.1 cm, p=0.006) was increased in the follow-up visit, which was improved in 69% and maintained in 17.2% of the patients. In sarcopenic patients, MUAC and MUAMC were significantly increased (MUAC, 25.8 to 26.6 cm, p=0.012; MUAMC, 20.2 to 22.1 cm, p<0.001). CC increased from 32.3 to 32.8 cm, which was not significant (p=0.15). In the wound group, MUAMC increased significantly (18.7 to 22.6 cm, p=0.039).

The median hand grip strength (16.0 to 19.0 kg, p=0.0001) and gait speed (0.5 to 0.7 m/sec, p=0.008) were significantly increased, which were improved or maintained at the follow-up visit in 80.0% and 89.4% of patients, re-

Table 1. Patient characteristics and indications for oral nutrition supplement regimen at visit 1 (n=131)	
Age (year), mean (SD)	74.7 (6.8)
Gender (male), n (%)	75 (57.3)
ONS indication (primary diagnosis), n (%)*	
Cancer	55 (42.0)
Sarcopenia	60 (45.8)
Wound	27 (20.6)
Pressure ulcer	19 (14.5)
Burn	3 (2.3)
Surgery wound	3 (2.3)
Diabetic foot ulcer	1 (0.8)
Venous leg ulcer	1 (0.8)
Other	3 (2.3)
Other diagnosis	42 (32.1)
Concomitant diseases	
None	79 (60.3)
Diabetes mellitus	23 (17.6)
Chronic kidney disease	4 (3.1)

*Patients may have more than one disease. ONS: oral nutrition supplement; SD: standard deviation

spectively (Table 2). Although the hand grip strength did not increase significantly in patients with cancer (25.5 to 27.1 kg, p=0.20), it was improved in 66.7% and maintained in 8.3% of patients. In patients with sarcopenia, the median hand grip strength increased significantly (14.8 to 18.6 kg, p<0.001). In wound group, it did not change significantly.

At the follow-up visit, the amount of food consumption (with diet list) was not changed in 59.6%, while it was decreased in 19% and increased in 21.4% of patients. The serum PAB level increased from 20.48±14.59 g/L (Visit 1) to 24.33±12.90 g/L (Visit 2) (p=0.022). In patients with cancer and sarcopenia, the mean serum PAB level of the patients were increased from 18.65±11.28 to 22.88±10.44 g/L and 26.38±29.11 to 29.40±26.78 g/L, but that much difference did not show any statistical significance (p=0.11, p=19). In the wound group, both the mean serum prealbumin and albumin levels increased significantly (PAL, 20.47±20.98 to 25.11±18.37 g/L, p=0.05; albumin, 28.6–31.23 g/L, p=0.03).

Adverse events

During the course of the study, 14 patients (10.7%) experienced 14 adverse events (10 serious adverse events) (Table 3). In 9 of 10 serious adverse events, the outcome was death of the patient, while none of the deaths and serious adverse events was associated with the HMB/Arg/Gln application (Table 4).

Table 2. Changes in anthropometrics, muscle strength, gait speed, and LBM (n=122)			
	Baseline	**Follow-up**	**p**
Anthropometrics			
Weight (kg)	64.6 (34.8–100.0)	65.0 (35.4–95.0)	0.256
BMI (kg/m^2)	23.7 (14.5–44.4)	24.2 (14.7–42.2)	0.203
MUAC (cm)	25.3 (11.5–38.0)	27.0 (18.5–39.0)	0.017
MUAMC (cm)	21.7 (7.4–28.2)	22.2 (14.7–34.3)	0.0068
CC (cm)	36.5 (25–62)	37.7 (21.5–65)	0.001
Functional tests			
Hand grip strength (kg)	16.0 (1.0–54.0)	19.0 (6.0–60.0)	0.0001
Gait speed (m/sec)	0.5 (0.2–14.8)	0.7 (0.3–4.9)	0.008
Muscle mass (BIA)			
Lean body mass (kg)	35.3 (10.9–67.7)	37.7 (11.5–65.1)	0.092

Data are shown as median (min–max) p-value of the Wilcoxon test. Comparison could only be done for patients with data at baseline and follow-up.
BMI: body mass index; CC: calf circumferences; LBM: lean body mass; MUAC: mid-upper-arm circumference; MUAMC: mid-upper-arm muscle circumference

Discussion

According to the definition by the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is the loss of muscle strength and function with an extensive and progressive reduction in the skeletal muscle mass (2). Sarcopenia accelerates with age. In many studies, the prevalence is 5–25% in people aged between 60 and 70 years, and 11–50% in those aged >80 years (13, 14). Anthropometric measurements were used to predict the muscle mass in the past (15-18). In a recent study, Akin et al. (15) found the MUAMC cut-off values for muscle mass in elderly as 23.8 cm for men and 23.3 cm for women, and the study was conducted in Turkish population. Halil et al. (19) showed 68% of sarcopenia cases in a national nursing home project including 711 elderly residents. They used the handgrip strength for the diagnosis of sarcopenia according to the Cardiovascular Health Study criteria. Sarcopenia was associated with 1-year mortality independently from malnutrition in nursing home residents (20). Sarcopenia treatment included the supplementation of protein–energy needs (1.2–1.5 g/kg/day protein), active exercise, and correction of vitamin D deficiency and functional amino acids such as leucine (21).

Beta-hydroxy-beta-methylbutyrate (HMB) is derived from leucine. It has anti-catabolic effects on skeletal muscles and can reduce muscle damage through the inhibition of muscle protein degradation. It increases the protein synthesis in skeletal muscles through the IGF-1 expression and activation of the mTOR pathway (22-25). Portal et al. (26) showed an increased knee-flexion isokinetic force with HMB. Thomson et al. (27) mentioned an increased muscle strength without any change in the muscle mass. In animal models, the HMB supplementation was shown to increase the muscle mass and functions (28-29). Muscle tetanic force, glycogen and ATP content, resistance to acute muscle fatigue during intense exercise, and citrate synthesis activity were all increased with HMB. Kuriyan et al. (30) showed a negative correlation with age and plasma HMB concentration, which is positively correlated with appendicular lean mass and handgrip strength.

The fat-free mass (FFM) gain was shown in cancer cachexia and AIDS patients with HMB/Arg/Gln supplementation (8, 9). HMB was associated with an increased FFM, muscle strength, and muscle quality in the elderly who participated in a strength training program (31, 32). It was also associated with a decreased muscle breakdown in bed-ridden elderly in a nursing home (33). In a randomized, controlled, double-blind study, Deutz et al. (34) gave HMB to healthy elderly who were confined to complete bed rest for 10 days. The HMB supplementation prevented the decline in LMB (measured with DEXA) when compared to control. In chronic obstructive pulmonary disease, HMB combined to pulmonary rehabilitation improved muscle mass, mus-

Table 3. Adverse events (n=131)

Adverse event	n	%
Cardio-respiratory arrest	1	0.76
Diarrhea	1	0.76
Nausea	1	0.76
Oropharyngeal pain	1	0.76
Respiratory failure	1	0.76
Aspiration pneumonia	1	0.76
Skin rash	1	0.76
Death	7	5.30
Total	14	10.70

Table 4. Characteristics of adverse events (n=131)

Seriousness	n	%
Non-serious	4	3.1
Oropharyngeal pain	1	
Diarrhea	1	
Nausea	1	
Rash	1	
Serious	10	7.6
Pneumonia aspiration	1	
Death	9	
Cardio-respiratory arrest	1	
Respiratory failure	1	
Other	7	10.7
Total	14	
Causality		
Non-serious	4	3.1
Not reported	2	
Related	2	
Serious	10	7.6
Related	0	0
No relation was reported	10	7.6
Total	14	10.7

cle strength, quality of life, and serum prealbumin levels of the patients (35). Daily administration of HMB/Arg/Gln in older adults aged 65–87 years for 6 months was shown to be associated with an increased LBM and lower-extremity strength as compared with isocaloric placebo (36). Recently, a meta-analysis including data of randomized controlled trials was published about the effect of HMB on muscle loss in the elderly, which indicated the preservation of muscle mass with HMB (37). Limitations of the analysis were small sample sizes, high rate of treatment withdrawal, and the absence of muscle strength measurement.

Our findings revealed a high rate of patient compliance with twice-daily dietary HMB/Arg/Gln supplementation in elderly patients. Withdrawal related to taste problems occurred only in two patients. HMB/Arg/Gln seems to be associated with improvement in terms of MUAC, MUAMC, and CC, as well as the hand grip strength and gait speed with lack of any serious adverse events. Although no significant improvement occurred in BMI and LBM, they were increased or maintained in two-thirds of the patients without any significant change in food consumption. Serum prealbumin levels were found increased at Visit 2, especially in the wound group. An improvement in the upper arm anthropometrics as well as the muscle strength and gait speed might precede the changes in the muscle mass in our cohort. This might be related with the treatment period that was only 8 weeks from baseline to follow-up. Regarding the suggested correlation between the muscle mass and strength in some studies, significant changes in the muscle mass may occur in case of a longer-term use of the HMB/Arg/Gln supplement (38, 39). Lauretani et al. (40) showed a more prominent decrease in muscle strength compared to muscle mass in the elderly, which was also mentioned in the EWGSOP II report (2). On the other hand, the ability to preserve the muscle mass is important, as all of our patients were older and underwent certain treatments for various diseases such as cancer.

In general, the HMB/Arg/Gln supplementation has been considered to be well tolerated by different patient populations (8). Likewise, our findings indicated favorable tolerability and safety profile of the HMB/Arg/Gln supplementation in a cohort of elderly patients with different therapeutic indications.

The first limitation to this study was insufficient data about the serum CRP of the patients to evaluate its relationship with the increase in serum prealbumin levels at Visit 2. Second, we did not give any exercise plans to the patients throughout the study. Various patient groups were included in the study, and it was impossible to maintain a standard physical rehabilitation program in all patients. None of our patients noted resistance exercise training during the study period. The third limitation was the absence of a control population. All of the patients were diagnosed with malnutrition. Although an energy/protein enriched diet or oral nutritional supplement were given to those without sufficient oral intake, most of the patients (78.6%) could not increase their daily food consumption. It would be better to evaluate the effects of HMB/Arg/Gln on the muscle mass and strength, including changes on diet and physical exercise in detail; however, this was an observational study, and it is not easy to maintain a standard diet and physical rehabilitation program to all patients with different diseases and medical problems.

In conclusion, the HMB/Arg/Gln supplementation applied twice a day for 8 weeks seems to improve the MUAC, MUAMC, muscle strength, and gait speed with a favorable tolerability and safety when used for different therapeutic indications among elderly clinical populations. Future larger-scale studies are needed to clarify these promising results with longer-term use.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine (1038/2012).

Informed Consent: Written informed consent was obtained from all individual participants who participated in this study.

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References

1. Grimby G, Saltin B. The ageing muscle. Clin Physiol 1998; 3: 209-18. [CrossRef]
2. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 16-31. [CrossRef]
3. Fitschen PJ, Wilson GJ, Wilson JM, Wilund KR. Efficacy of β-hydroxy-β-methylbutyrate supplementation in elderly and clinical populations. Nutrition 2013; 29: 29-36. [CrossRef]
4. Atherton PJ, Smith K, Etheridge T, Rankin D, Rennie MJ. Distinct anabolic signaling responses to amino acids in C2C12 skeletal muscle cells. Amino Acids 2010; 38: 1533-9. [CrossRef]
5. Eley HL, Russell ST, Baxter JH, Mukerji P, Tisdale MJ. Signaling pathways initiated by beta-hydroxy-beta-methylbutyrate to attenuate the depression of protein synthesis in skeletal muscle in response to cachectic stimuli. Am J Physiol Endocrinol Metab 2007; 293: E923-31. [CrossRef]
6. Witte MB, Barbul A. Arginine physiology and its implication for wound healing. Wound Repair Regen 2003; 11: 419-23. [CrossRef]
7. Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. Eur J Nutr 2010; 49: 197-210. [CrossRef]
8. May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. Am J Surg 2002; 183: 471-9. [CrossRef]
9. Clark RH, Feleke G, Din M, Yasmin T, Singh G, Khan FA, et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study. J Parenter Enteral Nutr 2000; 24: 133-9. [CrossRef]
10. Detsky A, McLoughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is Subjective Global Assessment of Nutritional Status? J Parenter Enteral Nutr 1987; 11: 8-13. [CrossRef]
11. Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, et al. Sarcopenia as a risk factor for falls in elderly individuals: Results from the ilSIRENTE study. Clin Nutr 2012; 31: 652-8. [CrossRef]
12. Fess E. Grip strength. In: Casanova JS (ed) Clinical assessment recommendations. 2nd ed, Chicago: American Society of Hand Therapists, 1992; pp. 41-5.
13. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and-women. Mech Ageing Dev 1999; 107: 123-36. [CrossRef]
14. Janssen I. Influence of sarcopenia on the development of physical disability: the Cardiovascular Health Study. J Am Geriatr Soc 2006; 54: 56-62. [CrossRef]
15. Akın S, Mucuk S, Öztürk A, Mazıcıoğlu M, Göçer Ş, Arguvanlı S, et al. Muscle function-dependent sarcopenia and cut-off values of possible predictors in community-dwelling Turkish elderly: calf circumference, midarm muscle circumference and walking speed. Eur J Clin Nutr 2015; 69: 1087-90. [CrossRef]
16. Landi F, Russo A, Liperoti R, Pahor M, Tosato M, Capoluongo E, et al. Midarm muscle circumference, physical performance and mortality: results from the aging and longevity study in the Sirente geographic area [ilSIRENTE study]. Clin Nutr 2010; 29: 441-7. [CrossRef]
17. Kawakami R, Murakami H, Sanada K, Tanaka N, Sawada SS, Tabata I, et al. Calf circumference as a surrogate marker of muscle mass for diagnosing sarcopenia in Japanese men and women. Geriatr Gerontol Int 2015; 15: 969-76. [CrossRef]
18. Beaudart C, Reginster JY, Slomian J, Buckinx F, Dardenne N, Quabron A, et al. Estimation of sarcopenia prevalence using various assessment tools. Exp Gerontol 2015; 61: 31-7. [CrossRef]
19. Halil M, Ulger Z, Varlı M, Döventaş A, Oztürk GB, Kuyumcu ME, et al. Sarcopenia assessment project in the nursing homes in Turkey. Eur J Clin Nutr 2014; 68: 690-4. [CrossRef]
20. Saka B, Ozkaya H, Karisik E, Akin S, Akpinat TS, Tufan F, et al. Malnutrition in nursing home and its association with sarcopenia and mortality. Eur Geriatr Med 2016; 7: 232-8. [CrossRef]
21. Wu G. Amino acids: metabolism, functions, and nutrition. Amino Acids 2009; 37: 1-17. [CrossRef]
22. Nissen SL, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. J Appl Physiol 2003; 94: 651-9. [CrossRef]
23. Zanchi NE, Gerlinger-Romero F, Guimarães-Ferreira L, de Siqueira Filho MA, Felitti V, Lira FS, et al. HMB supplementation: clinical and athletic performance-related effects and mechanisms of action. Amino Acids 2011; 40: 1015-25. [CrossRef]
24. Gerlinger-Romero F, Guimarães-Ferreira L, Giannocco G, Nunes MT. Chronic supplementation of beta-hydroxy-beta methylbutyrate (HMb) increases the activity of the GH/IGF-I axis and induces hyperinsulinemia in rats. Growth Horm IGF Res 2011; 21: 57-62. [CrossRef]
25. Cruz-Jentoft AJ. Beta-hydroxy-beta-methylbutyrate (HMB): From Experimental Data to Clinical Evidence in Sarcopenia. Curr Protein Pept Sci 2018; 19: 668-72. [CrossRef]
26. Portal S, Zadik Z, Rabinowitz J, Pilz-Burstein R, Adler-Portal D, Meckel Y, et al. The effect of HMB supplementation on body composition, fitness, hormonal and inflammatory mediators in elite adolescent volleyball players: a prospective randomized, double-blind, placebo-controlled study. Eur J Appl Physiol 2011; 111: 2261-9. [CrossRef]
27. Thomson JS, Watson PE, Rowlands DS. Effects of nine weeks of beta-hydroxy-beta-methylbutyrate supplementation on strength and body composition in resistance trained men. J Strength Cond Res 2009; 23: 827-35. [CrossRef]
28. Pinheiro CHJ, Gerlinger-Romero F, Guimarães-Ferreira L, de Souza AL Jr, Vitzel KF, Nachbar RT, et al. Metabolic and functional effects of beta-hydroxy-betamethylbutyrate (HMB) supplementation in skeletal muscle. Eur J Appl Physiol 2012; 112: 2531-7. [CrossRef]

29. Pimentel GD, Rosa JC, Lira FS, Zanchi NE, Ropelle ER, Oyama LM, et al. Beta-hydroxy-beta-methylbutyrate supplementation stimulates skeletal muscle hypertrophy in rats via the mTOR pathway. Nutr Metabol 2011; 8: 11-7. [CrossRef]
30. Kuriyan R, Lokesh DP, Selvam S, Jayakumar J, Philip MG, Shreeram S, et al. The relationship of endogenous plasma concentrations of β-Hydroxy β-Methyl Butyrate (HMB) to age and total appendicular lean mass in humans. Exp Gerontol 2016; 81: 13-8. [CrossRef]
31. Vukovich MD, Stubbs NB, Bohlken RM. Body composition in 70-year-old adults responds to dietary beta-hydroxy-beta-methylbutyrate similarly to that of young adults. J Nutr 2001; 131: 2049-52. [CrossRef]
32. Stout JR, Smith-Ryan AE, Fukuda DH, Kendall KL, Moon JR, Hoffman JR, et al. Effect of calcium β-hydroxy-β-methylbutyrate (CaHMB) with and without resistance training in men and women 65+ yrs: A randomized, double-blind pilot trial. Exp Gerontol 2013; 48: 1303-10. [CrossRef]
33. Hsieh LC, Chow CJ, Chang WC, Liu TH, Chang CK. Effect of beta-hydroxy-beta-methylbutyrate on protein metabolism in bed-ridden elderly receiving tube feeding. Asia Pac J Clin Nutr 2010; 19: 200-8.
34. Deutz NEP, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, et al. Effect of β-hydroxy-β-meythylbutyrate (HMB) on lean body mass during 10 days of bed restin older adults. Clin Nutr 2013; 32: 704-12. [CrossRef]
35. Olveira G, Olveira C, Dona E, Palenque FJ, Porras N, Dorado A, et al. Oral supplement enriched in HMB combined with pulmonary rehabilitation improves body composition and health related quality of life in patients with bronchiectasis (Prospective, Randomised Study). Clin Nutr 2016; 35: 1015-22. [CrossRef]
36. Ellis AC, Gower BA. Effects of supplemental arginine, glutamine and beta-hydroxy-beta-methylbutyrate on lean mass and strength in older adults. J Acad Nutr Dietetics 2012; 112: A32. [CrossRef]
37. Wu H, Xia Y, Jiang J, Du H, Guo X, Liu X, et al. Effect of beta-hydroxy-beta-methylbutyrate supplementation on muscle loss in older adults: A systematic review and meta-analysis. Arch Gerontol Ger 2015; 61: 168-75. [CrossRef]
38. Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. Am J Phys 1996; 270: E627-33. [CrossRef]
39. Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, et al. Health Aging And Body Composition Research Group. Strength and muscle quality in a well-functioning cohort of older adults: the Health, Aging and Body Composition Study. J Am Geriatr Soc 2003; 51: 323-30. [CrossRef]
40. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol 2003; 95: 1851-60. [CrossRef]

CLINICAL SCIENCE OF NUTRITION

Original Article

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Evaluation of patients treated by nutrition support teams and its effect on treatment cost

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ABSTRACT

Objective: Malnutrition is a condition that increases morbidity and mortality in patients, prolongs hospital stay, and increases treatment costs. The incidence of malnutrition remains a major problem in hospitalized patients despite improvements in nutritional support therapies. Previous studies have shown that treatment standardization can be achieved by using a multidisciplinary team that consists of doctors, pharmacists, nurses, and dieticians, which positively affects hospital costs and patients' health. In this study, we aimed to investigate the effect of nutritional support teams on treatment cost in our hospital.

Methods: A nutrition support team was established in April 2017 at our hospital and all patients who consulted the team between April 2017 and December 2018 were investigated retrospectively. In this period, the patients were evaluated for incidence of mortality, body mass index, changes in NRS-2002 score, enteral and parenteral nutrition rates, nutritional changes, and annual enteral and parenteral product costs and the effect of multidisciplinary nutrition on these parameters was assessed. Results of quantitative variables were defined as mean, median, and standard deviation. Qualitative variables were represented by frequency and percentage.

Results: A total of 511 patients were enrolled in the study. The mean age of the patients was 68.6 years (18–99) and 49.5% of them were female. Out of 511 subjects, 251 patients were hospitalized in intensive care units and 260 were in wards. Enteral nutrition was recommended in 275 patients, oral nutrition in 71 patients, and parenteral nutrition in 70 patients. The mortality rate was 61.6% in high-risk patients with an NRS2002 score >5 and 38.4% in moderate-risk patients with a score of 3–5. A total of 164 patients who received inappropriate parenteral nutrition were switched to oral or enteral nutrition. The NRS-2002 score was maintained in 267 patients and was decreased in 202 patients. The number of patients receiving parenteral nutrition was 8783 in 2016, which decreased to 6104 in 2018 with a decreasing rate of 30.5%. The number of patients receiving enteral nutrition were 4376 in 2016, which increased to 7582 in 2018 with an increasing rate of 42.2%. The total cost of enteral and parenteral products was decreased.

Conclusion: Giving the nutritional support to malnourished patients or those at high risk of malnutrition could have positive effects on many parameters such as reduction the NRS-2002 scores and hospital costs and choosing the correct nutritional route.

Keywords: Cost effectiveness, malnutrition, nutrition therapy, nutritional, support

Introduction

Although obesity is the main focus of health policy and research, malnutrition continues to be an important and common health problem even in developed countries. Malnutrition has been detected in about one-third of hospitalized patients in developed countries. If untreated, it has been shown to cause significant clinical outcomes including prolonged hospital stay, increased newly developing infection, mortality, and a 30-day re-admission rate. It has also been reported that the prevalence of malnutrition can reach up to 85% in long-term care centers (1).

In many sources, malnutrition has been defined as the inequality between consumed nutrients and differing metabolism requirements, and the need to diagnose and treat different populations with different screening tests has been proposed (2). Correct diagnosis and treatment in patients with malnutrition is critical to minimize the negative consequences associated with malnutrition. The screening methods used today are Subjective Global

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Assessment, Nutritional Risk Index, Mini Nutritional Assessment, Malnutrition Universal Screening Tool, and Nutritional Risk Screening-2002 (NRS-2002). In addition to these screening methods, it has been reported that 10% loss of body weight in the last 6 months should be considered as malnutrition (2).

The NRS-2002 screening test was developed by Kondrup et al. (3) for screening of malnutrition. NRS-2002 is based on the relationship between disease severity and nutritional status and is calculated by variables such as body mass index (BMI), weight loss, food intake, and general status. A nutritional plan is recommended in patients with an NRS-2002 score of ≥3, assuming the presence of risk of malnutrition.

Studies have shown that the screening of nutrition in hospitals is not done adequately and even in the centers where it is applied, many patients with malnutrition or malnutrition risk are not given adequate nutritional support treatment. The reasons for this situation are the inadequacies in screening, evaluation and treatment, deficiencies in the training of the relevant health personnel, and lack of necessary awareness (4). In recent years, the term "nutritional support" for patients with malnutrition has become an indispensable part of treatment rather than a method that supports treatment. Provision of nutritional support by a coordinated and multidisciplinary team has enabled standardization of treatment and a decrease in the incidence of complications (5).

The nutritional support team (NST) requires a multidisciplinary constitution including doctors, dietitians, nurses, and pharmacists. NST plays an active role in the assessment of nutrition and determination of nutritional requirements, making recommendations for correct nutritional therapy, and choosing the nutritional support pathway (6). The aim of this study was to determine the route of nutritional support treatment, changes in NRS-2002 scores according to age, and the effect of the recommendations on enteral and parenteral product usage and treatment costs.

Methods

Ethical approval was obtained from the ethics committee of the Faculty of Medicine of Kütahya University of Health Sciences with the decision number 2019/03 dated 27 February-2019.

In this study, NST was performed in a tertiary education research hospital with 443 beds, 79 of which were intensive care beds. The change in the number of inpatients remained constant over the years. In April 2017, a NST consisting of nurses, dietitians, pharmacists and physicians was established as a requirement by the Ministry of Health to increase the quality standards in healthcare. The aim of the NST team was to screen patients for the risk of malnutrition during their stay in the hospital and to regulate the treatment of patients at risk of malnutrition according to nutritional guidelines. Another aim of the team was to increase the nutritional care quality by monitoring the patients receiving total parenteral nutrition (TPN) and enteral nutrition (EN) treatment. For this purpose, the nurses working in intensive care and wards were introduced to the NRS-2002 form, which is used in the screening of malnutrition, and training was provided to teach them how to fill the forms correctly. In addition, the importance of nutrition, EN, and TPN administration was explained and protocols were established.

Patients over 18 years old who were hospitalized between April 2017 and January 2019 were included in the study. Pediatric patients, pregnant women, and patients hospitalized for less than 48 hours were excluded from the study. Malnutrition screening was performed on the first day of hospitalization with NRS-2002. The patients who were hospitalized for more than 48 hours, who had an NRS-2002 score ≥3, and who were referred to NST were followed-up and the patient-related data were recorded. Follow-up patients were re-evaluated by the NST team with NRS-2002 score at a maximum of one-week intervals. Age, gender, BMI, mean NRS-2002 score, recommended feeding route, NRS-2002 score, and mortality rates according to age groups were analyzed. Patients with BMI (kg/m²) <18.5 kg/m² were considered as undernourished; between 18.5–24.9 kg/m² was considered as normal; between 25–29.9 kg/m² was overweight; and patients with BMI ≥30 kg/m² were considered as obese. Age evaluation was made in six groups as 18–24, 25–34, 35–44, 45–54, 55–64, and 65+ years. The data used in the study were obtained from the team records.

Data on the types and costs of nutritional products used in service and intensive care units were obtained from hospital pharmacy unit records. The cost was calculated separately for each product and obtained by multiplying the number of products and unit price. Ready-to-use nutritional products were included in the enteral product cost and ready-to-use three-chamber bag systems containing amino acid, glucose, and fat emulsions were included in the TPN cost. The daily energy intake target of the patients was 25–30 kcal/kg/day, the protein target was 1.2–1.5 g/kg/day, and the protein target of the patients with renal failure who did not receive hemodialysis treatment was 0.8 g/kg/day.

Statistical analysis

IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) 20.0 package program was used for analysis. Results of quantitative variables were defined as mean, median, and standard deviation. Frequency and percentage (%) values were used for categorical variables.

Results

The rate of patients screened by NRS-2002 was 49.4% in 2017 and 91.3% in 2018. The rates of patients with malnutrition was calculated as 7.44% in 2017 and 7.48% in 2018 (Table 1). Although the number of patients screened increased, the rate of malnourished patients did not change. A total of 46.2% of patients with an NRS-2002 score of 3 or higher were treated by the NST. The number of patients who were followed-up was 511, with 251 (49.1%) being in intensive care. The number of patients who consulted the NST was 180 (35.2%) from internal services and 80 (15.7%) from surgical services. The patients from the surgical services were mostly admitted for cardiovascular surgery (n=24) and orthopedic (n=22) surgery, and the internal patients were mostly admitted for palliative (n=100) services. A total of 49.5% of the patients were female and the mean age was 68.5±19.2 years. The mean NRS-2002 score of all the patients consulted was 5.1±1.8, the mean NRS-2002 score of the patients consulted in intensive care units was 5.7±1.2, the mean NRS-2002 score of the patients consulted in surgical services was 4.5±1.5, and the mean NRS-2002 score of the patients consulted in internal services was found to be 4.6±1.4 (Table 2). The nutritional risk scores of the inpatients in the ICU was detected to be significantly higher (p=0.043) as compared to the scores of inpatients in other services. The number of patients recommended for enteral nutrition was 275 (53.8%) and the number of patients recommended for parenteral nutrition was 70 (13.6%). The recommendations of NST caused a 77% product change and 51% nutrition change in the physician's initial treatment plan. In terms of the risk of malnutrition, an NRS-2002 score of 3–5 was considered to be moderately risky, and patients with NST greater than 5 were considered at high risk of malnutrition. These high-risk patients were more likely to be in internal medicine and in palliative wards (Table 3). When the patients who were followed-up were classified according to their ages, the groups with the highest NRS-2002 score were between 18–24 and >65 years (Table 4). When compared with the follow-up score, the number of patients with NRS-2002 regression was 202 (39.5%). When the patients were grouped according to their BMI and NRS-2002 scores, it was found that the groups with the highest mortality rate were the groups with BMI between 18.5–24.9 and the group with NRS-2002 score >5 (Table 5).

The number of patients using TPN decreased from 7872 in 2016 to 5968 in 2018, with a decrease of 24.1% between the two years. The number of TPNs used decreased from 8783 in 2016 to 6104 in 2018, with a decrease of 30.5%. The number of patients using enteral products increased

Table 1. Screening and malnutrition ratios of hospitalized patients

Year	Total number of patients accepted for hospitalization	Number of inpatients >48 hours	Number of patients undergoing NRS-2002 malnutrition screening=n (%)	Number of patients at risk of malnutrition with NRS-2002 ≥ 3=n (%)
2017	15125	9426	4663 (49.4)	347 (7.44)
2018	19255	16155	14756 (91.3)	1104 (7.48)

NRS-2002: Nutritional Risk Screening-2002

Table 2. Age, gender and NRS-2002 scores of the patients

	Intensive Care	Internal services	Surgical services
Number of patients (n/%)	251/49.1	180/35.2	80/15.7
Female gender=n (%)	144 (28.2)	89 (17.4)	27 (5.3)
Age (Mean±SD)	65.9±22.7	71±26.7	80±18.7
NRS-2002 (Mean±SD)	5.7±1.2	4.6±1.4	4.5±1.5
Mortality rate=n (%)	75 (29.8)	32 (17.7)	5 (6.2)

NRS-2002: Nutritional Risk Screening-2002; SD: standard deviation

from 4376 in 2016 to 7582 in 2018, showing an increase of 42.2%. The number of enteral products used increased from 16,838 in 2016 to 25,753 in 2018, with an increase of 34.6%. The number of TPN use in the internal intensive care unit, which had the highest rate of consultation with the NST decreased from 1312 in 2016 to 192 in 2018. The number of TPNs used in the palliative service decreased from 2218 in 2016 to 959 in 2018. The total cost of enteral products and TPNs were found to decrease from 470,537,45 Turkish lira (TL) in 2016 to 416,306,03 TL in 2018. The cost of only TPN products was calculated as 429.714.38 TL in 2016 and 314.500.64 TL in 2018. In this calculation, the costs of the catheter operation and catheter-related developing complications were not added (Table 6).

Table 3. Grouping of inpatients according to the risk of malnutrition

	Moderate risk (NRS 3–5) Number of patients=n	High risk NRS >5 Number of patients=n
Internal medicine	42	11
Palliative	84	16
Oncology	7	2
Infection	6	0
Gastroenterology	2	0
Hematology	0	2
Cardiology	6	2
Cardiovascular surgery	21	3
orthopedics	20	2
General surgery	15	2
Thoracic surgery	6	3
Brain and nerve surgery	3	4
Ear nose throat	1	0

NRS: Nutritional Risk Screening

Table 4. NRS-2002 score of patients according to age groups

Age Group (years)	Average NRS-2002	The number of patients=n (%)
18–24	5.5	11 (2.2)
25–34	4.3	13 (2.7)
35–44	4.2	22 (4.3)
45–54	4.7	36 (7.1)
55–64	4.7	83 (16.4)
65+	5.3	346 (67.3)

NRS-2002: Nutritional Risk Screening-2002

Table 5. Mortality rate of patients according to body mass index

Body mass index (kg/m²)	Mortality rate
<18.5	20.5%
18.5–24.9	41.1%
25–29.9	23.2%
>30	15.2%

Table 6. Annual product use and change in cost

	Year 2016	Year 2017	Year 2018
Number of patients using TPN in hospital	7872	7258	5968
Number of TPNs used in hospital	8783	7893	6104
Number of patients using enteral products in hospital	4376	5790	7582
Number of enteral products used in hospital	16.838	22.237	25.753
Enteral + parenteral product cost (Turkish Lira)	470.537,45	445.095,16	416.306,03
Nutritional cost per patient (Turkish Lira)	38.41	34.10	30.72
TPN cost (Turkish lira)	429.714,38	394.096,86	314.500,64
Number of TPNs used in internal medicine intensive care unit	1312	1275	192
Number of TPNs used in palliative service	2218	1715	959

TPN: total parenteral nutrition

Discussion

The screening rate for determining the risk of malnutrition in hospitalized patients increased from 49.4% in 2017 to 91.3% in 2018. After the establishment of NST, the team explained the necessity of screening for malnutrition risk and the importance of clinical nutritional support to the health personnel, especially nurses, via an all-day training process. In addition to this training, the number of patients screened increased as a result of educating them about the need for NRS-2002 screening. Although the number of patients screened for malnutrition risk increased, there was no change in the proportion of patients at risk of malnutrition or malnutrition. The proportion of patients with malnutrition risk in inpatients did not change compared to the previous year (7.4%). In the literature, the malnutrition rate of hospitalized patients was found to be 15–60% and could be as high as 38–72% in ICU patients or elderly patients (7). The malnutrition rate in our hospital was found to be lower than what has been reported in the literature.

Nutritional status tends to deteriorate in hospitalized patients. Malnutrition is a condition that can cause both deterioration of the clinical outcome of the patient and increase the health costs as a result of the disease (8, 9). Studies have been shown that screening patients with malnutrition and providing adequate nutritional support may decrease the rate of complications and death due to nutrition and shorten the length of hospital stay. Evidence suggests that nutritional support should be initiated immediately to improve the clinical outcome of patients who are malnourished or at risk of malnutrition (10). The European Society for Parenteral and Enteral Nutrition recommends that nutritional risk screening (NRS-2002) should be performed in all hospitalized patients to determine the risk of malnutrition.

Nutritional support is indicated in medical situations where the disease-related risk of malnutrition increases, and even in cases of surgery or trauma. Reducing or preventing malnutrition is only possible with correct nutritional support therapy. It has been shown in the studies that when nutritional support is given by NST, the complications and treatment costs decrease (5). It was recommended that nutritional support should be managed under the supervision of a team of doctors, dietitians, pharmacists, and nurses (11). Enteral or parenteral nutrition was recommended for the patients at risk of malnutrition in the form of protein supplements in doses of 25–30 kcal/kg/day and 1.2–1.5 g/kg/day while taking the stress factors related to the disease into consideration.

In addition to providing the necessary nutrients, enteral nutrition helps to maintain intestinal structure and function and prevents bacterial translocation and stress ulcers. When determining the feeding route, enteral nutrition should be the first choice in patients with a functional gastrointestinal system (GIS) (12). Parenteral nutrition (PN) supplementation may need to be started or added in patients whose GIS cannot be used or if the daily target calories cannot be reached by enteral feeding (12, 13). The guidelines recommend that enteral nutrition should be the first choice because of its effectiveness in strengthening immune functions and lowering the cost of nutritional therapy. Enteral nutrition was the most commonly recommended feeding route in 53.8% of the patients that we followed. The second recommendation is oral supplementation to close the target calorie deficit needed for daily energy. PN support was initiated in patients who could not tolerate enteral nutrition. Enteral or PN therapy was not recommended in 34 (6.6%) patients with unstable hemodynamic status.

Because of the role of nutrition and enteral products in the etiology and progression of the disease, we need to consider the cost and value of nutritional interventions. Improving health care by providing optimal nutrition can contribute to the effectiveness and sustainability of healthcare systems. Studies have shown that the annual cost of medical nutrition employed in the treatment of malnutrition resulting from non-implementation of optimal nutrition management, including the use of food, chalks up to billions (14). The enteral feeding method has been shown to be more cost-effective than the parenteral feeding method (13). In our study, the number of patients using parenteral products and total cost was decreased as compared to the previous year. Under the guidance of the NST recommendations, it was found that the number of enteral products used and the number of patients using enteral products eventually increased as compared to the previous year.

When the mortality rates of the patients under follow-up were compared with NRS-2002 scores, it was found that the mortality rate was higher in patients with higher NRS-2002 scores. Although the NRS-2002 malnutrition screening test is not used as a marker of mortality, the high mortality rate of high scoring patients may be an important parameter for the newly developed indexes used as prognostic factors. In a study conducted by Gundogan et al. (15) in 2011, it was reported that the mortality rate was high in patients with high NRS-2002 score. They associated the high mortality rates with the inability to determine and treat malnutrition risk in inpatients. It is stated that this problem is mainly caused by the inadequacy of screening, evaluation, and application algorithms and nutritional education of hospital staff (15). In another study

evaluating the relationship between NRS-2002 score elevation and mortality, Maciel et al. (16) reported that the mortality rate in patients with moderate malnutrition with an NRS-2002 score of 3–5 was lower than the mortality rate in malnourished patients with an NRS-2002 score >5. In our study, the mortality rate was 38.4% in patients with NRS-2002 score 3–5 and 61.6% in patients with >5 score. Consistent with the results of other studies, a relationship between NRS-2002 and mortality was detected, where mortality increased as the NRS-2002 score increased.

van Schaik et al. (17), reported a decrease in the number of patients receiving TPN by 29% and a 40% reduction in TPN-related costs compared to the previous year as a result of monitoring of patients receiving TPN by dietitians. The findings of our study are in accordance with this result, as it was found that the rate of TPN used in hospital decreased by 30.5% compared to the previous year. Our results support previous studies in terms of the reduction of hospital costs by arranging proper nutrition for the patients under the guidance of NSTs (18). In addition, a decrease in TPN-related complications and associated costs can be expected. As our hospital records were not sufficient, this cost evaluation could not be performed. The decrease in the use of TPN was more pronounced in the palliative service and internal intensive care unit, where consultation with the nutrition team was greater.

The first limitation of our study was the collection of single-centered data. This resulted in a relatively small number of patients being followed-up. Although a hospital-wide NST was performed, the study did not include all patients with an NRS score of 3 or higher, as the nutritional support team was consulted according to the physician's request. Therefore, it is not possible to generalize the results.

In conclusion, conducting patient follow-ups according to the NST recommendations can positively influence many factors such as choosing the correct feeding route and an overall decrease in treatment costs. Considering these positive factors, it is recommended that NST should be expanded and nutritional support should be offered with a multidisciplinary approach to patients at risk of malnutrition.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kütahya Health Sciences University (February 2019).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.T.; Design – M.Ç.; Supervision – K.G.; Resources – E.Ö.K.; Data Collection and/or Processing – M.Ç.; Analysis and/or Interpretation – G.T.; Literature Search – K.G.; Writing Manuscript – K.G.; Critical Review – K.G.

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References

1. Jensen GL, Bistrian B, Roubenoff R, Heimburger DC. Malnutrition syndromes: a conundrum vs continuum. JPEN J Parenter Enteral Nutr 2009; 33: 710-6. [CrossRef]
2. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: Prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health 2011; 8: 514-27. [CrossRef]
3. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Educational and Clinical Practice Committee ErSoPaENE. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003; 22: 415-21. [CrossRef]
4. Hudson L, Griffith C, Chittams J, Compher C. Malnutrition identified by Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition is associated with more 30-day readmissions, greater hospital mortality, and longer hospital stays: a retrospective analysis of nutrition assessment data in a major medical center. JPEN J Parenter Enteral Nutr 2018; 42: 892-7. [CrossRef]
5. Jeong E, Jung YH, Shin SH, Kim MJ, Bae HJ, Cho YS, et al. The successful accomplishment of nutritional and clinical outcomes via the implementation of a multidisciplinary nutrition support team in the neonatal intensive care unit. BMC Pediatr 2016; 16: 113. [CrossRef]
6. Cooper C, Brierley ER, Burden ST. Improving adherence to a care plan generated from the Malnutrition Universal Screening Tool. Eur J Clin Nutr 2013; 67: 174-9. [CrossRef]
7. Lew CC, Yandell R, Fraser RJ, Chua AP, Chong MF, Miller M. Association between malnutrition and clinical outcomes in the inten-sive care unit: a systematic review. JPEN J Parenter E nteral Nutr. 2017; 41: 744-58. [CrossRef]
8. Schindler K, Pernicka E, Laviano A, Howard P, Schütz T, Bauer P, et al. How nutritional risk is assessed and managed in European hospitals: a survey of 21,007 patients findings from the 2007-2008 cross-sectional nutritionDay survey. Clin Nutr Edinb Scotl 2010; 29: 552-9. [CrossRef]
9. Khalatbari-Soltani S, Marques-Vidal P. The economic cost of hospital malnutrition in Europe; a narrative review. Clin Nutr ESPEN 2015; 10: 89-94. [CrossRef]
10. Jie B, Jiang ZM, Nolan MT, Efron DT, Zhu SN, Yu K, et al. Impact of nutritional support on clinical outcome in patients at nutritional risk: a multicenter, prospective cohort study in Baltimore and Beijing teaching hospitals. Nutrition 2010; 26: 1088-93. [CrossRef]

11. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017; 36: 49-64. [CrossRef]
12. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019; 38: 48-79. [CrossRef]
13. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN Guidelines on parenteral nutrition: intensive care. Clin Nutr 2009; 28: 387-400. [CrossRef]
14. Freijer K, Bours MJ, Nuijten MJ, Poley MJ, Meijers JM, Halfens RJ, et al. The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. J Am Med Dir Assoc 2014; 15: 17-29. [CrossRef]
15. Gündoğan K, Coşkun R, Sungur M, Güven M. Yatan hastalarda NRS2002 ile beslenme risk değerlendirilmesi. Turkish Journal of Medical & Surgical Intensive Care Medicine 2012; 3(Suppl 1): 49.
16. Maciel LRMA, Franzosi OS, Nunes DSL, Loss SH, Dos Reis AM, Rubin BA, et al. Nutritional risk screening 2002 cut-off to identify high-risk Is a good predictor of ICU mortality in critically Ill patients. Nutr Clin Pract 2019; 34: 137-41. [CrossRef]
17. van Schaik R, Van den Abeele K, Melsens G, Schepens P, Lanssens T, Vlaemynck B, et al. A protocol for sustained reduction of Total Parenteral Nutrition and cost savings by improvement of nutritional care in hospitals. Clin Nutr ESPEN 2016; 15: 114-21. [CrossRef]
18. Goldstein M, Braitman LE, Levine GM. The medical and financial costs associated with termination of a nutrition support nurse. J Parenter Enter Nutr 2000; 24: 323-7. [CrossRef]

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Time span of a total parenteral nutrition bag: From consultation to the end of administration

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ABSTRACT

Objective: A multidisciplinary nutrition support team (NST) aims to improve a patient's nutritional status. Nutritional support should be initiated promptly in patients who need it. Parenteral nutrition (PN) solutions have a risk of being unstable until 24 hours after preparation. The aim of this study was to determine the time span of the PN process, which starts from a consultation with an NST until the end of the administration of the solution, to demonstrate the appropriateness of the practice.

Methods: In this study, the timing of each process including NST consultation, evaluation of the patient by NST, delivery of the order label to the pharmacy, compounding process, delivery of the bags to the services/units, storage in the services/units, and duration of administration were prospectively followed and recorded by three pharmacists in a university hospital for two weeks in January 2017.

Results: A total of 12 patients' PN processes were followed and the duration of each stage was recorded by pharmacists. The mean duration of compounding PN±standard deviation (SD) was 5.18±0.87 minutes. The average (±SD) volume of PN was 1557±205.2 mL. The mean (±SD) duration of administration was recorded as 24 hours and 14 minutes±37.5 minutes. The mean (±SD) volume of residual PN solution was 106.9±30.3 mL and 41.6% of the waste was discarded as household waste rather than medical waste. The mean (±SD) room temperature during the administration of PN was 25.01±1.6°C.

Conclusion: With regard to stability problems of PN solutions, awareness among healthcare professionals should be raised in order to reduce the waiting period till administration. Minimizing waste-cost and the residual volume of PN is important to maintain the patients' nutritional requirements.

Keywords: Compounding, nutritional support team, parenteral nutrition

Introduction

Parenteral nutrition (PN) is preferred when a patient cannot be fed orally or enterally. The safe practices for PN therapy are comprehensive due to its multicomponent nature (1).

In a Task Force survey, most participants declared that they needed up to 20 adult PN bag per day in their institutions. Hospitals should have standard operating procedures for the ordering, compounding, appropriate usage, complication prevention, and management of PN to ensure patient safety and cost reduction (2).

There are two types of all-in-one systems: compounded bags (COBs) and commercial multi-chamber bags (MCBs). MCBs require less workload as compared to COBs. Special equipment, infrastructure, and trained staff are needed to administer COBs. On the other hand, for MCBs, the chamber seal is broken prior to the administration which allows mixing of the chambers and only requires the addition of trace elements and vitamins. Stability of non-activated MCBs varies with different manufacturers but usually has 12 to 24 months shelf-life at room temperature (3).

A nutrition support team (NST) consists of a clinician, dietitian, nurse, and pharmacist, however, the composition is variable in different hospitals. While providing nutrition assessment and determining nutritional needs, the NST aims to ensure appropriate and safe nutritional support to

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a patient. An NST improves the quality of patient care with improvements in patient nutrition status and clinical outcomes as well as reductions in cost. After hospitalization, routine screening of patients for malnutrition should be implemented and those at risk must be advised to consult the NST for further assessment of their malnourished status. In institutions using COB for PN therapy, physicians or dietitians under the supervision of physicians are responsible for prescribing PN orders, pharmacists or technicians under the supervision of pharmacists are responsible for receiving the orders and compounding PN, and nurses are responsible for the administration of PN and monitorization and destruction of PN bags (4).

In the proper practices of PN, the compounding, hang time, storage time, and maximal infusion rate of total nutrient admixture (TNA) are important. According to the literature, the maximum hang time for a TNA was 24 hours (3). Both for COBs and activated MCBs, the new beyond-use date is important and it is specified that infusion should not exceed 24 hours. Because of the concern for microbial contamination, the United States Pharmacopoeia (USP) recommends that intravenous fat emulsion (IVFE) products must be used within 12 hours of opening the original container if they are administered as a separate infusion. If the IVFE is admixed directly to the PN, the final PN formulation can be infused over a 24-hour period since it provides a safe vehicle with less infectious risks (2).

According to the USP 797 for medium-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, in proper storage conditions PN bags cannot be stored for more than 30 hours at controlled room temperature and no more than 9 days at a cold temperature (+4°C) (5).

Limited literature is available to demonstrate the PN preparation time while comparing MCBs and COBs (6-8). However, according to published literature, the timing of each process (time periods between consultation and evaluation of patient by NST, between evaluation of patient and label printing, between label printing and the end of compounding, between the end of compounding and delivery, and between delivery of bags and administration) and storage conditions in the services/units during administration has not been demonstrated together in one study. The aim of this study was to determine the time span of the PN process, which starts from a consultation with an NST until the end of the administration of the solution, to demonstrate the appropriateness of the practice.

Methods

This cross-sectional and observational study was conducted in a university hospital between 2 January 2013 to 13 January 2017. The patients who received a consultation with the NST for PN therapy for the first time were included in the study, while those who were already under nutritional therapy were excluded.

In this study, the timing of each process including NST consultation, evaluation of the patient by NST, delivery of the order label to the pharmacy, compounding process, delivery of the bags to the services/units, storage in the services/units, and duration of administration were prospectively followed and recorded by three pharmacists. Furthermore, the room temperature during PN storage and the temperature of the patient's room, sunlight exposure, decomposition conditions of unused quantities, and the number of wasted bags were also evaluated.

Statistical analysis

The values were given as a number (percentage) for categorical variables and as mean±standard deviation (SD) for continuous variables.

Results

During the study, a total of 12 NST consultations for new PN assessment were observed. Four of these consultations happened in surgical units, 6 in non-surgical units, and 2 in oncological units. Although the PN varies according to the bag volume (mean±standard deviation [SD] 1557±205.2 mL) the filling process takes place on an average of (±SD) 5.18±0.87 minutes (min). The average (±SD) duration of administration of PN bags time was 24 hours 14 minutes±37.5 minutes. The timing of each process from the consultation until the destruction of PN bags is given in Table 1.

The mean (±SD) temperature of the patients' room was 25.01±1.6°C (range: 21–26.5°C). It was determined that there was sunlight exposure during the daytime administration of 6 PN solutions. No medication was administered from the same catheter as PN in 6 patients, medications were given from the same catheter as PN in 2 patients, and PN infusion was stopped while the medication was administered in 3 patients.

An average of 106.9 mL of leftover PN solution was detected at the end of the infusion period and 41.6% of this waste was separated as household waste instead of medical waste.

Table 1. The time span of TPN processes			
Stages of process	**Median (minutes)**	**Minimum (minutes)**	**Maximum (minutes)**
The time between consultation and evaluation of the patient by NST	57.5	1	342
The time between the evaluation of patient and label printing	44	7	256
The time between label printing and the end of compounding	87	25	309
The time between the end of compounding and delivery	32	10	207
The time between delivery of bags and administration	56.5	5	90
The time between receiving a consultation and the beginning of TPN infusion	428.5	187	651
NST: Nutrition Support Team; TPN: total parenteral nutrition			

Discussion

The aim of this study was to determine the time span of the PN process, which starts from a consultation with an NST until the end of the administration of the solution, to demonstrate the appropriateness of the practice.

A multidisciplinary NST aims to improve a patient's nutritional status. According to a survey conducted by the American Society for Parenteral and Enteral Nutrition (ASPEN) in 2008 to evaluate the utility of NSTs in clinical practice, the average consult response time ranged from 10 minutes to 72 hours and a majority of participants (52.2%) declared that consultations were generally responded to within 24 hours. Only one-third of the respondents stated that their consult was addressed in less than 8 hours (9). Since the NST does not provide care for 24 hours in our institution, one of the consultations was responded to in 342 minutes because of a late-night consultation. However, in this study, it was determined that the consultations were responded to and patients were evaluated mostly within 1 hour (median 57.5 min) by NST. Compared to the ASPEN survey results, the consult response time was much faster in our institution.

Even though COBs are more time consuming than MCBs, the compounding time of PN reported by Pichard et al. (6) was 15 minutes. In a prospective, multi-center, randomized, comparative, single-blind study conducted by Yu et al. (7), the preparation times for 1886.5 mL COBs were evaluated in 115 patients on day 1 and day 5 postoperatively (12.13±5.62 minutes and 11.77±4.79 minutes, respectively). A study by Berlana et al. (8) reported that the mean time taken to prepare 82 PN solutions (1500±250 ml) was 14.09 minutes. Unlike other studies, COB preparation time was found to be shorter (5.18±0.87 minutes) in our study even though the PN volumes (mean 1557±205.2 ml) were similar. The usage of different compounder devices might be the explanation for this variation in preparation time, however, they could not be compared because the manufacturers of the devices were not mentioned in any of these studies.

According to the study by Didier et al. (10), bacterial growth in PN solutions occurred at 25°C only after 24–48 hours. In our study, the mean duration of administration was determined as 14±37.5 minutes and the mean room temperature during the administration of TPN was 25.01±1.6°C. At this temperature, the time period between the end of compounding and delivery (32 minutes, range: 10–207 minutes) and between delivery of bags and administration (56.5 minutes, range: 5–90 minutes) compared with the mean duration of administration (24 hours 14 minutes±37.5 minutes) showed that some PN solutions were at high risk for bacterial growth and instability. In this study, the maximum time between the end of compounding and delivery mostly depended on the lack or workload of staff in charge of the delivery and maximum time between delivery of bags and administration period depended on the lack of available nurses. By providing an adequate number of clinicians and staff, optimal time periods between the transition points can be achieved.

An average of 106.9 mL of leftover PN solution out of the mean PN volume of 1557±205.2 mL was detected at the end of infusion period, which means that almost 7% of the targeted volume and calorie intake could not be provided. Further, none of the clinicians or NST members were aware of that situation. Nurses should record waste amounts of PN nutrition and inform the NST, or they should readjust the PN infusion rate to minimize waste amounts.

Another important finding of this study was to detect differences in the practices of PN waste management since 41.6% of these wastes were separated as household

waste instead of medical waste. Waste management of these solutions should be standardized and all clinicians should perform the same practice.

Parenteral nutrition solutions are not drug delivery systems and the risk of incompatibility is high while administering PN solutions and drugs through the same catheter (11). In this study, 2 patients' medications were given from the same catheter with PN and in 3 patients the PN infusion was stopped while the medication was administered. Due to the involvement of a clinical pharmacist in our NST, all patients' medication was managed to ensure the prevention of drug incompatibility.

As no previous study in the literature has reported all these findings together, some findings could not be compared and discussed. Also, due to the limited number of observed PN bags, a statistical analysis was not performed in this study. Further studies are needed with more PN bag follow-ups to report statistical data and to compare the practices in different units and the timing periods of each process.

In conclusion, with regards to the stability problems of TPN solutions, awareness among healthcare professionals should be raised in order to reduce the unnecessary waiting period. Minimizing waste-cost and the residual volume of TPN is important to maintain the patients' nutritional requirements.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Due to the design of the study, informed consent was not taken.

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References

1. Bozzetti F., Forbes A. The ESPEN clinical practice guidelines on parenteral nutrition: present status and perspectives for future research. Clin Nutr 2009; 28: 359-64. [CrossRef]
2. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Safe Practices for Parenteral Nutrition. J Parenter Enteral Nutr 2004; 28: S39-S70. [CrossRef]
3. Alfonso JE, Berlana D, Ukleja A, Boullata J. Clinical, ergonomic, and economic outcomes with multichamber bags compared with (hospital) pharmacy compounded bags and multibottle systems: a systematic literature review. J Parenter Enteral Nutr 2017; 41: 1162-77. [CrossRef]
4. DeLegge MH, Kelly AT. State of nutrition support teams. Nutr Clin Pract 2013; 28: 691-7. [CrossRef]
5. US Pharmacopeial Convention, Inc. United States Pharmacopeia 27, Supplement 1. Chapter <797> "Pharmaceutical Compounding-Sterile Preparations" Revision Bulletin. Rockville, MD: US Pharmacopeial Convention, Inc.; 2018.
6. Pichard C, Schwarz G, Frei A, Kyle U, Jolliet P, Morel P, et al. Economic investigation of the use of three-compartment total parenteral nutrition bag: prospective randomized unblinded controlled study. Clin Nutr 2000; 19: 245-51. [CrossRef]
7. Yu J, Wu G, Tang Y, Ye Y, Zhang Z. Efficacy, safety, and preparation of standardized parenteral nutrition regimens: three-chamber bags vs compounded monobags-a prospective, multicenter, randomized, single-blind clinical trial. Nutr Clin Pract 2017; 32: 545-55. [CrossRef]
8. Berlana D, Almendral MA, Abad MR, Fernández A, Torralba A, Cervera-Peris M, et al. Cost, time, and error assessment during preparation of parenteral nutrition: multichamber bags versus hospital-compounded bags. J Parenter Enteral Nutr 2019; 43: 557-65. [CrossRef]
9. DeLegge M, Wooley JA, Guenter P, Wright S, Brill J, Andris D, et al. The State of Nutrition Support Teams and Update on Current Models for Providing Nutrition Support Therapy to Patients. Nutr Clin Pract 2010; 25: 76-84. [CrossRef]
10. Didier ME, Fischer S, Maki DG. Total nutrient admixtures appear safer than lipid emulsion alone as regards microbial contamination: growth properties of microbial pathogens at room temperature. J Parenter Enteral Nutr 1998; 22: 291-6. [CrossRef]
11. Bayraktar Ekincioğlu A, Demirkan K. Clinical nutrition and drug interactions. Turk J Surg 2013; 29: 177-86. [CrossRef]

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Nutritional assessment of intensive care unit patients aged ≥65 years using different screening tools

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ABSTRACT

Objective: The aim of the study was to evaluate the nutritional status of patients aged ≥65 years admitted to the intensive care unit (ICU), compare the compliance with the nutritional status screening tools, and determine the effect of malnutrition on mortality.

Methods: Patients who were admitted to ICU and could receive nutrition orally were included into this study. The Nutritional Risk Score 2002 (NRS-2002) and Mini Nutritional Assessment Short Form (MNA-SF) were administered, and the Nutritional Risk Index and Geriatric Nutritional Risk Index (GNRI) scores were calculated. Patients were divided into two groups according to their survival status. The nutritional status was evaluated and found to be in accordance with the screening tools.

Results: The rate of malnutrition/severe nutrition risk was found to be 28.4%–60%, and the normal nutritional status was 1.7%–33.3%. In-hospital mortality was 41.7%. The duration of stay in ICU (8.0±9.8 days; 20.5±20.0 days, p=0.03), duration of stay in hospital (16.9±14.4 days; 28.5±24.6 days; p=0.029) and mechanical ventilation duration (4.38±6.8 days; 15.56±17.2 days; p=0.01) in patients who survived were shorter than in patients those who died. The male gender, patients with an NRS-2002 score ≥5 and NRI score ≥81.2 had higher mortality rates (respectively, p=0.013, p=0.019, p=0.036). The NRS-2002 was found to have the highest sensitivity; NRI was the highest specificity screening tool.

Conclusion: The risk of malnutrition/severe nutrition risk was found to be 28.4%–60%. We found that the male gender, NRS-2002 ≥5, and NRI ≥81.2 were associated with higher mortality. The NRS-2002 was found to have the highest sensitivity; NRI was the highest specificity screening tool. We think that the usage of one screening tool for predicting malnutrition in elderly patients is not sufficient in the diagnosis of malnutrition, and these methods should be evaluated together.

Keywords: GNRI, geriatric patient, intensive care, malnutrition, MNA-SF

Introduction

Malnutrition is defined as "subacute or chronic malnutrition that causes functional capacity, lean tissue mass and cell decline as a result of malnutrition and inflammatory activity" (1). Intensive care patients are highly susceptible to the development of malnutrition. Especially when the elderly population is considered, malnutrition has many negative consequences, such as impaired muscle function, muscle weakness, bone fractures, decrease in immune function, bone mass and cognitive function, anemia, pressure sores, postoperative healing, delayed wound healing, and edema. This clinical process leads to an increase in the length of stay in the intensive care unit (ICU), as well as an increase in morbidity and mortality. Therefore, a planned and scheduled nutritional assessment should be implemented in hospitals (2, 3). However, no assessment alone has sufficient sensitivity and selectivity to determine the nutritional status (4).

The purpose of nutrition screening is to identify individuals with malnutrition or those at risk for malnutrition to achieve a more comprehensive nutritional assessment and support (5). The assessment of nutritional status in the elderly is important in defining nutritional deficiency and related diseases (6, 7). A number of screening tools have been developed to determine the risk of malnutrition in elderly patients. Some of those are the Nutritional Risk

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Screening 2002 (NRS-2002) and Mini Nutritional Assessment Short Form (MNA-SF) (8, 9).

The NRS-2002 is a nutritional assessment test used for intensive care unit (ICU) patients to determine the risk of malnutrition, to find malnourished patients, and to evaluate the adequacy of nutritional support in hospitalized patients (10).

The Nutrition Risk Index (NRI) was developed in 1991 to evaluate the effectiveness of perioperative total parenteral nutrition in patients undergoing thoracic or abdominal surgery (11).

Geriatric Nutrition Risk Index (GNRI) is an evaluation method designed especially to predict morbidity and mortality risk of elderly hospitalized patients. Since it is often difficult to evaluate the normal body weight of the elderly, this method uses the term ideal body weight instead of the usual body weight in NRI. GNRI is calculated using a special formula that uses serum albumin and body weight loss together (12).

The aim of this study was to evaluate the nutritional status of patients aged ≥65 years admitted to ICU, using the NRS 2002 and MNA-SF scales and NRI and GNRI scoring systems, to determine their usefulness as a screening test, to compare compliance, and to determine the effect of malnutrition on mortality.

Methods

This prospective study was approved by the Başkent University Non-interventional Clinical Research Ethics Committee, dated 01/19/2018 and numbered KA17/365. It was carried out in patients voluntarily admitted, aged ≥65 years, with at least 24-hour hospitalization at the Başkent University Ankara Hospital Internal and Surgical Sciences Intensive Care Unit. The patients managed by intensivists are admitted to our ICU from different departments.

Patients aged ≥65 years in who oral intake was possible, or who were receiving oral enteral nutritional support following the ICU admission, were included in the study. Patients who received the enteral nutrition support at home via gastrostomy, jejunostomy, or nasogastric tube before hospitalization were excluded from the study. However, patients who needed any nutritional intervention during their stay in the ICU were routinely evaluated by the Nutrition Support Team to provide nutritional support in accordance with the calculated energy and protein requirements of the patients. During this follow-up, oral intake was applied to patients who could not receive oral nutrition due to invasive or noninvasive mechanical ventilation support. During the follow-up, enteral/parenteral feeding was given to patients who had oral intake, but later could not receive oral nutrition because of invasive or noninvasive mechanical ventilation support.

The age, gender, height, and body weight were recorded at the ICU admission. The NRS-2002 was recommended by the European Parenteral and Enteral Nutrition Association (ESPEN), especially for nutritional assessments, were used to determine the nutritional status within the first 24 hours; the MNA-SF, recommended by the International Society for Gerontology and Geriatrics and the International Academy of Nutrition and Aging for the assessment of the nutritional status of geriatric patients, was administered at the patient's site by the study conductor (13).

NRI: [1.519×albumin g/dL)]+[41.7×(final body weight/customary body weight)×100]

GNRI: [1.489×albumin (g/L)]+[41.7×(body weight/ideal body weight)]

The patients were divided into two groups, according to their survival status and their nutritional status, and clinical characteristics were evaluated. The nutritional status of the patients was grouped according to the results of the screening tools (Table 1).

The body mass index (BMI) of the patients (kg/m^2) was calculated using their body weight and height. BMI values were grouped according to the World Health Organization classification (BMI <18.50, underweight; 18.50-24.99, normal weight; 25.00-29.99; mild overweight, ≥30.00; overweight) (14). The Acute Physiology and Chronic Health Score II (APACHE II) was calculated to determine the mortality risk of patients and physical examination was performed to collect the vital data. Patients included in the study were followed up during their stay in ICU and other wards, and their clinical characteristics were recorded. Patients' ICU and hospital stay durations, mechanical ventilation durations, need for renal replacement therapy, vasoactive drug infusion, sepsis, and septic shock were determined. Biochemical tests were performed in the Baskent University Ankara Hospital Biochemistry Laboratory. Serum albumin, hemoglobin, and C-reactive protein (CRP) levels were recorded from the laboratory findings.

Statistical analysis

In the study, the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (NCSS LLC, Kaysville,

Table 1. Malnutrition ratings by screening tools	
Scanning tools	**Nutritional status/risk**
GNRI	
>98	Normal nutritional status
92≤GNRI≤98	Mild nutrition risk
82≤GNRI<92	Moderate nutrition risk
<82	Severe nutrition risk
NRI	
>100	Normal nutritional status
97.5<NRI<100	Mild nutrition risk
83.5≤NRI≤97.5	Moderate nutrition risk
<83.5	Severe nutrition risk
MNA-SF	
12–14	Normal nutritional status
8–11	Under risk for malnutrition
0–7	Malnutrition
NRS-2002	
1–2	Normal nutritional status
3–4	Under risk for malnutrition
≥5	Malnutrition

MNA-SF: Mini Nutritional Assessment Short Form; NRS-2002: Nutritional Risk Screening Test 2002; NRI: Nutritional Risk Index; GNRI: Geriatric Nutritional Risk Index

Utah, USA) was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, median, frequency, and ratio), the Kolmogorov-Smirnov test and box plot graphs were used for the normal distribution of quantitative data. Student's t-test was used for the comparison of the groups with normal distribution, and the Mann-Whitney U test was used for the non-normal distribution. Pearson's chi-squared test and the Fisher-Freeman-Halton test were used for the comparison of qualitative data, and diagnostic screening tests and ROC analysis were used to determine the cut-off point. The results were evaluated with a 95% confidence interval and $p<0.05$ significance level.

Results

A total of 60 patients, 28 females and 32 males aged ≥65 years, who were followed in the ICU, were included in our study. The average age of all patients was 78.3±8.6 years. The average BMI of the patients was 25.3±5.4 kg/m^2 (slightly overweight). It was determined that 40% of the patients were admitted to the Department of Chest Diseases. When the patients' admission reasons were evaluated, the first listed were respiratory causes (50.0%), and 73.3% were hospitalized for medical treatment. COPD and hypertension with 48.3% and diabetes mellitus with 41.7% were the leading comorbidities. Of the 60 patients, only 2 had no concomitant disease, while 8 had only one. Other patients had multiple comorbidities. The average APACHE II score at the ICU admission was 18.9±5.6 (Table 2).

Demographic and clinical characteristics of the patients are shown in Table 3. When evaluated in terms of in-hospital survival, 58.3% of the patients were alive (n=35), and 41.7% (n=25) were in the dying group. There was no difference between the groups in terms of gender, age, and BMI. The serum albumin levels were significantly higher in the surviving patients compared to those who died (3.0±0.6 g/dL and 2.7±0.6 g/dL, p=0.048, respectively).

The frequency of sepsis and septic shock was similar in patients who died and survived. Inotropic use was found to be higher in patients who died than those who survived (96.0% versus 28.6%, p=0.00). Invasive/noninvasive mechanical ventilation was performed in 48 patients, consisting all of dying patients (n=25) and 23 (65.7%) of surviving patients. The duration of mechanical ventilation was significantly higher in patients who died than in patients who survived (15.6±17.2 days versus 4.4±6.8 days, p=0.01).

When the two groups were examined according to the total length of hospitalization in the ICU and hospital, the mean hospitalization time of the patients who died was longer than of those who survived. According to these results, the difference between the two groups was statistically significant (p=0.03 vs. p=0.029, respectively).

Malnutrition and/or severe nutrition risk ratios of all patients included in the study were found to range between 28.4% and 60% when evaluated with GNRI, NRI, MNA-SF, and NRS-2002, and the normal nutritional status was detected to be 1.7%-33.3% (Table 4).

When evaluated according to GNRI, 28.4% of all patients, 25.7% of surviving patients, and 32% of those who died were at risk of severe nutrition and 33.3% of all patients, 34.3% of surviving patients, and 32% of those who died were found to be in normal nutritional status. The difference between the groups was not statistically significant (p>0.05).

According to NRI, 53.4% of all patients, 64% of patients who died, and 45.7% of surviving patients were at risk of

Table 2. Inpatient clinics in the name of patients in the intensive care unit, the reasons for hospitalization in intensive care unit, the treatments applied, and comorbidities

Features of patients	n =60	Features of patients	n=60
Hospitalization (%)		**Treatment (%)**	
Chest diseases	40.0	Medical	73.3
Nephrology	11.7	Surgical	26.7
General surgery	8.3	**Comorbidities status (%)**	
Oncology	6.7	COPD	48.3
Obstetrics	5.0	Hypertension	48.3
Cardiology	3.3	Diabetes mellitus	41.7
Gastroenterology	3.3	Cardiovascular disease	38.3
Urology	1.7	Chronic renal failure	35.0
Other	20.0	Cancer	13.3
Reason for hospitalization (%)		Chronic liver failure	3.3
Respiratory	50.0	APACHE II Score (average)	18.9±5.6
Postoperative	16.7		
Gastrointestinal	11.7		
Renal	10.0		
Hematologic	5.0		
Cardiovascular	3.3		
Trauma	3.3		

APACHE II: Acute Physiology and Chronic Health Evaluation II; COPD: chronic obstructive pulmonary disease

severe nutrition; and 3.3% of all patients and 5.7% of surviving patients had normal nutritional status. According to the NRI results, there were no patients in the normal nutritional status class. The difference between the groups was not statistically significant (p>0.05).

According to the MNA-SF results, 35% of all patients, 25.7% of surviving patients, and 48% of patients who died were at risk of malnutrition; and 25.0% of all patients, 37.1% of surviving patients, and 8% of those who died were classified as having normal nutritional status. The difference between the groups was statistically significant (p=0.027).

The difference between NRS-2002 scores was statistically significant (p=0.02). When NRS-2002 results were evaluated, 60% of all patients, 45.7% of surviving patients, and 80% of patients who died were at risk of malnutrition, and 1.7% of all patients and 2.9% of surviving patients were evaluated as having normal nutritional status. According to the NRS-2002 results, there were no patients in the dying group with the normal nutritional status.

The cut-off point for NRI was 81.2 and below, according to mortality. For the NRI cut-off value, sensitivity was 64%, specificity was 74.29%, positive predictive value was 64%, and negative predictive value was 74.3% (Table 5).

The cut-off point for MNA-SF was found to be 9 and below, according to mortality. For the MNA-SF cut-off value, sensitivity was 68%, specificity was 60%, positive predictive value was 54.8%, and negative predictive value was 72.4% (Table 5).

The cut-off point for NRS-2002 was found to be 5 or higher according to mortality. For the cut-off value of NRS-2002, sensitivity was 80%, specificity was 54.29%, positive predictive value was 55.6%, and negative predictive value was 79.2% (Table 5).

When NRI, MNA-SF, and NRS-2002 domains were compared in binary, there was no statistically significant difference between NRI and MNA-SF in predicting mortality (p=0.958; p>0.05). There was no statistically significant

Table 3. Demographic and clinical characteristics of patients				
	Total (n=60)	**Surviving (n=35)**	**Died (n=25)**	**p**
Female/Male %	46.7/53.3	67.9/50.0	32.1/50.0	0.162
Age (year, ave.)	78.3±8.9	78.0±8.9	78.7±9.0	0.772
BMI (kg/m^2)	25.3±5.4	24.9±4.7	25.9±6.3	0.469
Albumin, ave., g/dL	2.8±0.6	3.0±0.6	2.7±0.6	0.048*
Hemoglobin, ave., g/dL	10.6±1.9	10.4±1.9	10.8±2.0	0.367
CRP, ave., mg/L	83.1±68.0	77.8±75.7	90.5±56.3	0.482
Sepsis existence (%)	31.7	28.6	36.0	0.098
Presence of septic shock (%)	25.0	17.1	36.0	0.098
Inotropic drug use (%)	56.7	28.6	96.0	0.00**
The need for renal replacement therapy (%)	30.0	28.6	32.0	0.775
Mechanical ventilation (days, ave.)	8.9±13.2	4.4±6.8	15.6±17.2	0.01*
ICU stay (days)	13.3±16.1	8.0 ±9.8	20.5±20.0	0.03*
Hospital stay (days)	21.9±20.1	16.9±14.4	28.5±24.6	0.029*
APACHE II score, ave.	18.9±5.6	17.3±5.12	21.2±5.58	0.07

T-test, Pearson's chi-squared; *p<0.05, **p<0.001. BMI: body mass index; CRP: C-reactive protein; ICU: intensive care unit; APACHE II: Acute Physiology and Chronic Health Evaluation II

difference between NRI and NRS-2002 in predicting mortality (p=0.621; p>0.05). There was no statistically significant difference between MNA-SF and NRS-2002 in predicting mortality (p=0.593; p>0.05).

Among the factors that were shown to have univariate effects on mortality and a significance level <0.15, the effects of gender, albumin, inotropic drug use, sepsis, NRS-2002, MNA, and NRI measurements were evaluated using the logistic regression analysis (Table 6).

When the risk factors affecting mortality were evaluated using the backward logistic regression analysis, the model was found to be significant, and the model's explanatory coefficient (71.7%) was good. The ODDS ratio of male gender on mortality was 6.679 (95% CI, 1.50-29.68). The ODDS value of NRS-2002 being ≥5 was 6.093 (95% CI, 1.34-27.6) and the NRI of 81.2 and above had an ODDS of 4.281 (95% CI, 1.10-16.65). The effects of the male gender, NRS-2002, and NRI on mortality were determined as independent risk factors (Table 6).

Discussion

Aging is a progressive and irreversible physiological process that affects the structures and functions of all organs and systems. Geriatric syndromes are more common with the increase in the elderly population. Malnutrition has a high prevalence in the geriatric population and causes serious morbidity and mortality. Intensive care patients are also at risk of severe malnutrition. Therefore, although early detection and treatment planning are very important, there may be delays in diagnosis and treatment (15). The absence of a gold standard method or biochemical marker used in the diagnosis of malnutrition also makes it difficult to identify patients at risk.

In our study, we evaluated the nutritional status of patients aged ≥65 years who were admitted to ICU with screening tools, compared the compatibility of these methods with each other, and examined the relationship between malnutrition and mortality. The rate of all patients in the normal nutritional status range was 1.7%-33.3%, and the rate of malnutrition and/or severe risk of nutrition was determined as 28.4%-60%. When studies on this subject are examined, it is known that the prevalence of malnutrition varies between 30% and 50% in ICU patients (8, 13, 16). In the study conducted by Giner et al. (17), the malnutrition rate was found to be 42% in ICU patients. In a study conducted by Kaiser et al. (18) with MNA in 2010, malnutrition rates were found to be 5.8% in the elderly population, 13.8% in the elderly in a nursing home, and 38.7% in the hospitalized elderly. In a study conducted by MNA-SF in 2,327 elderly patients admitted to Hacette-

Table 4. Assessment of nutritional status of patients according to screening tests

Features of Patients	Total (n=60)	Surviving (n=35)	Died (n=25)	p
GNRI, ave. (SD)	91.3±15.8	92.5±15.2	89.5±16.8	0.471
Normal nutritional status, %	33.3	34.3	32.0	0.921
Mild nutrition risk, %	15.0	17.1	12.0	
Moderate nutrition risk, %	23.3	22.9	24.0	
Severe nutrition risk, %	28.4	25.7	32.0	
NRI, ave. (SD)	82.6±10.9	85.0±11.2	79.4±9.8	0.05
Normal nutritional status, %	3.3	5.7	0.0	0.411
Mild nutrition risk, %	5.0	5.7	4.0	
Moderate nutrition risk, %	38.3	42.9	32.0	
Severe nutrition risk, %	53.4	45.7	64.0	
MNA-SF, ave. (SD)	8.8±3.4	9.5±3.5	7.8±3.1	0.061
12–14 points normal nutritional status	25.0	37.1	8.0	0.027*
8–11 points at risk of malnutrition	40.0	37.1	44.0	
0–7 points malnutrition	35.0	25.7	48.0	
NRS-2002, ave. (SD)	4.7±1.1	4.4±1.2	5.2±0.8	0.05
1–2 normal nutritional status	1.7	2.9	0.0	0.02*
3-4 at risk of malnutrition	38.3	51.4	20.0	
≥5 malnutrition	60.0	45.7	80.0	

*p<0.05. Pearson's chi-squared, Fisher's exact test. MNA-SF: Mini Nutritional Assessment Short Form; NRS-2002: Nutritional Risk Screening Test 2002; NRI: Nutritional Risk Index; GNRI: Geriatric Nutritional Risk Index

Table 5. Diagnostic screening tests and ROC curve results for NRI, MNA-SF, NRS-2002 by mortality

	Diagnostic scan			ROC curve				
	Cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% Confidence interval	p
NRI	≤81.2	64.00	74.29	64.0	74.3	0.663	0.522–0.804	0.033*
MNA-SF	≤9	68.00	60.00	54.8	72.4	0.667	0.529–0.804	0.029*
NRS-2002	≥5	80.00	54.29	55.6	79.2	0.703	0.573–0.834	0.008**

*p<0.05, **p<0.01. MNA-SF: Mini Nutritional Assessment Short Form; NRS-2002: Nutritional Risk Screening Test 2002; NRI: Nutritional Risk Index

pe University Geriatrics Unit, the risk of malnutrition was found to be 28% (19). In our study, the malnutrition rate was found to be 35% for all patients, 48% for deceased patients, and 25.7% for surviving patients with the MNA-SF evaluation, and a significant difference was found between risk groups.

In another study, GNRI and NRI scores of 113 patients aged ≥75 years were calculated, and their nutritional status was evaluated. When patients were evaluated with NRI, the risk of severe malnutrition was 67.3%, and the risk of severe malnutrition was 27.4% with GNR (20). In our study, the malnutrition rate was 53.4% in patients when the NRI method was used. In another study, anthropometric and biochemical parameters of 241 elderly patients were examined, and the nutritional status and nutritional risk were evaluated using both GNRI and MNA. Although there was no difference between malnutrition and high

Table 6. Logistic regression analysis of risk factors affecting mortality				
	p	ODDS	95% CI	
			Lower	Upper
Gender (M)	0.013*	6.679	1.503	29.682
NRS-2002 (≥5)	0.019*	6.093	1.342	27.662
NRI (≤81.2)	0.036*	4.281	1.101	16.647
*p<0.05, CI: confidence interval; NRS-2002: Nutritional Risk Screening Test 2002; NRI: Nutritional Risk Index				

nutritional risk when death, infection, and pressure sores were evaluated at the end of 6 months follow-up, it has been found that GNRI had a stronger relationship with mortality (21). Malnutrition rates may have differed from other studies due to differences in patient population, age group, concomitant chronic diseases, and screening methods included in our study.

In our study, it was observed that there was a difference in predicting malnutrition between GNRI, NRI, NRS-2002, and MNA-SF methods. When the patients were evaluated with the GNRI method, malnutrition and/or the severe nutrition risk ratio was 28.4%; 53.4% with NRI, 60% with NRS-2002, and 35% with MNA-SF. In another study, three screening tools-MNA-SF, NRS-2002, and Malnutrition Universal Screening Tool-were used to evaluate malnutrition in elderly patients, and it was found that the nutritional risk and/or malnutrition rate varied greatly between 47.2% and 97.6% (22). The inconsistencies of nutritional status screening tools to predict malnutrition suggest that a single screening tool may be inadequate to identify patients at risk.

Malnutrition causes increased morbidity and mortality in ICU patients, as well as the need for mechanical ventilation and the ICU and hospital stay duration (23). In the study conducted on the inpatients of the Internal Medicine Geriatrics Clinic of Istanbul Medical Faculty in 2010, the rate of malnutrition at the time of hospitalization was found to be 45.5%. In this study, it was found that the duration of hospitalization was longer (18.9±19.1 and 11.3±11.3 days, respectively) when the malnutrition risk group was compared with the nonrisk group (24). In a study conducted in the United Kingdom, malnutrition was found in 46% in internal diseases, 45% in chest diseases, and 27% in surgical patients during hospitalization. It was shown that the severity of malnutrition was increased in 78% of these patients during hospitalization (25).

In our study, the duration of hospital stay and mechanical ventilation was found to be longer in patients who died in ICU. As the severity of the disease increases, there is an increase in respiratory and hemodynamic requirements, and therefore, the duration of both mechanical ventilation and ICU stay are expected results. On the other hand, it has been reported that a prolonged hospital stay increases the risk of malnutrition (26). Patients are at risk of severe psychological and catabolic stress during their stay in hospital. Subsequently, a decrease in the body weight occurs due to the energy deficit resulting from malnutrition. The nutritional status of patients may worsen significantly during their stay in the ICU, usually due to many factors. Some of these are patient-related causes, and some are iatrogenic causes (27). There are two problems that affect each other negatively. We think that the duration of stay in ICU may affect malnutrition, and malnutrition may negatively affect the duration of ICU stay.

According to the nutritional status screening methods, malnutrition category may be related to a low serum albumin level, high CRP value, and active disease and inflammation. CRP levels are also increased in association with increased cytokine production with aging (28). Inflammatory cytokines in the liver (tumor necrosis factor, interleukin 1, interleukin 2, interleukin 6) promote the synthesis of acute-phase proteins and suppress the albumin synthesis. Therefore, a decrease in serum albumin concentrations may reflect inflammatory conditions in addition to nutritional status (29). Decrease in albumin levels may also be associated with long-term impaired energy balance and decreased protein stores. Therefore, it is necessary to evaluate the serum albumin level together with other nutritional status screening methods to identify individuals at risk (30). Every 2.5 g/L decrease in serum albumin increases the risk of mortality by 24%-56%. In elderly patients, the albumin level of 3.2 g/dL or lower is the determinant of morbidity and mortality (31). In our study, the serum albumin level was shown to be lower and the CRP level was higher in patients who died compared to patients who survived. Likewise, the average age of our patient group was 78.3±8.6 years, which may be associated with an increased mortality risk.

The aim of the nutrition screening tools is to identify the patient at risk of malnutrition at the right moment and ear-

ly. Therefore, the screening tool should be specific and sensitive (32). In our study, while the NRS-2002 had higher sensitivity than the MNA-SF and NRI, NRI was found to have a higher specificity than NRS-2002 and MNA-SF. In another study, the specificity of NRS-2002 was higher than that of MNA-SF, whereas the sensitivity of MNA-SF was higher than that of NRS-2002 (33). It is observed that there is a difference between tests, especially in the detection of patients at risk for malnutrition. This may make it difficult to identify patients at risk of malnutrition when we evaluate patients using a single method.

When we evaluated the risk factors affecting mortality, it was found that the male gender increased mortality 6.6 times, the NRS-2002 ≥5 increased mortality 6 times, and the NRI ≥ 81.2 increased mortality 4.2 times. In their study involving 358 patients aged 65 years and over who applied to a long-term care unit, Cereda et al. (21) found that the male gender was 1.7 times riskier in their mortality analysis using GNRI and MNA. In our study, we found that the effect of male gender factor on mortality was higher in elderly patients followed up in the ICU. We think that this rate may be higher because our sample size was limited to 60 patients, and our population consisted of intensive care patients. We think that the high effect of NRS-2002 and NRI screening method on mortality is due to the higher value of the NRS-2002 components. The APACHE II score and albumin were some of the parameters used in the calculation of the NRI score in the patient group who died.

This provides an objective evaluation with the fact that nutrition screening tools such as GNRI and NRI can be performed quickly and easily, even in non-cooperating patients. The MNA-SF and NRS-2002 are advantageous in that they do not require any biochemical tests and additional costs (24). However, considering the elderly patient group included in our study, problems such as memory loss, cooperation difficulties, and dementia make history taking difficult for the NRS-2002 and MNA-SF screening tools.

Our study had a small sample size and was single centered, so the results do not represent a general population. Another important disadvantage is that although the assessment of malnutrition in the elderly is of great importance in the assessment of sarcopenia, we could not perform the relevant measurements in patients due to lack of necessary equipment.

In conclusion, in our study, when elderly patients with oral intake admitted to the intensive care unit were evaluated with GNRI and NRI scoring system and NRS-2002 and MNA-SF screening tools, the risk of malnutrition and/or severe nutrition risk was 28.4%-60%, and the incidence of malnutrition and/or severe nutrition increased in patients who died. It was found that the male gender increased mortality 6.6 times, the NRS-2002 score ≥5 increased it 6 times, and the NRI score ≥81.2 increased it 4.2 times. Since the determination of nutritional status was accepted as the first step of malnutrition treatment, it is important to have a reliable and easy-to-implement tool in the admission of patients to ICU. In our study, while the NRS-2002 had a higher sensitivity than MNA-SF and NRI, the NRI was found to have a higher specificity than NRS-2002 and MNA-SF. However, due to the lack of a gold standard screening method and inconsistency between screening tools to predict malnutrition, it may be difficult to determine the patient nutritional status. Therefore, we think that the evaluation of the methods together and reviewing them together with biochemical and anthropometric parameters may be more effective in predicting malnutrition.

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References

1. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of +adult malnutrition (undernutrition). J Acad Nutr Diet 2012; 112: 730-8. [CrossRef]
2. Btaiche IF, Chan LN, Pleva M, Kraft MD. Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. Nutr Clin Pract 2010; 25: 32-49. [CrossRef]
3. Waitzberg DL, Correia MI. Nutritional assessment in the hospitalized patient. Curr Opin Clin Nutr Metab Care 2003; 6: 531-8. [CrossRef]
4. Moral AR, Uyar M. Yoğun Bakım Hastalarında Nütrisyon. In: Şahinoğlu AH, editor. Yoğun Bakım Sorunları Ve Tedavileri 3. İstanbul: Nobel Tıp Kitabevleri 2011.p.525-42.

5. Pekcan G. Beslenme Durumunun Saptanması. Baysal A. Ve diğerleri (Ed). Diyet El Kitabı. Ankara. Hatiboğlu Basım ve Yayım San. Tic. Ltd. Şti; 2011.s.67-142.
6. Visvanathan R. Under-nutrition in older people: A serious and growing global problem. J Postgrad Med 2003; 49: 352-60.
7. Bendich A. Fundamentals of nutrition and geriatric syndromes. Bales CW, Ritchie CS, Wellman NS editors. Handbook of Clinical Nutrition and Aging. New York. Humana Press; 2009.p.235-65.
8. Sahyoun NR, Jacques PF, Dallal GE, Russell RM. Nutrition Screening Initiative Checklist may be a better awareness/educational tool than a screening one. J Am Diet Assoc 1997; 97: 760-4. [CrossRef]
9. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging 2009; 13: 782-7. [CrossRef]
10. Secher M, Villars H, Abellan van Kan G, Vellas B. The Mini Nutritional Assessment (MNA) after 20 years of research and clinical practice. Clin Gerontology 2007; 17: 293-310. [CrossRef]
11. Kondrup J, Allison S, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening. Clin Nutr 2003; 22: 415-21. [CrossRef]
12. Delegge M. Evrensel Malnütrisyon Tarama Yöntemi. Malazgirt Z, Topgül K, editors. Nütrisyon ve Gastrointestinal Hastalık. Nobel Matbaacılık. İstanbul. Nobel Tıp Kitapevleri; 2011.p.9-17.
13. Bouillanne O, Morineau G, Dupont IC, Vincent JP, Nicolis I, Benazeth S, et al. Geriatric Nutritional Risk Index: a newindex for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005; 82: 777-83. [CrossRef]
14. WHO Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series No: 894. Geneva: World Health Organization, 2000. Available from: http://www.who.int/healthinfo. Erişim tarihi: 10/05/2018.
15. Sayhan MB, Oğuz S, Ümit H, Sayhan ES, Eralp MO, Akdur G, et al. Evaluation of risk factors and clinical characteristics of elderly patients with acute upper gastrointestinal hemorrhage. Tr J Emerg Med 2012; 12: 157-62. [CrossRef]
16. Peterson SJ, Sheean PM, Braunschweig CL. Orally fed patients are at high risk of calorie and protein deficit in the ICU. Curr Opin Clin Nutr Metab Care 2011; 14: 182-6. [CrossRef]
17. Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. Nutr J 1996; 12: 9-23. [CrossRef]
18. Kaiser MJ, Bauer JM, Rämsch C, Uter W, Guigoz Y, Cederholm T, et al. Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. J Am Geriatr Soc 2010; 58: 1734-8. [CrossRef]
19. Ülger Z, Halil M, Kalan I, Yavuz BB, Cankurtaran M, Güngör E, et al. Comprehensive assessment of malnutrition risk and related factors in a large group of community-dwelling older adults. Clin Nutr 2010: 29; 507-11. [CrossRef]
20. López-Gómez JJ, Fernández A, Ballesteros-Pomar MD, Casariego AV, Laranjo CB, Vicente AF, et al. Screening of the nutritional risk in elderly hospitalized patients with different tools. Endocrinol Nutr 2011; 58: 104-11. [CrossRef]
21. Cereda E, Pusani C, Limonta D, Vanotti A. The ability of the Geriatric Nutritional Risk Index to assess the nutritional status and predict the outcome of home-care resident elderly: a comparison with the Mini Nutritional Assessment. Br J Nutr 2009; 102: 563-70. [CrossRef]
22. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med 2006; 34: 15-21. [CrossRef]
23. Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. Chest 2004; 125: 1446-57. [CrossRef]
24. Cankurtaran M, Saka B, Sevnaz S, Varlı M, Döventaş A, Yavuz BB, et al. Türkiye huzurevleri ve bakımevleri nutrisyonel değerlendirme projesi. In: Arıoğul S, Atlı T, editors. 5. Akademik Geriatri Kongresi 2012 Kongre Özet Kitabı; 2012 May 23-27; Antalya, Turkey. Ankara: Türkiye; 2012. pp.12.
25. McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital. BMJ 1993; 308: 945-8. [CrossRef]
26. Correia IT, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003; 22: 235-9. [CrossRef]
27. Cereda E. Nutritional screening and mortalitiy in newly institutionalised eldery:A comparison between Geriatric Nutritional Risk Index and the Mini Nutritional Assesment. Clin Nutr 2011; 30: 793-8. [CrossRef]
28. Roubenoff R, Parise H, Payette HA, Abad LW, D'Agostino R, Jacques PF, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study. Am J Med 2003; 115: 429-35. [CrossRef]
29. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathology. Part III: albumin and disease state. JPEN 1991; 15: 476-8. [CrossRef]
30. Ballmer PE. Causes and mechanisms of hypoalbuminaemia. Clin Nutr 2001; 20: 271-3. [CrossRef]
31. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991; 100: 1619-36. [CrossRef]
32. Tripathy S, Mishra JC. Assesing nutrition in the critically ill elderly patients: A comparison of two screening tools. Indian J Care Med 2015; 19: 518-22. [CrossRef]
33. Zhou J, Wang M, Wang H, Chi Q. Comparison of two nutrition assessment tools in surgical elderly inpatients in Northern China. Nutr J 2015; 14: 2-8. [CrossRef]

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The effect of nutritional support on nutritional status and quality of life as well as on inflammatory markers and cardiac functions in patients with cardiac cachexia due to chronic heart failure

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ABSTRACT

Objective: Cardiac cachexia (CC) is defined as a loss of at least 6% of total body weight in 6 months due to chronic heart failure (CHF). The prevalence of CC in patients with NYHA class II-IV is estimated to be approximately 12%-15%. There are only a few studies that demonstrate the effects of malnutrition treatment on nutrition, physical activity, quality of life (QoL), and clinical course of the disease. This study aimed to evaluate the effect of nutrition treatment on anthropometric measurements, fat free mass (FFM), muscle strength, physical performance, and QoL together with cardiac functions and immunity in patients with CC.

Method: This was a prospective clinical intervention study. Patients with NYHA stage II-IV CHF (n=725) followed-up in Internal Medicine and Cardiology Departments were screened for CC. Eighteen patients with CC were enrolled in the study. The control group included 18 healthy adults. Nutritional status assessment, anthropometric measurements, gait speed, muscle strength, bioelectrical impedance analysis (BIA Tanita, Japan), biochemical analyses, and cytokine measurements were performed. Cardiac functions were assessed by echocardiography. Nutrition support treatment was given to patients with CC, and they were followed-up for next 3 months. QoL was measured with "Ferrans and Powers" Quality of Life Index (cardiac version). Similar studies were repeated after follow-up.

Results: After excluding all other reasons for cachexia, the prevalence of CC was 2.5% in our patients with CHF. The patients with CC had higher serum C-Reactive Protein (CRP) and IL-6 levels than the healthy controls. After nutrition support treatment, the QoL scores and visceral fat level significantly increased in patients with CC. Although mid-upper arm circumference (MUAC), handgrip strength, FFM, fat mass, and serum albumin levels increased, they were not statistically significant.

Conclusion: When compared to previous studies, our CC prevalence rate was lower. Nutrition support therapy can reverse weight loss in patients with CC, which can also improve QoL. An important limitation to the study is the low number of patients that is related with the exclusion criteria regarding every type of inflammatory disease, acute medical problems, and cancer. Therefore, further studies with more patients are needed.

Keywords: Cardiac cachexia, chronic cardiac failure, nutrition support treatment

Introduction

Cardiac cachexia (CC) is defined as secondary to chronic heart failure (HF) and non-edema weight loss of 6% or more in 6 months, regardless of any other underlying disease. Common muscle and fat loss occurs in the extremities (1). While muscle protein synthesis decreases, synthesis of acute phase proteins increases (2). In addition to loss of muscle tissue, decrease in fat and bone mass is also observed (3). It is considered that 12%-15% of patients with NYHA class II-IV have CC; and 29% of patients with CC are lost within 6 months (4).

Studies show that survival rates of patients with cachexia with body mass index (BMI) above 29 kg/m^2 are 1-3 years more (5). In another study, the increase in BMI was found

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to be protective in patients with HF followed for a year; and the lowest risk of death was found in patients with BMI of 30.0-34.9 kg/m^2. This condition is known as the paradox of obesity; and patients with BMI below 20 kg/m^2 have a high risk of mortality (6).

Immunological cytokine activation is considered to play an important role in the pathophysiology of CC. In 1990, Levine et al. (7) demonstrated the association between tumor necrosis factor-alpha (TNF-α) and HF. Increased levels of plasma TNF-α are the most important predictors of weight loss. Apart from TNF-α, intercaline-1 (IL-1) and interleukin-6 (IL-6) also play a role in catabolism (8, 9).

In 50% of patients with HF, poor nutrition was detected. The daily energy needs of the patients with CC were increased, and the protein requirement was 1.5-2 g/kg/day (10). The imbalance associated with the use of energizing nutrients increases daily energy, protein, and fat requirements. However, it should be kept in mind that excess fat and carbohydrate intake may also increase oxygen consumption and therefore impair the clinical picture (11). It is recommended that patients with critical illnesses should be given 25 kcal/kg diet daily, 1.2-1.5 g/kg protein should be given, carbohydrates do not exceed 6 g/kg/day, and fats do not exceed 2.5 g/kg/day (12).

Heart failure is associated with immobilization, fatigue, gastrointestinal symptoms and early satiety. (13). This can lead to severe malnutrition. To increase muscle mass and improve exercise capacity, energy reserves need to be replaced; thus nutritional status should be improved. Despite the decrease in physical activity in patients with CC, the daily energy demand increases as a result of increased inflammation and catabolic process (14).

Only a few studies show the results of prevention of weight loss with nutritional support therapy. This prospective longitudinal study aimed to investigate the effects of nutritional therapy on anthropometric measurements, fat free mass (FFM), and muscle strength as well as physical performance and quality of life in patients with CC. Possible changes in cardiac functions and immune system that may occur during nutritional follow-up of patients were also examined.

Methods

Operation type and population

In this prospective longitudinal study, 725 patients who were followed-up at an outpatient clinic between August 2014 and May 2015 in Istanbul Medical Faculty Internal Medicine and Cardiology Departments or who were treated inpatient during the study were screened. Eighteen patients with stage II-IV HF and CC were included in the study. Eighteen healthy adults were included in the control group. The criteria for inclusion and exclusion are given in Table 1.

Nutritional status assessment

Two same nutritional nurses in the Clinical Nutrition Unit of Istanbul Faculty of Medicine performed nutritional status assessment and anthropometric measurements of the patients. Subjective global assessment test was used for nutritional status assessment (15). BMI, mid-upper arm circumference (MUAC), and calf circumference were measured during anthropometric analyses. MUAC is measured from the midpoint of the distance between the acromion of the scapula and the ulna olecranon projection in the upper arm. The calf circumference is measured at the widest point of the calf.

Nutrition support plan (NDP)

The daily energy requirement of patients diagnosed with CC was calculated by formula (Harris Benedict Formula, stress factor and activity factor) (16). Daily protein requirements were planned to be 1.2-1.5 g/kg/day. The European Journal of Clinical Nutrition and Metabolism (ESPEN) was used to determine the daily energy and protein requirements (17). The diet lists were prepared based on these accounts. The dietary list compliance was done by taking daily food consumption lists during polyclinic con-

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Having consent	Those with chronic inflammatory disease
Being 18 years and older	GFR <30 mL/min/1.73 m^2
Identifying NYHA Grade II-IV HF and CC by clinical and laboratory methods	Chronic liver disease
Involuntary loss of 6% or more weight without edema in the last 6 months	Organ transplantation
	Any acute medical problem except HF
	Cancer
	Immunosuppressive therapy
	ICU requirement1
	(1If occurs during the follow-ups, they will be excluded from the study)

GFR: glomerular filtration rate; CC: cardiac cachexia; HF: heart failure; ICU: intensive care unit

trols. The patients who could not adapt were provided with supplemented meals with energy- and protein-enriched meals or their needs during the follow-up period. After 3 months of nutritional support plan, the patients were re-evaluated.

Determination of cytokines

Five milliliters of venous blood samples were taken from the patients included in the study and the healthy individuals in the control group. IL-1beta, IL-6, IL-10, and TNF-alpha levels in the serum samples were determined by ELISA kit with sandwich enzyme immunoassay method. Blood samples taken from the patients were incubated for 20-30 min at room temperature; and they were then centrifuged at 2000-3000 RPM for 10 min. The supernatant was taken to the microcentrifuge tube and stored at −80°C until the day of the test. The standard mix in the lyophilized state was diluted with diluent. Three hundred microliters of mix diluent was added to seven microcentrifuge tubes: 300 µL of the standard solution was added to the first tube and mixed, and 300 µL was transferred to the second tube, and the same procedure was done until the sixth tube. The mix diluent in the last tube was used as the zero standard. Fifty microliters of standards were added to the eight predefined standard wells, respectively. Fifty microliters of the samples were added to the sample wells. The plate was closed and incubated for 2 h at room temperature. After the incubation, the wells were washed six times with wash buffer. Fifty microliters of prepared Biotin conjugate was added to all wells. The plate was again closed and incubated for 2 h at room temperature. After incubation, the wells were again washed six times. Fifty microliters of prepared streptavidin horseradish peroxidase was added to all wells. The plate was closed and incubated for 30 min at room temperature. The wells were washed six times with the wash buffer. Fifty microliters of TMB substrate solution was added to all wells. The plate was closed and incubated for 10 min at IL1-β, 25 min at IL-6 and TNF-alpha, 15 min at IL-10 at room temperature in the dark. Fifty microliters of the stop solution was added, and the plate was read in an ELISA reader at 450 nm in 10 min. The logarithmic regression equation of the standard curve was calculated according to the OD values corresponding to the concentration of the standards. According to the OD values of the samples, the corresponding sample concentrations were calculated according to this equation. Cytokine measurements were performed before and after NDP.

Echocardiography

The echocardiography (ECO) measurements were made according to the recommendations of the American Society of Echocardiography with the General Electronic VIVID 7 device and 3.5 MHz probe (18). EF, PAP, left ventricular end diastolic diameter, left ventricular end-systolic diameter, interventricular septum diameter, and posterior wall diameters were recorded. The same cardiologist performed the ECO before and after the NDP.

Scoring of the quality of life

The "Ferrans and Powers" Quality of Life Index, which was developed to measure general health, was applied to all patients (n=18) by face-to-face interviews (19). The scale consists of two parts, and it includes questions on satisfaction and importance. The scale has four subsections: health and function, socioeconomic, psychological/spiritual, and family. The scores for each subsection and the total scale score ranged from 0 to 30. Higher scores indicate better quality of life. Two researchers performed life quality scoring before and after the NDP.

Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis (TANITA, BC-532) was used to evaluate the body composition. FFM, fat mass, and visceral fat level were evaluated during the measurement. The same two nurses performed the BIA examinations before and after the NDP. Before the BIA, the patients were asked to refrain from activities requiring physical force and not to eat until 2 h. All patients were evaluated before noon and after urine/defecation so that the measurements did not show an unbalanced distribution.

Hand strength measurement and walking speed

Muscle strength assessment was obtained by the standard hand dynamometer (Janmar, USA) three times from the dominant hand. Existing hand measurement was performed in patients with an upper extremity. Measurement of handgrip strength was made in the sitting position, shoulder adduction and neutral rotation, elbow at 90° flexion, forearm midrotation and support, and wrist neutral. Muscle strength measurement results were evaluated according to the standards determined in EWGSOP II data (20). Existing hand measurement was performed in patients with an upper extremity. The walking speed was assessed by conducting the 4-m distance at normal speed. The walking speed was obtained by dividing 4 m by the time (s) through which this distance was exceeded (m/s). The same expert made the measurements before and after NDP.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) version 17 program was used for statistical analysis. The average, standard deviation, lowest, highest, median, 25th and 75th percentile, ratio and frequency values were used in descriptive statistics of the data. The categorical variables were compared with the

chi-square test. The results of the variables were compared with Mann-Whitney U, Student T, and Wilcoxon tests. The p value <0.05 was considered significant.

Consent

The consent was obtained from each patient according to the Helsinki Declaration. The Istanbul University Istanbul Medical Faculty Ethics Committee approved the study (File No: 2014/925). Istanbul University Scientific Research Projects Unit with project no: 52928 supported the recruitment of the cytokine ELISA kits used in the study.

Results

The study included 18 patients with CC (CC prevalence: 2.5%, 13 male, 5 female) and 18 healthy controls (13 male, 5 female). The mean age was 63.2±17.5 years (range 24-83 years) in the patients with CC, and 59.7±16.2 years in the control group (range 24-85 years). The mean weight and BMI of the patients before the treatment was 63.3±14.1 kg and 22.4±4.5 kg/m^2, and the control group was 78.6±12.1 kg and 27.8±3.7 kg/m^2, respectively. The results of the initial ECO examination are given in Table 2.

Table 2. Comparison of measurements of the patients and healthy individuals

	Healthy control group (n=18)	Cardiac cachexia group (n=18)	p
Weight (kg)	78.6±12.1	63.3±14.1	0.004
BMI (kg/m^2)	27.8±3.7	22.4±4.5	0.001
Right MUAC (cm)	31.3±2.8	25.6±4.0	<0.001
Right CC (cm)	37.5±3.0	34.6±3.9	0.019
EF%	66±7	31±12	<0.001
PAP (mmHg)	23.5±2.5	46.8±15.3	<0.001
LVESD (cm)	3.0±0.4	5.1±1.2	<0.001
LVEDD (cm)	4.7±0.5	6.1±1.1	<0.001
Pro-BNP (pg/mL)	69 (30-148)	2131 (928-9170)	<0.001
BIA-FFM (kg)	53.6±9.8	46.1±8.2	0.044
BIA-fat (%)	28.3±6.5	19.5±10.2	0.008
BIA- visceral fat (kg)	12±5	9±5	0.172
BIA-bone (kg)	2.8±0.5	2.5±0.4	0.05
Right hand strength (kg)	35.2±9.6	26.9±6.7	0.007
Walking speed (m/s)	1.23±0.23	0.92±0.37	0.018
Albumin (g/dL)	4.3±0.4	3.9±0.7	0.020
CRP (mg/L)	1.9 (1.2-3.9)	13.1 (10.4-12.5)	0.014
TNF-alpha (pg/mL)	2.31 (2.10-3.04)	3.18 (2.13-4.81)	0.07
IL-1 (pg/mL)	1.31 (1.18-1.57)	1.39 (1.26-1.60)	0.339
IL-6 (pg/mL)	2.39 (2.01-2.78)	6.11 (4.30-18.52)	0.001
IL-10 (pg/mL)	49.05 (45.7-57.0)	51.25 (49.1-61.6)	0.214
Health and functional score	24.4±3.4	14.9±4.7	<0.001
Psychological score	26.0 (22.1-29.6)	18.0 (17.1-21.3)	0.001
Total score	25.1±4.3	18.2±3.8	<0.001

BMI: body mass index; MUAC: mid-upper arm circumference; CC: calf circumference; EF: ejection fraction; PAP: pulmonary artery pressure; LVESD: left ventricle end-systolic diameter; LVEDD: left ventricle end diastolic diameter; Pro-BNP: brain natriuretic peptide; BIA: bioimpedance analysis; FFM: fat free mass; CRP: c-reactive protein; TNF: tumor necrosis factor; IL: interleukin

Mid-upper arm circumference , calf circumference, FFM, BIA-fat percentage, bone mass, muscle strength, and walking velocities of patients and healthy individuals are given in Table 2. The serum IL-6 level was found to be significantly higher in patients with CC; although the serum TNF-alpha level was higher in the patients, the difference was not statistically significant (Table 2). The quality of life scores of healthy individuals were significantly higher than of patients with CC (Table 2).

One patient who underwent heart transplantation during the study, one patient diagnosed with lung cancer, and six patients hospitalized in the intensive care unit for various reasons were excluded from the study. After 3 months of NDP, weight, BMI, and visceral fat significantly increased in ten patients who completed the study (Tables 3 and 4). While MUAC, hand muscle strength, fat percentage, FFM, and serum albumin levels were increased after NDP, this increase was not statistically significant (Table 4). No sig-

Table 3. Dietary and nutritional support treatments of patients who completed the study

Patient no	Gender/age	BMI1	BMI2	DEN	DPN	Diet	ONS
1	E, 63	24.8	26.7	2000	80	100%	Absent
2	K, 24	16.3	18.5	1750	55	70%	1.5 kcal/mL product (600 kcal/day)
3	E, 67	29.7	30.6	1500	85	60%	0.9 kcal/mL diabetic product (600 kcal/day)
4	E, 54	23.9	25.9	1900	80	60%	2.0 kcal/mL product (800 kcal/day)
5	K, 83	24.6	29.1	1500	75	50%	1.5 kcal/mL product (750 kcal/day)
6	E, 71	18.4	19.6	1800	80	50%	1.5 kcal/mL product (900 kcal/day)
7	E, 80	16.3	17.4	1900	65	75%	2.0 kcal/mL product (400 kcal/day)
8	E, 58	19.3	20.1	2000	75	60%	1.0 kcal/mL diabetic product (800 kcal/day)
9	K, 76	19.6	21.0	1500	60	100%	Absent
10	E, 61	27.6	27.9	2000	80	100%	Absent

DEN: daily energy need; DPN: daily protein need; ONS: oral nutrition supplement; BMI: body mass index (kg/m^2); BMI1: initial BMI; BMI2: Third month control of BMI

Table 4. Comparison of mean and median values of the measurement parameters before and after the nutritional support plan (n=10)

	Before NSP	After NSP	p
Weight (kg)	63.6±14.7	66.0±15.1	0.05
BMI (kg/m^2)	22.19±5.07	23.21±5.31	0.034
Right MUAC (cm)	26.0±4.4	26.6±3.6	0.48
Left MUAC (cm)	25.9±4.2	26.8±3.4	0.18
Right CC (cm)	34.2±3.9	33.1±4.7	0.26
Left CC (cm)	33.9±4.2	33.5±4.6	0.65
BIA-FFM (kg)	46.3±8.7	49.7±7.5	0.168
BIA-fat (% median)	26.4 (19.6-30.3)	22.4 (14.6-27.7)	0.237
BIA-visceral fat level	9±4	11±5	0.042
Right hand strength (kg, median)	30 (26-37)	30.5 (29-31)	0.228
Left hand strength (kg)	28.9±6.7	29.4±4.5	0.596
Walking speed (m/s)	1.04±0.33	1.05±0.32	0.86

NSP: nutritional support plan; BMI: body mass index; MUAC: mid-upper arm circumference; CC: calf circumference; BIA: bioimpedance analysis; FFM: fat free mass

nificant difference was observed in the cardiac functions of the patients under medical treatment after NDP (Table 5).

There was no significant difference in the serum albumin, CRP, and cytokine levels before and after NDP (Table 6). A significant increase was observed in the total quality of life score (median: 21.1 [18.2-25.6] vs 22.3 [16.7-25.4], p=0.005).

Discussion

Heart failure is observed in approximately 1%-2% of the adult population in the developed countries. The prevalence of HF increases up to ≥10% in individuals aged 70 years and older. In these patients, the average five-year survival was reported as 50% (21). HF establishes a continuous catabolic state with neurohumoral and immunological complex changes, and it affects nutritional status through energy and substrate metabolism and increased cytokine burden. CC is defined as 6% weight loss in the past 6 months, unrelated to diuretic treatment and unintentionally, without any other underlying disease (cancer, hyperthyroidism, liver disease, etc.). Involuntary weight loss and low BMI are associated with poor prognosis in HF and are associated with a decreased survival of KK (18% survival is 50%) (4).

Table 5. The comparison of the ECO measurements before and after the nutritional support plan (n=10)

	Before NSP	After NSP	p
EF (%)	33±12	36±12	0.136
PAP (mmHg)	46±14	45±13	0.867
LVESD (cm)	4.9±0.8	4.8±0.9	0.221
LVEDD (cm)	6.0±0.7	5.9±0.9	0.445
IVST (cm)	1.1±0.2	1.1±0.2	0.411

NSP: nutritional support plan; EF: ejection fraction; PAP: pulmonary artery pressure; LVESD: left ventricle end-systolic diameter; LVEDD: left ventricle end diastolic diameter; IVST: interventricular septum thickness

Table 6. Laboratory parameters before and after the nutritional support plan (n=10)

	Before NSP	After NSP	p
GFR (mL/min)	61±21	68±32	0.308
Albumin (g/dL)	4.1±0.6	4.4±0.4	0.101
CRP (mg/L, median)	3.8 (1.5-15.1)	3.1 (1.7-5.8)	0.285
Hgb (g/dL)	12.2±2.1	12.1±2.4	0.783
TNF-alpha (pg/mL)	3.52±1.66	3.18±1.21	0.551
IL-1 (pg/mL)	1.58±0.67	1.42±0.52	0.144
IL-6 (pg/mL, median)	3.28 (2.15-9.97)	3.43 (2.88-11.53)	0.721
IL-10 (pg/mL)	70.27±36.67	64.17±29.25	0.546

NSP: nutritional support plan; GFR: glomerular filtration rate; CRP: c-reactive protein; TNF: tumor necrosis factor; IL: interleukin

In our study, the prevalence of CC was found to be 2.5%. One of the reasons for lower prevalence rates in previous studies may be the exclusion of the individuals with all other diseases who can perform cachexia from our study. On the other hand, when talking about the current prevalence data, possible values were mentioned (22). Increased inflammation and sarcopenia (decreased muscle strength and muscle mass) can be seen in HF. CC causes significant changes in muscle, fat, and bone tissue that make up the body composition (22). Our study aimed to evaluate the possible effects of NDP on anthropometric measurements, muscle mass and muscle strength, physical performance, quality of life, cardiac functions, and immune system in patients with advanced stage II-IV cardiac arrest.

In a study conducted by Anker et al. (1, 2), when compared with CC, non-cachectic HF and healthy individuals, BMI was found to be lower in patients with HF than in those with CC. The muscle, fat, and bone tissues decrease in CC. In our study, compared to in healthy subjects, weight and BMI were found to be lower in patients with CC. Similarly, MUAC, calf circumference, and hand strength measured from both sides were lower in patients with CC than those in healthy subjects. When measured by bioelectric impedance analysis, fat percentage, FFM, and bone mass were significantly lower in patients with CC. The serum albumin levels were found to be low because of inflammation and increased catabolic rate; the serum CRP and IL-6 levels were found to be high in the CC group. This result is similar to the results of the previous studies (23).

Rozentryt et al. (23) were able to increase weight and BMI with high-calorie, protein-rich oral NDP in patients with CC. They found that this increase was found in the fat tissue when examined with DEXA. In our study, there were also significant increases in weight and BMI values of our patients when compared to before and after NDP. In BIA analysis, visceral fat percentage (p=0.042) was found to be significantly increased; total fat content, bone mass and muscle mass were also found to be increased by 2.5%, 1.25%, and 3.4%, respectively, but these increases were not statistically significant. The fact that patients with only

CC were included in the study, thus the number of patients being low, and the presence of patients who were excluded during the study were among the most important limiting factors of our study. Another limitation was that during the study, no exercise program was applied and patients' daily activity levels could not be measured.

In a study conducted by Levine et al. (7), the serum albumin levels were not different between patients with CC, patients with non-cachectic HF, and healthy individuals; and the serum IL-6 levels were found to be high in patients with CC. In our study, serum albumin levels were low and serum CRP levels were found to be high in patients with CC. The serum albumin level may be low because of malnutrition and increased catabolic process, but also because of high acute phase response (negative acute phase reactant). The serum IL-6 level was also found to be high in our patients.

In their study, Levine et al. (7) showed that the role of cytokines in patients with HF and CHD was shown by the increased serum TNF-alpha levels. In another study conducted by Anker et al. (1), the serum TNF-alpha levels were found to be significantly higher in patients with CC. However, in our study, although the serum TNF-alpha level was higher in the patient group compared to the healthy control group, this increase was not statistically significant. This may be related to the small number of patients.

The quality of life reflects the multidimensional effect of a clinical condition and treatment on the patient's daily life. Compared to healthy individuals, patients with HF have significantly impaired qualities of life. In our study, life scores of patients with CC were also lower than of the healthy controls. In the study by Rozentryt et al. (23), positive results were obtained in quality of life scales of patients with high-calorie, protein-rich oral NDP. Similarly, in our study, the total quality of life scores of the patients with CC significantly increased after NDP.

In conclusion, the weight loss can be prevented with effective nutritional support plan in patients with CC, and quality of life can be positively affected. The most important limiting factor of the study was the inability to take enough cases in the study group because of inclusion conditions. Although there was an increase in many anthropometric measurements after treatment in a limited number of patient groups, this difference was not statistically significant. Hence, new studies are needed to examine a large number of cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine (No: 2014/925).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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References

1. Anker S, Ponikowski P, Clark A, Leyva F, Rauchhaus M, Kemp M, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. Eur Heart J 1999; 20: 683-93. [CrossRef]
2. Anker SD, Clark AL, Teixeira MM, Hellewell PG, Coats A. Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 1999; 83: 612-5. [CrossRef]
3. Kotler DP. CAchexia. Ann Intern Med 2000; 133: 622-34. [CrossRef]
4. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997; 349: 1050-3. [CrossRef]
5. Cruz-Jentoft A. European Working Group on Sarcopenia in Older People: Sarcopenia: European consensus on definition and diagnosis. Report of the European Workign Group on Sarcopenia in Older People. Age Ageing 2010; 39: 412-23. [CrossRef]
6. Selter JG, Curtis JP, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: Body mass index and outcomes in patients with heart failure. J Card Fail 2003; 9: S80. [CrossRef]
7. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990; 323: 236-41. [CrossRef]
8. Sharma R, Coats AJ, Anker SD. The role of inflammatory mediators in chronic heart failure: cytokines, nitric oxide, and endothelin-1. Int J Cardiol 2000; 72: 175-86. [CrossRef]
9. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997; 96: 526-34. [CrossRef]
10. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007; 73: 298-309. [CrossRef]
11. Berger MM, Chiolero RL. Enteral nutrition and cardiovascular failure: from myths to clinical practice. JPEN J Parenter Enteral Nutr 2009; 33: 702-9. [CrossRef]

12. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013; 14: 542-59. [CrossRef]
13. Poehlman ET, Scheffers J, Gottlieb SS, Fisher ML, Vaitekevicius P. Increased resting metabolic rate in patients with congestive heart failure. Ann Intern Med 1994; 121: 860-2. [CrossRef]
14. Toth MJ, Gottlieb SS, Goran MI, Fisher ML, Poehlman ET. Daily energy expenditure in free-living heart failure patients. Am J Physiol 1997; 272: E469-E75. [CrossRef]
15. Detsky AS, Baker J, Johnston N, Whittaker S, Mendelson R, Jeejeebhoy K. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987; 11: 8-13. [CrossRef]
16. Harris JA, Benedict FG. A biometric study of basal metabolism in man: Carnegie institution of Washington; 1919.
17. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003; 22: 415-21. [CrossRef]
18. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58: 1072-83. [CrossRef]
19. Durmaz T, Özdemir Ö, Özdemir BA, Keleş T, Bayram NA, Bozkurt E. Factors affecting quality of life in patients with coronary heart disease. Turk J Med Sci 2009; 39: 343-51.
20. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2018; 48: 16-31. [CrossRef]
21. Katz AM, Katz PB. Disease of the heart in the works of hippocrates. Br Heart J 1962; 24: 257-64. [CrossRef]
22. Freeman LM. The pathophysiology of cardiac cachexia. Curr Opin Support Palliat Care 2009; 3: 276-81. [CrossRef]
23. Rozentryt P, von Haehling S, Lainscak M, Nowak JU, Kalantar-Zadeh K, Polonski L, et al. The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: a randomized, double-blind pilot study. J Cachexia Sarcopenia Muscle 2010; 1: 35-42. [CrossRef]

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Evaluation of feeding interruption for enteral nutrition in intensive care unit patients

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ABSTRACT

Objective: Intensive care patients are at a high risk of malnutrition due to an oral intake failure. Enteral nutrition (EN) is considered to be the gold standard for such patients. However, even if everything is done properly, it is also known that there may be inconsistency between the calculated calorie requirements and the amount of calories given to the patient. There is no gold standard to minimize the EN interruption. The aim of this study was to determine the main factors involved in the EN cutting in an intensive care unit (ICU).

Methods: This study was done prospectively after an ethical approval and patient relatives' informed consent in 1489 study day of 80 ICU patients between September 2013 and September 2014 were obtained. The causes of the EN interruption were grouped under seven main categories (1. gastrointestinal dysfunction, 2. airway management, 3. tracheoesophageal fistula, 4. diagnostic and surgical reasons, 5. mechanical problems, 6. metabolic and hemodynamic instability, and 7. maintenance and position change). A total of 16 factors with subgroups were determined for analysis. Demographic data, the presence of dialysis, state of consciousness, comorbidities, and calculated calories and calorie intake were recorded. The patient's caloric needs were calculated on a daily basis using the Harris–Benedict formula.

Results: In our study, it was determined that 17.1% of the calories calculated as the EN support could not be applied to patients due to interruptions. The EN interruption factors were found to be the airway management (39.7%), mechanical problems (15.4%), metabolic and hemodynamic instability (14.1%), maintenance and position change (12.8%), and gastrointestinal dysfunction (12.8%).

Conclusion: The airway management and enteral feeding tube mechanical problems were the most frequently observed EN interruption factors. The awareness of EN interruption factors is important in preventing this problem.

Keywords: Enteral nutrition, intensive care, nutritional discontinuation

Introduction

A better understanding of the molecular and biological effects of nutrition over the last 30 years has contributed positively to the nutritional treatment of intensive care patients (1). In terms of nutrition, homeostasis refers to metabolic regulatory mechanisms that work to maintain the body's physiological function, energy, and other nutrient stores in a stable state (2). Therefore, nutritional support is considered as an important component of the management strategy of intensive care patients. However, although nutrition is very important, despite the current formulations used, most intensive care patients do not receive the targeted number of calories. Malnutrition causes an increase in nasocomial infections, prolonged hospitalization and intensive care hospitalization, and increased complications and increased rates of re-hospitalization in ICU (3-5).

In a recent review evaluating malnutrition rates in patients hospitalized in the ICU, they were ranging between 37.8% and 78.1% in heterogeneous intensive care patients (6). This ratio clearly shows that there are some uncontrolled factors related to the nutrition of the patients followed up in the ICU (7-9).

The difference between the calculated and given nutritional values has been described in different studies (7).

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Although various measures have been proposed to support the nutritional status of these patients, currently, a common guideline is not available. Updated guidelines provide some recommendations. However, the exact reasons for not reaching the desired calorie target cannot be clearly determined.

The aim of this study was to determine the causes of EN discontinuation in ICU patients, at what stage and with which factors the interruption occurred, and the difference between the calculated and given calorie amount.

Methods

This study was conducted prospectively between September 2013 and September 2014 at the Department of Anesthesiology and Reanimation, Pamukkale University, Medical Faculty Hospital, with the approval of the institutional ethics committee and consent of the patient's relatives. Eighty patients aged >18 years, with or without the mechanical ventilator support, were included into the study. Patients <18 years who were on the oral parenteral treatment, who were treated with total parenteral nutrition, and whose hospitalization was <3 days were excluded from the study.

To record the study data, a database form was created, and the forms of the discontinuation were grouped as the gastrointestinal dysfunction, airway management, tracheoesophageal fistula, diagnostic and surgical reasons, metabolic and hemodynamic disorders, and care and position changes (7, 10). Subgroups were added under these seven main headings to detail the reasons (Table 1). The patient ages, body mass index, gender, and diagnosis for hospitalization at the intensive care unit were recorded. The Acute Physiology and Chronic Health Assessment (APACHE) II score and Glasgow Coma Scale were used for the general status assessment, and the Nutritional Risk Assessment Scale (NRS) 2002 was used for the nutritional status assessment.

Nutrition was provided by the enteral route via the nasogastric tube or gastrostomy tube using readymade commercial products. During the study, products with immune nutrition such as fish oil, glutamine, arginine, etc. were not used. Caloric requirements of the patient were calculated daily using the Harris-Benedict formula.

Calculated and dispensed volumes of the nutrition products used during the study were recorded by calculating whether the nutrition was discontinued and the reason for discontinuation, duration, and rates of the discontinuation. The daily calories that could be applied were divided by the calculated calories, and the ratio was obtained. The non-given percentage was used. In addition, concomitant diseases, hemodialysis requirements, and consciousness status of the patients were also recorded. The patients were divided into three groups according to their discharge from the ICU, as those who were discharged, who returned to the service, and those who died.

Table 1. Factors leading to discontinuation of enteral nutrition

GIS dysfunction
Vomiting
Diarrhea
Abdominal distension
Excess residual amount
Airway Management
Intubation or extubation
Tracheal tube displacement
Opening of tracheostomy
TEF occurrence
Depending on Diagnostic and Surgical Procedures
Fiberoptic gastroscopy and gastrostomy opening
Transfer to the Radiology Department
Stopping pre-op feeding
Mechanical Problems
Feeding pump dysfunction/deficiency
Gastric tube occlusion and malposition
Catheter malposition/dysfunction
Metabolic and Hemodynamic Instability
MAP <40
Maintenance and change of position

GIS: gastrointestinal system; TEF: tracheoesophageal fistula; MAP: mean arterial pressure

Statistical analysis

The Statistical Program for Social Science version 11 (SPSS Inc.; Chicago, IL, USA) was used in the analysis of the data obtained. In the comparison of the averages, if there was no homogeneous distribution in the groups where the sample t-test was used, the Mann-Whitney U test was used. Sample t-test was used to evaluate the homogeneity of the groups. The one-way analysis of variance and Kruskall-Wallis test were used to compare more than two averages. The relation between two variables

Table 2. Descriptive characteristics of the patient population					
	Number	**Percentage (%)**	**Average**	**SD**	**Median**
Age			64.71	17.82	69
Gender					
Female	33	42.3			
Male	45	57.7			
Hospitalization diagnosis					
Shortness of breath	55	70.5			
Circulatory failure	12	15.4			
Neurological pneumonia	5	6.4			
Trauma	3	3.8			
Malignity	2	2.6			
	1	1.3			
Number of patient follow-up days			18.85	16.40	13
Body mass index			23.16	3.87	23
APACHE II Score			31.30	5.23	32
NRS 2002 Score			3.50	0.50	3.50
Dialysis					
Yes	16	20.5			
No	62	79.5			
Consciousness					
Closed	25	32.1			
Open	53	67.9			
Exit status					
Discharged	18	23.1			
Transfer to another service	18	23.1			
Exitus	42	53.8			

SD: standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; NRS: Nutrition Risk Assessment Scale

was examined using Pearson's and Spearman's correlation coefficients. Pearson's chi-squared test and Fisher's exact chi-squared test were used to analyze categorical data. The significance level was accepted as $p<0.05$.

Results

When the records of the 80 patients included in the study were examined, it was found that the calorie rates of 2 patients were very high. These 2 patients (a 77-year-old male, the non-given ratio: 100%; a 43-year-old male, the non-given ratio: 77%) were excluded from the study because of the possibility that the analyses would have affected the power and could be due to an error during registration. The data of the remaining 78 patients for 1471 days were used in the analyses. The average follow-up period was 18.85±16.40 days. There were 4 patients who were hospitalized for 60 days or more, which affected the distribution homogeneity. The median of the sequence was 13 days (Table 2).

The average age of patients was 64.71±17.82 (19-93); 25% were older than 78, and 25% were younger than 54. Of the patients followed, 33 were female, and 45 were

male. Descriptive characteristics of the patient population are presented in Table 2. It can be seen that the most common reason for hospitalization is respiratory failure. In our study, it was observed that only 82.9% of the calculated nutritional support could be given to patients. As a result, it was found that 17.1% of the targeted nutritional treatment could not be given to patients, and this rate ranged from 3% to 61%, varying from one patient to another.

One patient with tracheoesophageal fistula (TEF) and three patients who underwent diagnostic/surgical procedures were excluded from the study after being labeled as missing data (missing value) due to a low number. Reducing the number of groups in multiple group comparisons has a positive effect on statistical power. As a result, relational analyzes were performed in four groups of 74 patients due to interruption.

According to these variables, the most common cause of disruption in EN is airway management (39.7%) (Table 3). According to the results of the analysis, the factors causing interruption (gastrointestinal dysfunction, airway management, mechanical problems, metabolic and hemodynamic instability) differed in terms of inefficient calories and inefficient percentage, and thus were evaluated using the post-hoc Tukey and Mann-Whitney U tests. In conclusion, although the most common cause of the EN interruption was the airway management, it was observed that the highest amount of interruption was under the heading of "Metabolic and Hemodynamic Instability" (Table 4). In the subgroup of hemodynamic instability, the mean arterial pressure change (MAP<40) was the only variable constituting this subgroup (Tables 1 and 3).

Percentages of nutrition that could not be given were analyzed using the chi-squared test via the following percentage groups: <10%, 10%-19.9%, 20%-29.9%, and <30%. There was no significant difference in terms of age, gender, state of consciousness, and presence of hemodialysis in the groups with high percentage of nutrition could not be given. When the percentages that were not given were compared in terms of the ICU exit status, APACHE II, and NRS 2002 scores, there was no significant difference found between the groups ($p<0.05$). When the reasons for interruption and the percentages that could be given were compared, some significant differences were observed (Table 5). The reason for the interruption due to the maintenance and position change remained at 10% in most patients. Interestingly, 1 of the patients in this group was found to have a cut-off >30%. On the other hand, 45.5% of the patients in the metabolic and hemodynamic instability group had an interruption ≥30%. Among the reasons for the interruption were the gastrointestinal system dysfunction and within the mechanical problems groups, it was observed that the interruption was mostly <10%. The airway management was the most frequent cause of interruption, but in 54.8% of the patients in this group, the interruption was 10%-19.9%.

Table 3. Distribution of the factors that cause interruption of enteral nutrition in patients

	%	%
Gastrointestinal dysfunction		12.8
Vomiting	–	
Diarrhea	1.3	
Abdominal distension	2.6	
Excess residual amount	9	
Airline management		39.7
Intubation or extubation	28.2	
Tracheal tube displacement	–	
Opening of tracheostomy	11.5	
TEF occurance		1.3
Depending on diagnostic and surgical procedures		3.8
Fiberoptic gastroscopy and gastrostomy opening	–	
Transfer to the Radiology Department	1.3	
Stopping preoperative feeding	2.6	
Mechanical problems		15.4
Feeding pump dysfunction/deficiency	–	
Gastric tube occlusion and malposition	15.4	
Catheter malposition/dysfunction		14.1
Metabolic and hemodynamic instability		
Mean arterial pressure <40	14.1	
Maintenance and position change		12.8

TEF: tracheoesophageal fistula

Discussion

Critical patients are exposed to many adverse conditions in addition to their illness leading to intensive care. Malnutrition may rapidly develop in these patients, and it may adversely affect the healing of underlying diseases. Malnutrition has been reported to develop in up to 78% of ICU patients (6). Today, although various measures have

Table 4. Causes of interruption, calories cut, and non-given percent

	Patient (n)	Non-given calories Mean±SD	Non-given %	*Airway management (p) non-given %	*M/hemodynamic instability (p) non-given %
Gastrointestinal associated	10	3552±2436.45	16.8±12.38	0.560	0.051
Airwave management	31	3629.35±2777.51	17.29±8.19		0.013
Associated mechanical problems	12	3697.05±2647.93	19.33±12.8	0.841	0.118
Metabolic hemodynamic instability	11	4852.72±4200.75	28.45±15.41	0.013	

SD: standard deviation

Table 5. Correlation between interruption reasons and grouped interrupted amounts

	Grouped non-given percentages				
Reason for interruption	<10	10–19.99	20–29.99	30–100	Total
Maintenance and position change	9	0	0	1	10
	90.0%	0%	0%	10.0%	100.0%
Gastrointestinal dysfunction	4	3	1	2	10
	40.0%	30.0%	10.0%	20.0%	100.0%
Airwave management	6	17	4	4	31
	19.4%	54.8%	12.9%	12.9%	100.0%
Mechanical problems	5	3	1	3	12
	41.7%	25.0%	8.3%	25.0%	100.0%
Metabolic/hemodynamic	1	3	2	5	11
	9.1%	27.3%	18.2%	45.5%	100.0%
Total	25	26	8	15	74
	33.8%	35.1%	10.8%	20.3%	100.0%

been proposed to support the nutritional support of these patients, the reasons for not reaching the desired calorie target cannot be determined clearly. The variability of the difference between the calculated and given percentage is likely to be very causal, and ICU facilities, treatment options, and disease-related factors are effective (7-10).

In a study conducted by Heyland et al. (11), which was one of the first studies to determine the causes of the EN withdrawal in 1995 and examined 99 patients, it was found that 52% of patients could not tolerate enteral feeding, and the most common cause of interruption were gastrointestinal residual problems (11). In a study by Adam and Baston (12), 1929 daily data of 193 patients treated in five ICUs were examined, and it was found that only 76% of the targeted calorie amount could be given to patients. In a study by McClave et al. (13) evaluating 339 days of enteral nutrition in 44 patients, only 78.1% of the calories prescribed by the physician could be given to patients. In this study, the most common cause of interruption was also found to be a high gastric residual volume. In a more recent study from the Netherlands, the data of 55 hospitalized patients were evaluated, and it was observed that 87% (5-113) of the prescribed calories could be given (7). This study, different from ours, examines the methods of giving. While the amount that could be given by the pump was 85%, the amount given by gravity was 88%. In their study, Martin et al. shared the data of 152 patients and showed that 80% of the calorie value could be given. In this study, the most important cause of EN discontinuation was an inadequate hospital-based logistics (a delay between the EN prescribing and intake, including the preparation of enteral diets and delivery to the ICU ward) (14). As it can be seen, it is not possible to extract

data from the studies on this subject for definite reasons and their solutions. In addition to medical practices, many factors (logistics, personnel, etc.) that can sometimes be difficult to standardize, can also affect this process.

In our study, different from previous literature, we found that the airway management was the most common factor causing the discontinuation of EN in patients treated in the ICU (39.7%). As a subgroup, the intubation/extubation process was the factor that caused the highest amount of disruption. However, when we look at quality, we see that in 20% of our patients, the amount of interruption was less than 10%, and in 55%, it was between 10% and 20%. As a result, the airway management is a common cause of EN interruption, but when the interrupted amounts are evaluated, its negative impact on reaching the target calories is limited.

In our study, metabolic and hemodynamic causes led to a 14.1% nutrition interruption. Although it is in the third place, when we consider it as a quality, we see a different picture. Approximately, 45% of the metabolic and hemodynamic interruptions are in the group ≥30%. This ratio indicates the severity of the reason for interruption. In EN, non-obstructive mesenteric ischemia, which disrupts the function of the intestines, is a troublesome condition affecting the prognosis negatively, and its mortality is 80% (15). Elderly patients with cardiovascular disease, arrhythmia, and aortic insufficiency are at risk for mesenteric ischemia without bowel obstruction. Diabetes, smoking, and the presence of sepsis or a previous major infection increase the risk. Vasoconstriction-enhancing agents such as digoxin or alpha-adrenergic agonists applied in the ICU constitute a risk for ischemia (16). In general, all vasopressors may increase the risk of mesenteric ischemia without bowel obstruction, whether hemodynamically stable or unstable. Therefore, it is not easy to calculate the patient's risk for ischemia. Vasopressors applied to hypotensive patients carry more risk than normotensives (16). While some studies have stated that the presence of intestinal content is a predisposing factor for the development of mesenteric ischemia without intestinal obstruction (17, 18), there are studies that claim otherwise (19, 20). However, some authors recommend EN to be discontinued in the presence of a low mean arterial pressure (16, 17). The practical approach applied in our clinic is to stop EN when the mean arterial pressure falls below 40 mmHg.

In our study, the rate of interruption due to mechanical problems was 15.4%, and this was due to the occlusion and malposition of the gastric tube. When we look at the distribution within the group, the EN cut-off rate was 10% and below in 40% of the patients. This rate varies between 7.9% and 11% in the literature (12, 14). It is basically a factor that can be corrected by education and carries a moderate risk in terms of quality.

To mention some limitations regarding the method of the study, the study was planned to include patients receiving total parenteral nutrition therapy. However, since the number of patients fed with total parenteral nutrition was quite low (seven patients), it was not thought that it would be impossible to obtain a meaningful comparison, thus only data of the patients fed with EN were included into the study. In addition, the study was planned as a single-center study, reflecting the experience and data of our clinic. It is a small scale study. The small number of patients was one of the study limitations.

In our study, we found that 17.1% (3%-61%) of the calories calculated daily during the EN administration could not be applied to patients. While the most common reason for the EN interruption was the airway management, the amount of interruption was not very high. The patient care and position, which are relatively insignificant factors, become important risk factors when combined with other factors. In this regard, certain situations in which EN will not be interrupted can be determined, and the percentage lost at this stage can be reduced by education. However, necessary precautions should be taken with regard to the aspiration risk. The vasopressor use and mesenteric ischemia are both difficult to detect and take precaution. However, the most serious loss in our study is related to the application in this regard.

In our study, the airway management and enteral feeding tube mechanical problems were the most common EN cessation factors. It is expected that the findings of this study may contribute to the awareness of EN nutritional cessation factors and to prevent this problem in our practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Pamukkale University School of Medicine (04/2013).

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

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References

1. Marik PE. Enteral nutrition in the critically ill: myths and misconceptions. Crit Care Med 2014; 4: 962-9. [CrossRef]
2. Nompleggi DC. (Çev. Özcan A.) Yoğun bakım hastasında nütrisyon desteği. (Eds) Irwin RS, Rippe JM. Irwin and Rippe's intensive care medicine. (Çev. Ed. Tulunay M, Cuhruk H) Güneş Tıp Kitap Evi 2014.p.2181-5.
3. Sharma K, Mogensen KM, Robinson MK. Pathophysiology of Critical Illness and Role of Nutrition. Nutr Clin Pract 2019; 34: 12-22. [CrossRef]
4. Yeh DD, Peev MP, Quraishi SA, Osler P, Chang Y, Rando EG, et al. Clinical Outcomes of Inadequate Calorie Delivery and Protein Deficit in Surgical Intensive Care Patients. Am J Crit Care 2016; 25: 318-26. [CrossRef]
5. Patel JJ, Hurt RT, McClave SA, Martindale RG. Where's the Evidence? Crit Care Clin 2017; 33: 397-412. [CrossRef]
6. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review. J Parenter Enteral Nutr 2017; 41: 744-58. [CrossRef]
7. De Jonghe B, Appere-De-Vechi C, Fournier M, Tran B, Merrer J, Melchior JC, et al. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001; 1: 8-12. [CrossRef]
8. Huang J, Yang L, Zhuang Y, Qi H, Chen X, Lv K. Current status and influencing factors of barriers to enteral feeding of critically ill patients: A multicenter study. J Clin Nurs 2019; 28: 677-85. [CrossRef]
9. Kozeniecki M, Pitts H, Patel JJ. Barriers and Solutions to Delivery of Intensive Care Unit Nutrition Therapy. Nutr Clin Pract 2018; 33: 8-15. [CrossRef]
10. Petrosino BM, Christian BJ, Wolf J, Becker H. Implications of selected problems with nasoenteral tube feedings. Crit Care Nurs Q 1989; 12: 1-18. [CrossRef]
11. Heyland D, Cook DJ, Winder B, Brylowski L, Van deMark H, Guyatt G. Enteral nutrition in the critically ill patient: A prospective survey. Crit Care Med 1995; 23: 1055-60. [CrossRef]
12. Adam S, Batson S. A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. Intensive Care Med 1997; 23: 261-6. [CrossRef]
13. McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, et al. Enteral tube feeding in the intensive care unit: factors impedingadequate delivery. Crit Care Med 1999; 27: 1252-6. [CrossRef]
14. Martins JR, Shiroma GM, Horie LM, Logullo L, Silva Mde L, Waitzberg DL. Factors leading to discrepancies between prescription and intake of enteral nutrition therapy in hospitalized patients. Nutrition 2012; 28: 864-7. [CrossRef]
15. Park WM, Gloviczki P, Cherry KJ Jr, Hallett JW Jr, Bower TC, Panneton JM, et al. Contemporary management of acute mesenteric ischemia: Factors associated with survival. J Vasc Surg 2002; 35: 445-52. [CrossRef]
16. McClave SA, Chang WK. Feeding the hypotensive patient: does enteral feding precipitate or protect against ischemic bowel? Nutr Clin Pract 2003; 18: 279-84. [CrossRef]
17. Kles KA, Wallig MA, Tappenden KA. Luminal nutrients exacerbate intestinal hypoxia in the hypoperfused jejunum. JPEN J Parenter Enteral Nutr 2001; 25: 246-53. [CrossRef]
18. Scaife CL, Saffle JR, Morris SE. Intestinal obstruction secondary to enteral feedings in burn trauma patients. J Trauma 1999; 47: 859-63. [CrossRef]
19. Revelly JP, Tappy L, Berger MM, Gersbach P, Cayeux C, Chioléro R. Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. Intensive Care Med 2001; 27: 540-7. [CrossRef]
20. Turza KC, Krenitsky J, Sawyer RG. Enteral feeding and vasoactive agents: suggested Guide. Practical Gastroenterology 2009.pp.11-22.

CLINICAL SCIENCE OF NUTRITION

Case Report

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Zinc deficiency might occur in patients receiving parenteral nutrition

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ABSTRACT

Zinc is an essential trace element. Many important enzymatic activities are zinc dependent. Therefore, it is not surprising that zinc deficiency is clinically expressed in rapidly growing tissues. The clinical features of zinc deficiency are not specific. The clinical manifestations of zinc deficiency include inadequate growth, hypogonadism, anorexia, alopecia, diarrhea, taste, and smell alterations, impaired wound healing, skin lesions, and diminished immune function. Acquired zinc deficiency is an uncommon entity. Zinc deficiency is defined most frequently in patients who had burns, malabsorption, severe losses from the gastrointestinal tract, and total parenteral nutrition (PN) with inadequate or no zinc in the nutrient mixture. In this case report, we present a 46-year-old female patient with altered mental status due to zinc deficiency, who was operated for ulcerative colitis, and who was fed with PN for a long time that did not contain zinc in the nutrient mixture.

Keywords: Deficiency, parenteral nutrition, zinc

Introduction

Zinc is an essential trace element that has a ubiquitous subcellular presence and is involved in catalytic, structural, and regulatory roles in the human body. It has been identified as a part of 120 different enzymes, such as carbonic anhydrase, carboxypeptidase, alkaline phosphatase (ALP), oxidoreductases, transferases, ligases, hydrolases, lyases, and isomerases (1). Endogenous stores of zinc are mobilized in the fasting state, but do not meet metabolic needs during anabolism because the net movement of zinc is into tissues, and circulating zinc is reduced. Although the syndrome of zinc deficiency cannot be identified easily, zinc deficiency does have a pronounced effect on nucleic acid metabolism, thus influencing protein and amino acid metabolism (2).

In healthy individuals, dietary zinc deficiency does not occur, mainly because zinc is widely distributed in food. Zinc deficiency has been described in a variety of patient populations including patients with advanced age, alcohol use disorder, postoperative status, burns, malabsorption syndromes, wound drainage, or gastrointestinal (GI) losses (2). Since zinc is involved in many processes, the clinical features of zinc deficiency are not specific. The clinical manifestations of zinc deficiency include inadequate growth, hypogonadism, anorexia, alopecia, diarrhea, taste, and smell alterations, impaired wound healing, and diminished immune function (1-5).

Trace element and vitamin supplements should be provided for long-term parenteral nutrition (PN). In 1976, prior to the routine inclusion of trace elements in PN, Kay et al. published one of the first case series of zinc deficiency in patients receiving PN and also noted that symptoms are responsive to the addition of zinc (3, 6). By 1979, the Nutrition Advisory Group of the American Medical Association recommended the routine addition of trace elements, such as zinc, copper, chromium, and manganese, to PN (1, 3). After the shortage of trace elements production in the USA in 2014, many diseases have been reported due to PN-dependent trace elements deficiency (3, 4).

We report a case of a woman with altered mental status due to zinc deficiency who received long-term PN and who was operated on for inflammatory bowel disease.

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Case Presentation

A 46-year-old female patient who had been treated for ulcerative colitis for 13 years was admitted to our clinic for abdominal pain, severe diarrhea, and depleted health status. She had received high doses of steroids and 5-aminosalicylic acid medication. She had been hospitalized in a gastroenterology clinic elsewhere for >3 months receiving intravenous antibiotics, steroids, and PN.

On admission, she was offered three-stage colectomy. The first step of surgery was emergent total colectomy with end ileostomy that would be followed by proctectomy and ileal pouch-anal anastomosis (IPAA) and diverting ileostomy after 6 months and eventually ileostomy takedown.

After emergent total colectomy, she was started on oral intake and was discharged on postoperative day 12 with oral loperamide to reduce ileostomy output. During her hospital stay, she took oral and PN supplements. Her nutrition risk screening score was 6, and weight loss was >15% in the last 3 months.

After 6 days from discharge, she was admitted to the emergency clinic with high stoma output. She had signs of dehydration. Her laboratory results were as follows: blood glucose level 81 mg/dL (70-99 mg/dL), white blood cell 18,300/mm^3 (3500-10,000/mm^3), hemoglobin 9.6 g/dL (11.5-15.1 g/dL), hematocrit 33.4% (34.4%-44.2%), blood urea 96 mg/dL (17-43 mg/dL), creatinine 2.3 mg/dL (0.6-1.2 mg/dL), serum sodium 136 mmol/L (135-148 mmol/L), serum potassium 5.2 mmol/L (3.5-5.5 mmol/L), ionized calcium 4.92 mg/dL (4.64-5.28 mg/dL), serum chloride 107 mmol/L (98-106 mmol/L), aspartate aminotransferase/alanine aminotransferase within normal limits, serum albumin 2.1 g/dL (3.5-5.5 g/dL), total protein 6.8 g/dL (6.7-8.6 g/dL), ALP 27 U/l (33-96 U/L), and C-reactive protein (CRP) 17 mg/dL (0-10 mg/dL).

Rehydration and loperamide were started followed by PN with high doses of proteins (2 g/kg), vitamins, and trace elements. She experienced pneumonia that was treated with intravenous piperacillin and tazobactam. Although there was progression in clinical and nutritional status and laboratory tests, the patient's mental status was reduced. She showed agitation, dyslexia, and unresponsiveness to physical stimuli. Serum electrolyte levels were normal in this period. A neurology consultant evaluated the patient, and cranial magnetic resonance imaging was performed, revealing no pathology. Then, trace element levels were studied. Serum zinc level was below normal limits [40 µg/dL (60-120 µg/dL)], and serum copper level was within normal limits [75 µg/dL (70-140 µg/dL)].

A dose of 10 mg intravenous zinc was administered daily. After 3 days, she showed progression in her mental status, and after 8 days, she was completely normal. Serum zinc level was within normal limits [82 µg/dL (60-120) µg/dL)] after intravenous treatment. She was discharged after 12 days of intravenous zinc initiation.

Completion proctectomy with IPAA and further ileostomy takedowns were later performed uneventfully.

Discussion

Zinc deficiency is rarely seen in healthy individuals because zinc is widely distributed in food. However, prolonged use of PN and abnormal loss from the GI tract (diarrhea, fistula, stoma, or bariatric surgery) also cause zinc deficiency, such as other trace elements. Zinc deficiency may be asymptomatic or lead to lethal clinical manifestations extending to coma. Zinc, which is the most commonly used trace element after iron in the body, deficiency should not be neglected.

Long-term use of PN and GI losses, such as diarrhea, fistula, or ileostomy, may cause zinc deficiency. Zinc deficiency may be asymptomatic but may lead to mental problems and coma as well. Zinc is the second most utilized trace element after iron in the body; therefore, zinc deficiency probability should always be kept in mind.

Major national shortages of vitamin and trace element products for PN formulations have occurred in the late 1980s, the late 1990s, and finally between 2009 and 2014 (3). Several studies have been reported due to trace element deficiency during this shortage (3, 4). Although our patient manifested mental problems due to zinc deficiency, the clinical manifestations of zinc deficiency could also include erosive eczema, alopecia, cheilitis, anorexia, abdominal pain, hypogonadism, depression, and coma (1-5). Altered mental status can occur in the setting of severe deficiency and may be explained partially by hyperammonemia resulting from the impairment of the urea cycle when zinc levels are decreased. However, we did not measure blood ammonia levels.

The clinical features of zinc deficiency are non-specific because it is involved in so many processes. The diagnosis of zinc deficiency is difficult. Zinc deficiency for this patient was diagnosed primarily by laboratory measurement. It cannot be easily ascertained whether the patient experienced clinical sequelae of zinc deficiency (1, 4). Although there were many clinical findings (prolonged use of PN, excess loss of stoma, decrease in turgor, amenorrhea, low ALP levels, and susceptibility to infection) in our patient,

the diagnosis of zinc deficiency was delayed. Plasma zinc levels are decreased during times of stress and infection. Zinc levels can be decreased in hypoalbuminemia due to sepsis as it is bound to albumin and alpha-macroglobulins in the blood. Furthermore, zinc has been found to correlate negatively with CRP (1). In addition, the low level of ALP may be significant for zinc deficiency (3), and it may even be an alert situation for zinc deficiency.

The use of PN created a unique situation in which it was possible to feed individuals with purified diets specifically deficient in trace elements, such as zinc (2). In patients with no oral intake or PN alone, approximately 3 mg/day zinc maintained zinc balance in the absence of GI losses (1). The current American Society for Parenteral and Enteral Nutrition clinical guidelines recommended that the supplementation of PN for zinc is 2.5-5 mg/day. Excessive GI losses, sepsis, and hypercatabolic states require additional supplementation. Patients with enterocutaneous fistula and diarrhea, as well as similar to our patient with severe loss of stoma, may require 12-17 mg/L fluid. Therefore, in patients with fistula, diarrhea, and intestinal drainage, a dose of 12 mg zinc should be added for each liter of loss (1). Amino acid infusions also increase urinary zinc losses. In the kidney, zinc infusions enhance distal reabsorption of zinc, and amino acid infusion increases proximal secretion (2). In our case, zinc treatment was delayed despite long-term PN and high-volume loss from stoma, and additional amino acid infusion was observed in addition to PN. These two states further deepened zinc deficiency.

In cases of zinc deficiency, clinical improvement is quite rapid, with results seen in 2 days and resolution in 2 weeks (1). In our case, clinical improvement was started on day 3, and resolution was seen on day 8.

In conclusion, zinc deficiency should be in the differential diagnosis of patients particularly with GI losses and receiving long-term PN with unexplained mental or metabolic disorders.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

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References

1. Jin J, Mulesa L, Carrilero Rouillet M. Trace elements in parenteral nutrition: considerations for the prescribing clinician. Nutrients 2017; 9: E440. [CrossRef]
2. Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. Gastroenterology 2009; 137: 7-12. [CrossRef]
3. Sant VR, Arnell TD, Seres DS. Zinc deficiency with dermatitis in a parenteral nutrition-dependent patient due to national shortage of trace minerals. JPEN J Parenter Enteral Nutr 2016; 40: 592-5. [CrossRef]
4. Franck A. Zinc deficiency in a parenteral nutrition-dependent patient during a parenteral trace element product shortage. JPEN J Parenter Enteral Nutr 2014; 38: 637-9. [CrossRef]
5. Jakubovic BD, Zipursky JS, Wong N, McCall M, Jakubovic HR, Chien V. Zinc deficiency presenting with necrolytic acral erythema and coma. Am J Med 2015; 128: e3-4. [CrossRef]
6. Kay RG, Tasman-Jones C, Pybus J, Whiting R, Black H. A syndrome of acute zinc deficiency during total parenteral alimentation in man. Ann Surg 1976; 183: 331-40. [CrossRef]