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AIMS AND SCOPE

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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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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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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- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at clinscinutr.org.

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

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- 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-

ticles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

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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KEPAN SOCIETY OF CLINICAL ENTERAL PARENTERAL NUTRITION-TURKEY
CLINICAL SCIENCE OF NUTRITION

EDITORIAL

Dear Colleagues,

We are pleased to launch the Clinical Science of Nutrition, which will be published on April 2019 under the ownership of Clinical Enteral Parenteral Nutrition Association of Turkey (KEPAN).

As you already know, Turkey has made significant progress in the field of nutrition in the last 20 years. Within this period, both Turkey has become one of the most abstract-submitting countries at ESPEN and, the number of articles published in international journals from Turkey has increased by each day. In the light of these ongoing developments, we can proudly say that our country is now in a more visible and active position in the international arena. All these developments have suggested to us that it is time to launch an international journal that belongs to Turkey. Our main aim with this journal, which will cover all aspects of nutrition and all branches of the subject, is not only to publish studies from Turkey but also to serve as a bridge between the East and West by increasing the regional efficiency. In the near future, we hope that our journal will become a periodical that attracts publications from many countries, especially from the countries in our region.

- We will accept and process manuscript submissions online. Authors will be able to track the progress of their submission via the journals online manuscript system.
- Our journal will implement the open access publication model, which means our content will be available online, free of charge.
- Submissions will be provided with a first decision within 4 to 6 weeks of the initial submission. Manuscripts accepted for publication will be published online in ahead of print format with an assigned DOI.
- Prior to publication all articles will be edited by a native English speaker and the grammatical mistakes will be corrected.
- Submitted manuscripts will be scanned through a plagiarism detection software (iThenticate) against the risks of plagiarism and duplication before evaluation.
- Table of content alerts of published content will be sent to the researchers who are published in international journals in the field of nutrition.

Our first target is to have Clinical Science of Nutrition accepted for TÜBİTAK ULAKBİM TR Index within the first year and PubMed within the next 3 years. The following step will be indexed in the Science Citation Index Expanded.

We are aware that we can achieve these goals only with the support of our dear colleagues. In this sense, I would like to thank you in advance for your interest and valuable support on behalf of the editorial board and look forward to receiving your valuable manuscript submissions.

Sadık Kılıçturgay
Editor in Chief

CLINICAL SCIENCE OF NUTRITION

Invited Review

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Current approach to perioperative nutrition in the ERAS age

R. Haldun Gündoğdu

ABSTRACT

Enhanced recovery after surgery (ERAS) is a multidisciplinary and multimodal program designed to minimize the response to surgical trauma and normalize the patient as early as possible. While managing the perioperative process of the patient, ERAS protocols a change from classical and dogma-based treatments to modern concepts with a radical change. Its basic philosophy is to provide early recovery by supporting mobilization and gastrointestinal functions without causing complications. This protocol consists of many different elements, and when they are applied together, they support each other. Nutrition is an important part of ERAS protocols, and it directly affects clinical outcomes. The recommended perioperative nutritional management algorithm for patients to be operated with ERAS protocols starts with a routine nutritional assessment and aims at early oral/enteral feeding at each stage. The aim of this compilation is to review current perioperative nutritional recommendations in the period in which ERAS protocols are adapted to all areas of surgery.

Keywords: Accelerating postoperative recovery, enteral and parenteral nutrition, ERAS, perioperative nutrition

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Introduction

Of the patients who are admitted to general surgery clinics, 10%-35% are malnurished (1-7). Although the primary diseases such as cancer, trauma, acute inflammation, obstruction, or fistulas are the leading causes of this condition, advanced age, a previous chronic disease, and low socioeconomic status are additional risk factors. Moreover, the issue of iatrogenic malnutrition should not be forgotten. The malnutrition that develops during hospitalization is called "iatrogenic malnutrition," and it is reported to be seen at a rate between 10% and 50% by various researchers (3, 8). Knowing the causing factors (Table 1) plays an important role in preventing the worsening of the nutritional problem, which already exists at the time of hospitalization, and in the regulation of appropriate treatment. Malnutrition rates at the time of hospitalization in surgical clinics dealing with patients with cancer range between 50% and 80% (2, 9-14).

The effect of malnutrition on postoperative complications and mortality rates has long been known (Table 2). In the study published by Studley et al. (15) in JAMA in 1936, it was shown that the mortality increased with the increase of preoperative weight loss in patients undergoing peptic ulcer surgery, and this became a classic book knowledge, with the results of many subsequent studies parallel to this research (16, 17). Malnutrition increases not only mortality, but also all infectious complications, total morbidity, a prolonged hospital and intensive care unit stay, and costs (Figure 1). In a study published in 2011, it was shown that the health expenditures required for the treatment of patients with malnutrition were as twice as high as those without malnutrition and that malnutrition acted as an independent risk factor on mortality (18).

The basic philosophy of enhanced recovery after surgery (ERAS) protocols, defined as the multimodal and evidence-based perioperative care concept, is to reduce metabolic stress due to surgical trauma and to enable the return to normal activity as soon as possible by supporting normalization of functions in a short time. Preoperative optimization, prehabilitation, perioperative modern nutritional management, standard anesthesia and analgesia regimens, and early mobilization are the main components of ERAS protocols (19-24).

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A proper and safe nutritional support during the perioperative period can solve many problems that may arise due to malnutrition. In the period when ERAS protocols are on the agenda, the nutritional needs of patients who will undergo major surgeries are included in the guidelines of many associations (25-29).

Nutrition is one of the main elements of ERAS protocols since it includes important issues such as preoperative fasting, oral carbohydrate loading, optimizing preoperative nutritional status, and early oral feeding. Therefore, the issue of perioperative nutrition management for patients to be operated with ERAS protocols should be reviewed in the light of current information.

Table 1. Iatrogenic malnutrition factors
Lack of recording the body weight
Lack of a clear description of responsibilities
Lack of nutritional knowledge
Frequent fasting of the patient for examination purposes
Continuous blood-letting for examinations
Poor documentation of food intake
Loss of appetite due to environmental changes
Surgery in a malnourished patient
Postoperative long-term use of glucose and saline solutions
Delayed nutritional support leading to irreversible depletion

Table 2. Effects of malnutrition on surgical outcomes
• Impaired wound healing o Opening of incision o Leakage from the anastomosis
• Decreased resistance to infections o Postoperative pneumonia o Postoperative wound infection o Increase in intraabdominal infections o Postoperative urinary infection
• Impairment of adaptability o Insufficiency in adaptation after intestinal resections o Prolonged paralytic ileus
• Delay in recovery
• Pressure ulcers

Importance of ERAS Protocols

ERAS recommends changes for the whole patient's journey, starting from the outpatient clinic before the operation and ending up at home after being discharged (Figure 2).

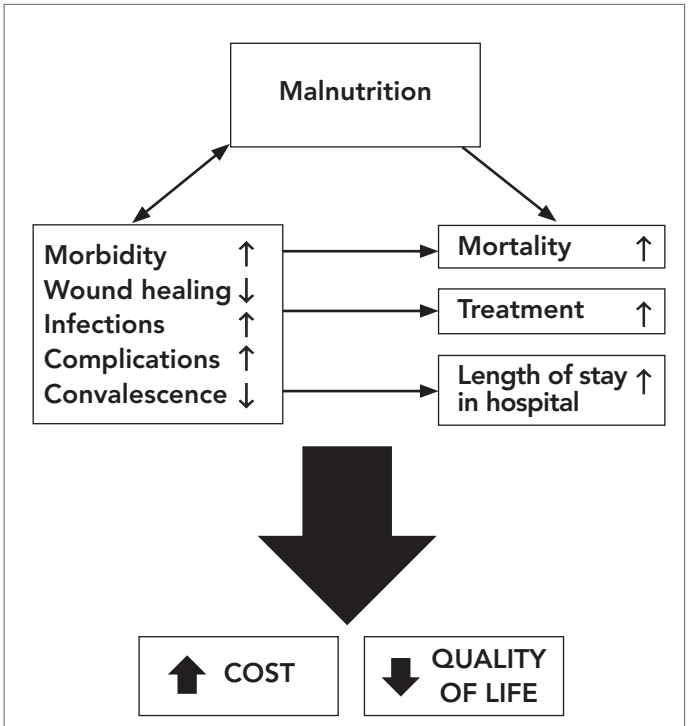

Figure 1. Results of malnutrition

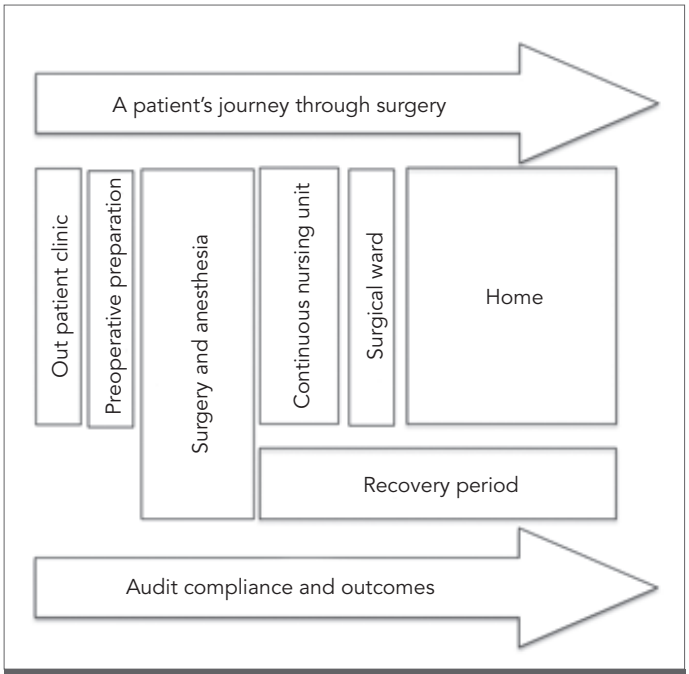

Figure 2. The journey of a surgical patient

One of the most important factors in the improvement after surgery is to fight against the metabolic trauma caused by surgery. ERAS aims to reduce the metabolic response to trauma thanks to modern surgery, anesthesia, analgesia, and some support applications. Thus, the process will end up with less damage and a quick recovery. The important point to note is that ERAS are not only surgeon's non-traditional practices, but also the performance of a trained team (23, 24, 26). Although there are the contributions of different team members in the process from the hospital admission to full recovery, surgeons, anesthesiologists, and nurses come to the forefront as the main actors. Under the leadership of these basic members of the team, all health professionals who will take part in the process should audit at least once in 15 days and evaluate the results and conduct training activities.

ERAS protocols go beyond the traditional and even dogmatic surgical and anesthetic applications, and they bring innovations that can be described as radical. The protocol includes more than 20 evidence-based elements to be applied in the perioperative period (Table 3) (23, 24, 26, 30, 31). These elements are grouped together by the ERAS Association in a way to include minor differences in guidelines prepared according to systems (http://erassociety.org/guidelines/list-of-guidelines/).

It is not possible to obtain good results by using one or more of the elements included in ERAS protocols. When all of the recommendations are implemented by a trained team, the contributions to the postoperative recovery process are seen. Each element has a synergical effect on another. The key issues such as proper management of pain, early mobilization, and providing early oral feeding through the proper management of gastrointestinal motility are supported by the use of many other elements.

In all recently published meta-analyses, it has been shown that the duration of hospitalization is reduced by 2-3 days, and the complications decrease by 30%-50% by applying ERAS protocols in major surgeries (32-35). The effect of adherence to protocols on the results is very clear. Mortality decreases by 42%-50% when the compliance to ERAS is higher than 70% (36, 37). As the cost analysis of ERAS protocols was puplished, it was understood that it also provided a very important advantage in this sense (38, 39). In particular, the cost analysis from the Canadian Alberta hospital chain was impressive, and it showed a profit of $2800-5900 per patient with ERAS protocols (40).

Prehabilitation

The necessity of medical optimization before surgery has gained a general acceptance. There have been many improvements in preoperative cardio-pulmonary preparation in the last 30 years, and as a result of this, mortality rates have been reduced (41). However, the same success could not be achieved with the complication rates arising with the coexisting problems such as obesity, diabetes, modern lifestyle, hypertension, and old age. In this sense, all patients who are to undergo major surgery should be operated after their general conditions are maximized to achieve success. In the recent years, the concept of prehabitation that is recommended to be performed in the preoperative period has been developed instead of the concept of postoperative rehabilitation (42).

Patients with diabetes should be well prepared preoperatively and should be closely monitored in the postoperative period. Patients with high levels of glycosylated hemoglobin (HBA1c) preoperatively remain approximately 1 mmol/L higher than patients with normal preopera-

Table 3. Components of ERAS protocol

Preoperative	Intraoperative	Postoperative
Preadmission counseling	Surgical incisions	Blood sugar management
Preoperative mechanical bowel preparation	Prevention of intraoperative hypothermia	Postoperative non-opioid analgesia
No prolonged fasting preoperatively	Mid-thoracic epidural analgesia	Early removal of urinary catheter
Preoperative oral carbohydrate loading	Short-acting anesthesia protocol	Stimulation of gut motility
Assessment of nutritional status and nutritional support if necessary	Prevention of postoperative nausea and vomiting	Early feeding / early enteral nutrition if necessary
Preoperative optimization	Perioperative fluid management	Early mobilization
Prehabilitation	No drains	Early discharge criteria
No premedication	Laparoscopic and robotic surgery	Audit of compliance and outcomes
Thromboprophylaxis	No nasogastric tubes	
Antimicrobial prophylaxis		

tive HbA1c levels, and additionally, more complications develop in these patients (43). As recommended in many guidelines, the blood glucose level should be aimed at around 140-180 mg/dL. Patients should be operated after the preparations are completed in the areas such as quitting cigarette smoking and alcohol consumption 4 weeks prior to the operation, exercise programs, reducing the risk of co-morbid diseases by conducting required consultations, and many other similar subjects.

Preoperative Nutritional Management

Surgical trauma results in significant endocrine and metabolic changes that increase catabolism. It also disrupts the immune response and reduces insulin resistance. In addition, inadequate food intake over 14 days causes an increase in morbidity and mortality (25). Planned or unplanned fasting along with surgical trauma results in an increased nutritional risk. With the widespread use of neoadjuvant chemo-radiotherapy in cancer patients, an additional burden to the deterioration of the nutritional status has emerged for patients receiving these treatments (44).

The European "NutritionDay" data of approximately 15,000 patients indicated the metabolic risk as a factor affecting hospital mortality, especially in the elderly (45). The high-risk patients in hospitals are mostly in the surgical, oncology, and geriatric clinics, and in intensive care units. The factors affecting the complication rates in hospitals are the severity of the disease, age over 70 years, surgery, and cancer. Considering the demographic developments in the Western world, surgeons must also deal with the risk in elderly patients undergoing major cancer surgery. Nutritional management is therefore an interdisciplinary field and has become a "necessity" for resource savings in the period of limitations in the health economy. Nutritional risk screening should definitely be performed at the time of hospitalization, and it should also involve the metabolic aspect of the surgery. There are many screening tools, but the Nutrition Risk Screening (NRS-2002) method is the one that has been officially proposed and validated by the European Society for Parenteral, Enteral Nutrition (ESPEN) (46). High complication rates were found in patients who were determined to be at risk with NRS. Preoperative tomography has been proven to be a valuable method in the detection of sarcopenia in patients with sarcopenic cancer (47).

Serious metabolic risk should be considered in the presence of one or more of the following criteria:

- Weight loss >10%-15%
- Body mass index <18.5 kg/m^2
- Serum albumin <30 g/L

However, it should always be kept in mind that serum albumin levels alone are not indicator of the nutritional status (48). Although albumin is a good laboratory parameter for postoperative morbidity, it does not give a clear information about the nutritional status due to its distribution in a large pool in the body, long half-life, and due to its changing levels in many diseases.

There is an indication of a nutritional plan in a patient who is unable to take 60% of his or her normal food for longer than 10 days in the preoperative period (29). In addition, even if no specific malnutrition is detected, there is an indication for perioperative nutritional support in a patient who is expected not be able to take food orally for more than 7 days.

There are different approaches to preparing the patient for surgery in terms of nutrition, which can be used in combination (25, 29, 49):

- Nutritional support if severe metabolic risk exists,
- Metabolic preparation (oral carbohydrate administration),
- Immunological modulation.

Postponement of the operation to complete the energy-protein deficiency or at least stop the hypercatabolic process is discussed only when there is a serious malnutrition or metabolic risk. If there is an indication of nutritional support, enteral route should be preferred. Enteral nutrition should be performed before hospitalization to prevent nosocomial infections. At this point, oral nutritional supplements (ONS) have an important role (29, 50, 51).

In severe malnutrition, parenteral nutrition is recommended in patients who can not be fed orally or enterally enough (52, 53). There is an indication of parenteral nutrition in patients with malnutrition, for whom enteral nutrition is not appropriate or in whom there is intolerance, including patients who have an impaired gastrointestinal system (GIS) function due to postoperative complications and who cannot receive and absorb adequate oral/enteral nutrition. Combined enteral-parenteral nutrition should be considered in patients who cannot meet 60%-75% of their energy requirement by enteral route (29, 54). Oral or parenteral nutrition support is usually maintained for approximately 7-14 days (14, 29, 48).

Obese patients constitute another group that is often neglected by surgeons. Many physicians think these patients are an energy and protein store and believe that there is no need for an aggressive nutritional therapy in the preoperative period. However, most these patients have sar-

copenic obesity, and their dry body masses are very low. This poses a serious risk for postoperative complications. In fact, when mortality is considered in surgical intensive care patients, morbid obesity is an independent predictor (55).

Keeping patients hungry at the preoperative night affects postoperative insulin resistance and negatively affects the results (56). The metabolic burden provided by perioperative hypoglycemia due to one-night fasting was clearly demonstrated, and the dogmatic information about preoperative fasting has changed completely (56, 57). Consumption of oral solid foods at night and liquids up to 2-3 h prior to surgery does not increase the risk of aspiration during anesthesia. Oral use of sugary fluids can be recommended for many patients because it does not prevent gastric emptying. It was shown that the oral solution containing 12.5% maltodextrin as the main substance decreases preoperative thirst, hunger, anxiety (58), and postoperative insulin resistance (56). Oral carbohydrate administration reduces postoperative nitrogen and protein loss (59), resulting in improved preservation of lean body mass and muscle strength (60). Patients who will undergo surgery should be given 800 mL of carbohydrate-rich liquid food until midnight preoperatively and 400 mL 2-3 h before the operation to ensure metabolic toughness. This practice has also been shown to significantly shorten the duration of hospital stay after surgery (57). Intravenous glucose infusion may be used in very few patients who cannot take food orally or enterally.

Postoperative Period

In the majority of patients after major abdominal surgery, the stomach returns to normal myoelectric functions within 24-48 h, the small intestines return to propulsive function within 12-24 h, and the colon returns to normal contractility within 48-72 h. Therefore, cessation of oral food after surgery in many patients is unnecessary, and it can be resumed within a few hours after surgery. It was shown[48] that a 75%-90% success rate was achieved when the feeding was started within 6-24 h postoperatively. It is now information based on clear evidence that early oral/enteral nutrition reduces infectious complications, regulates the metabolic response to surgery, and shortens hospital stay (61-63). It was also shown that the anastomotic leakage did not increase after GI tract operations with early feeding. Therefore, there is no valid reason for fasting for a long time after surgery. Oral feeding can be started without delay even after the operations with GIS anastomosis. In patients undergoing upper GI anastomosis, enteral nutrition can be performed via a tube placed distal to the anastomosis, and these patients may also drink ONS. In these patients, the nasojejunal tube or needle catheter jejunostomy (NCJ) placement as an enteral access is also suitable (64). After surgery, enteral tube feeding is started within 24 h and at a low rate (5-10 mL/h). The rate of administration is increased 10-20 mL/h per day. GI tolerance should be monitored carefully by performing abdominal examination. The most important issue that distresses clinicians is that it is not easy to distinguish GI intolerance due to early feeding and the early postoperative complications of major abdominal surgery. In such a situation, taking the easy ways such as interrupting feeding does not solve the problem. There are two critical moves to achieve optimal bowel functions. Early delivery of nutrients to the intestines and early correction of the changes in the pH or electrolytes (potassium>4 mEq/L, magnesium>2 mEq/L) are very important.

Postoperative early feeding, which is one of the most important components of achieving the targeted result with ERAS protocols, is supported by the combined use of some other elements included in the application. Thus, while long-term ileus is prevented, it is also possible to increase tolerance to early oral food intake. Early oral food intake is facilitated by many applications, such as avoiding preoperative fasting, analgesia at the mid-thoracic level, modern anesthesia management, target-specific perioperative fluid therapy, and early mobilization.

However, oral nutrition is unfortunately still delayed for some reasons (Table 4) (48). By changing a number of traditional, harmful, and unnecessary routines, the factors that prevent the transition to normal nutrition can be solved in the early period.

Parenteral Nutrition

While emphasizing the most important aims of ERAS protocols as giving oral food as soon as possible, using the digestive tract effectively, and early discharge, a question such as "Does parenteral nutrition still exist in this algorithm?" may come to mind. However, it is seen that it holds its own position in the recommendations made for perioperative period in the current guidelines (25, 29). There is a need for preoperative parenteral nutrition in patients with malnutrition who cannot receive oral feeding for 7 days for various reasons, and postoperative parenteral nutrition is needed in patients in whom oral/enteral feeding cannot be started within 7 days due to complications. In addition, in the daily practice, there are many patients in whom it is required to use both enteral and parenteral nutrition.

Discharge and Follow-Up

The follow-up of the nutritional status, including written monitorization of oral food intake, after major abdominal

Table 4. Factors that prevent early oral feeding
• Lack of understanding well the potential benefits of early feeding
• Poor understanding the postoperative ileus
• Unnecessarily waiting for the markers that are thought to show bowel activity
• Concern about complications o Aspiration o Bowel ischemia o Fear that feeding may cause anastomotic leakage
• Lack of feeding tube placement protocols
• Lack of communication among team members

surgery is a very important responsibility. Diet counseling, which is to be performed clearly enough for the patient, is also recommended. Oral calorie intake will be insufficient for months in most patients who undergo GI tract and pancreatic surgery. Reduction in appetite, deterioration of enteral tolerance due to "dumping" symptoms, bloating, and diarrhea are reasons that can cause this situation. If NCJ is placed during surgery, it should not be removed during discharge from the hospital. If necessary, 500-1000 kcal/day supplementary enteral nutrition may be given to patient through NCJ, even if he or she is able to receive oral food. After being trained, many patients will be able to do this on their own. Although it is not possible to prevent more weight loss, it has been proved that it can be reduced with oral supplementation. Even if patients with malnutrition in the preoperative period (especially those operated for upper GIS cancer) are managed without any problems during the period at the hospital, they should be discharged with ONS prescription, after explaining the correct and appropriate usage, and with the recommendations that they should be consumed as a supplement to normal food for 4-8 weeks. The quality of life is also significantly better in patients in whom supplementation is administered.

The Role of Pharmaconutrition

In recent years, the effects of some nutrients used for nutrition support in the perioperative period on the immune system have been investigated and discussed more seriously. There are different views on terminology, but when mentioning the effects of nutrients on the immune system, "pharmaconutrition" may be a more appropriate nomenclature.

The main nutritional elements that affect the immune system in various ways and about which investigations are made are arginine, glutamine, nucleotides, omega-3 fatty acids, fiber, prebiotics, probiotics, various antioxidants, and glutathione. The prominent biochemical effects of these formulas are increasing the cell membrane stability, supporting gastrointestinal mucosal integrity, enhance cellular immune response, and increase the blood flow in ischemic tissues. Thus, it is aimed to decrease postoperative infective complications and general morbidity as clinical results. Regardless of the nutritional status of the patient, there is strong evidence that preoperative pharmaconutrition reduces the length of hospital stay and postoperative complications (66-70). The SONVI study showed that postoperative complications could be reduced by the combined use of ERAS protocols and immune nutrients (71). In a recently published meta-analysis, the effect of different combinations of immune nutrients on mortality, morbidity, and the length of hospitalization in patients undergoing major abdominal surgery was investigated (72). The results of a total of 7116 patients in 83 randomized controlled trials were evaluated. It was found that immune nutrients decreased morbidity, mortality, and the duration of hospital stay. In the ESPEN and ASPEN guidelines, it is strongly suggested that pharmaconutrition should be administered for 5-7 days preoperatively and for 1 week postoperatively in patients who are to undergo major cancer surgery (25, 73). It is recommended that these products be used in patients who have a serious risk and will have a major operation (esophagectomy, gastrectomy, pancreatoduodenectomy) due to neck (laryngectomy, pharyngectomy) and abdominal cancer.

In a recent meta-analysis that examined many aspects of pharmaconutrition, 19 randomized controlled trials were evaluated, and with the conclusion that it reduced wound infections and hospital stay, it was suggested to be a part of the ERAS program in the upper GI cancer surgery (74).

The subject of the recent discussion is related to the timing of pharmaconutrition. It is examined whether the results are affected by its administration in the preoperative, postoperative, or perioperative period. While the benefits of perioperative pharmaconutrition were supported in a recent meta-analysis, it was shown that only preoperative administration did not affect the outcomes (68). In another meta-analysis published in the same year, it was found that there was no difference between standard oral supplements and immune nutrients in terms of the effect on outcomes, when they remained limited within the preoperative period (75).

The impacts of these specific products on the cost were also discussed and evaluated in many studies. Contrary to popular belief, these formulas have been shown to be cost-effective in many studies. In a systematic review of

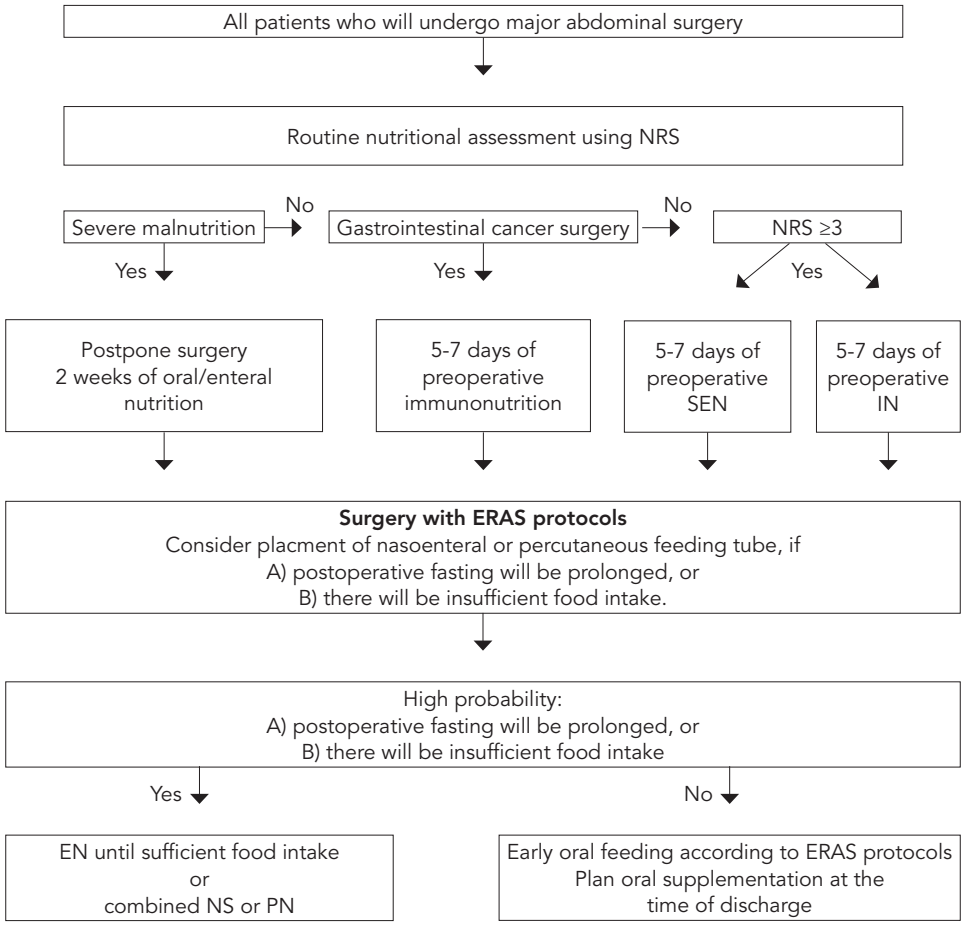

Figure 3. Perioperative nutritional planning algorithm

cost analysis of perioperative pharmaconutrition in patients undergoing GI cancer surgery, there were six prospective, randomized, controlled trials evaluated (76). Compared to standard oral supplements, it was shown that special products were more advantageous in terms of the total costs.

Conclusion

Nutrition is an important part of ERAS protocols, and nutritional status is an independent predictor of clinical outcomes. The perioperative nutritional management algorithm proposed for patients to be operated according to ERAS protocols starts with a routine nutritional evaluation and proceeds by targeting oral/enteral nutrition at each stage (Figure 3). Patients included in ERAS, especially the ones with malnutrition, nutrition should be integrated into the protocol to ensure an optimal perioperative management.

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Review

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Determination of the patients and management of their nutritional therapies with a new algorithm and a new multidisciplinary team for dysphagia

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ABSTRACT

Many studies have shown that the nutritional status of patients significantly affects the prognosis of treatment. The term dysphagia is used to describe swallowing disorders in clinical trials. This is the most difficult group about the ways in which nutritional treatment should be given to the patients who have functional gastrointestinal system but have the risk of aspiration due to dysphagia and blurred consciousness. A new algorithm has been developed to help clinicians make nutritional treatment decisions in this patient group in accordance with the experience of the Dysphagia Unit operating in our hospital since May 2017. The basic objective of the algorithm is to supply all nutritional needs of patients with dysphagia by minimal invasive procedures, minimal risk of infection, and minimal complication.

Keywords: Algorithm, dysphagia, clinical nutrition unit, dysphagia unit, swallowing disorders

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Introduction

Many studies have shown that the nutritional status of patients significantly affects the prognosis of treatment. The treatment of malnutrition and the appropriate support for the patient during treatment prevent bad clinical outcomes and reduce mortality. The treatment plan should be specified according to patient and treatment options, taking into account the general indications of nutritional supplementation. The most difficult group about the ways in which nutritional treatment should be given is patients who have functional gastrointestinal system but have the risk of aspiration due to dysphagia and blurred consciousness. On the other hand, avoidance from complications of total parenteral nutrition, instability in the timing of the use of the nasogastric tube, or percutaneous endoscopic gastrostomy (PEG) tube is the most common problem in this patient group.

The term dysphagia is used to describe swallowing disorders in clinical trials. Patients with dysphagia may be encountered in the hospital or community. The severity of dysphagia can be in different degrees, or it can affect the lives of individuals in different dimensions. Approximately 50% of the elderly with dysphagia ate less, 44% had weight loss, and 41% experienced anxiety or panic attacks during mealtimes (1). Therefore, there is a close relationship between dysphagia and nutritional status.

Patients with signs of dysphagia, even if they are obvious or slightly evident, should be evaluated by health professionals experienced in the diagnosis and treatment of dysphagia. These professional teams should include clinical nutritionists, otorhinolaryngologists, neurologists, and swallowing physiotherapists.

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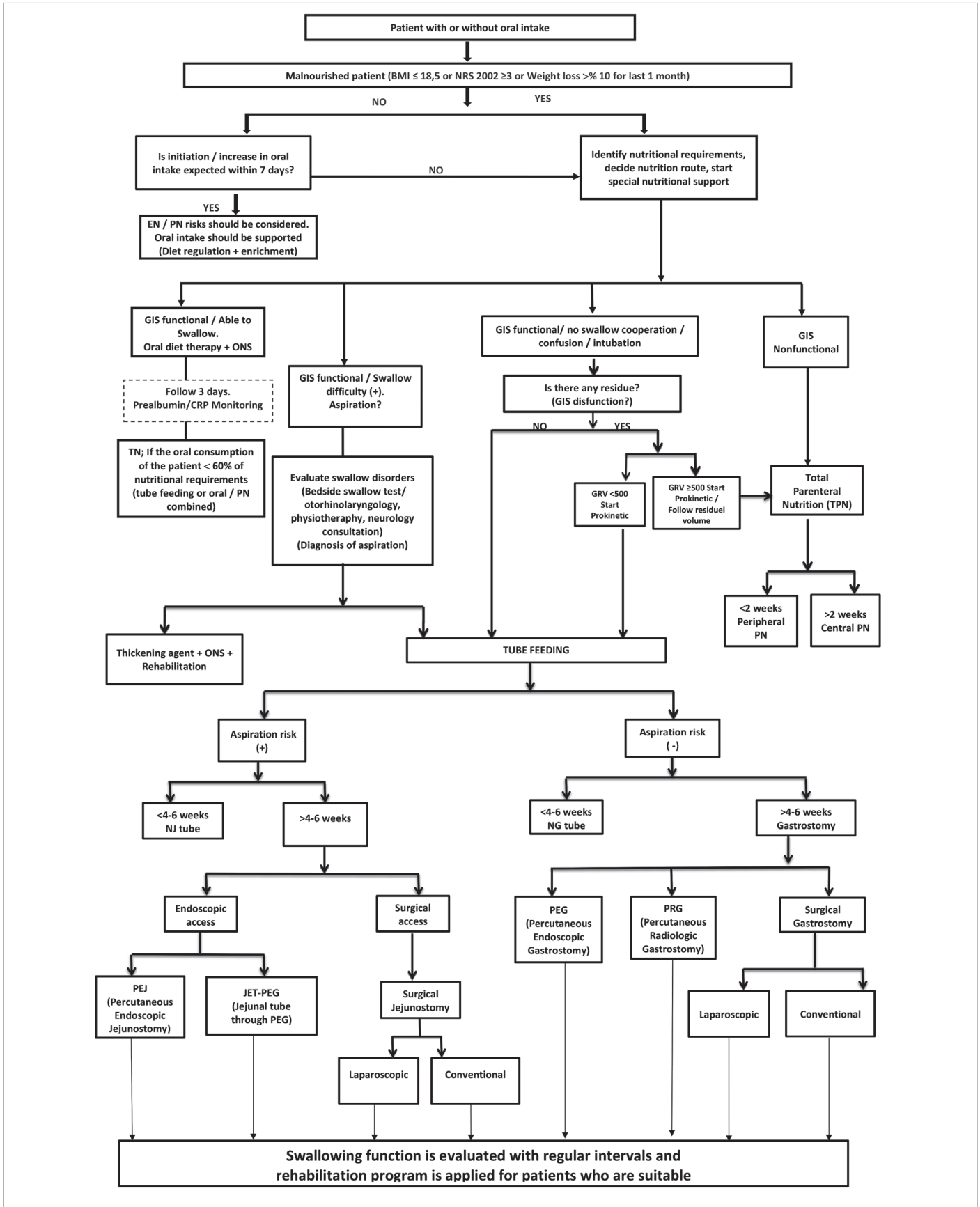

Figure 1. The algorithm used in the diagnosis and treatment of patients with malnutrition, especially with dysphagia

The aim of the present study was to present a treatment algorithm that can be used in the nutritional management of patients with dysphagia by evaluating the literature information and the experiences of the dysphagia team in our hospital.

Methods

The Dysphagia Unit of our hospital has been operating since May 2017. The 1-year experiences of the Dysphagia Unit have been evaluated.

The Dysphagia Unit in our hospital is a multidisciplinary team. It consists of neurologists, otorhinolaryngologists, and physiotherapy specialists in addition to the Clinical Nutritional Unit that includes gastrointestinal surgeons, gastroenterologists, dieticians, and nurses.

All patients with dysphagia are evaluated by this team. Swallowing dysfunctions are evaluated by otorhinolaryngologists with bedside swallowing test and direct laryngoscopy (these evaluations will be made by the fiberoptic endoscopic evaluation of swallowing, which is the most objective evaluation method) in the coming period. Central/peripheral nervous systems and neuromuscular diseases are evaluated by neurologists. As a result of these evaluations, patients who are suitable for swallowing physiotherapy are followed up by physical therapists. Patients whose diagnosis and rehabilitation process are completed are taken over by the Clinical Nutritional Unit, and nutritional therapy is planned.

There was a need to establish an algorithm to standardize the procedure and to provide practical convenience to all clinicians after a 1-year experience of the Dysphagia Unit.

The algorithm of this multidisciplinary study is presented in Figure 1.

Discussion

Health professionals should keep in mind that dysphagia may develop in people with acute or chronic neurological diseases and those who have undergone surgery or radiotherapy to the upper aerodigestive tract.

The cause of dysphagia can be either acute cerebral event, progressive neurological disorders, trauma, surgery, or diseases of the upper aerodigestive tract; it may also develop or worsen as a result of sepsis, respiratory diseases, or cognitive disorders (2).

The estimated prevalences of oropharyngeal dysphagia are 60% in nursing home residents and 12%-13% in hospitalized patients (3). Dysphagia prevalence in the general population >50 years old was reported to be 16%-22%. Specific conditions that may present with dysphagia include 27%-100% of patients with stroke, adults with learning disabilities (36% of patients with learning difficulties in the hospital and 5.3% of those in the community present with dysphagia) and between 48% and 100% of individuals with motor neurone disease (4). However, there are significant differences in the mentioned prevalences due to the time required to complete the evaluation and the variability in the application period (e.g., in stroke, the incidence of presentation with aspiration risk is 51% on admission, 27% on day 7, 6.8% at 6 months, and 2.3% after 6 months) (5).

If the diagnosis of dysphagia is delayed, this will lead to deficiencies in food and fluid intake that will result in nutritional deficiencies, infection, sepsis, and pneumonia. To avoid eating because of dysphagia may also lead to social isolation and high morbidity, mortality, and cost (3, 6). As a result, particularly since it is not always obvious that a patient has dysphagia, the patient should be assessed and managed by a multidisciplinary and skilled team.

Owing to the complex nature of dysphagia and the variation of its presentations, we recommend a multidisciplinary approach to make decisions that are based on individual patients' symptoms rather than specific diagnosis. The management of patients with dysphagia should take into account the appropriateness of intervention in individual cases, and all ethical/legal issues and decision processes should include the patient, family, and dysphagia teams. Dysphagia specialists should inform the clinical teams, especially before the clinician decides on invasive procedures, such as PEG.

In the management of patients with dysphagia, the patients should also be evaluated for swallowing disorders and nutritional and social status by health professionals experienced on the subject:

- The risks and benefits of modified oral nutrition support and/or enteral tube feeding,
- Recurrent pulmonary infections,
- Mobility,
- Dependency on others while eating,
- Perceived palatability and appearance of food or drink,
- Level of alertness,
- Compromised physiology,
- Impaired oral hygiene,
- Compromised medical status,

- Metabolic and nutritional requirements,
- Immune system disorders (e.g., immunocompromized),
- Presence of comorbidities.

The nutritional status of the patients is an important parameter in the early or recovery period following cerebrovascular disorders. Poor nutritional status is associated with delayed recovery, mortality, infectious complications, swallowing difficulty, and reduced activities of daily living (ADLs) (7, 8). The number of patients with protein-energy malnutrition was shown to increase by approximately 60% (16.3%-26.4%) in the first week after a stroke, leading to a higher mortality rate and a lower ADL (9). Nutritional support for patients with cerebrovascular disorders in the early period is known to result in better clinical outcomes, with studies showing that early nutritional therapy, especially with enteral feeding, improves nutritional status and is associated with lower mortality rates (10). An intensive nutritional therapy in patients with stroke may improve physical function to a greater extent than standard care in subacute and rehabilitation settings (11). Therefore, nutritional support may be a potential therapeutic strategy with better clinical outcomes for patients with postcerebrovascular disorder.

There are a number of possible treatment modalities that may help to maintain or improve the nutritional status of patients with oropharyngeal dysphagia. These include modification of the consistency, temperature, and/or taste of liquids and food.

The choice of PEG for long-term nutritional support in patients with neurological dysphagia compared with that of the nasogastric tube has been proposed as a level A recommendation in ESPEN's guideline of geriatric patients. Tube feeding is not recommended in patients with terminal dementia (evidence level; C) (12). However, the sociocultural realities of our country affect the decisions to be made in this regard. The right management should be constituted via a Dysphagia Unit that includes different disciplines.

In our algorithm, we planned a path according to these opinions to provide the least risk and highest benefit in patients with suspected swallowing disorders. We aimed to prevent the negative results of malnutrition due to dysphagia, to diagnose possible silent aspirations, and to reduce or delay invasive procedures, such as PEG, with swallowing rehabilitation, especially in appropriate patients. In addition, we aimed to increase the quality of life of the patients fed with a nasogastric tube or PEG by providing the transition to oral route by swallowing rehabilitation. We were able to achieve success, especially in young patients with trauma, in our clinical practice even with a limited number of patients.

While creating the algorithm, the ESPEN and ASPEN guidelines have been considered to determine the application, and we have attempted to offer functional solutions to the problems that we have encountered in clinical practice (13, 14).

The basic objective of the algorithm is to supply the nutritional requirements of patients with dysphagia by minimal invasive procedures, minimal risk of infection, and minimal complication.

In conclusion, dysphagia is a swallowing disorder that should be treated with a multidisciplinary approach. The algorithm that we use is not a certain application for each patient. However, each center should establish a multidisciplinary treatment algorithm for patients with swallowing disorders. In this regard, the algorithm we offer may be a preliminary study.

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Association of inflammation with nutritional status, lean body mass, and physical activity in non-dialysis-dependent chronic kidney disease

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ABSTRACT

Objective: Patients with chronic kidney disease (CKD) are susceptible to systemic inflammation and nutritional disorders, which are associated with morbidity and mortality. The aim of the present study was to evaluate the relationship between nutritional status, lean body mass, physical activity, and systemic inflammation in patients with stage 3-5 non-dialysis-dependent CKD.

Methods: A total of 55 predialysis patients with CKD were included in this cross-sectional study. Patients were divided into two groups according to the Subjective Global Assessment: 35 with normal nutritional status (NN) and 20 with malnutrition (MN). Anthropometric measurements, fat-free mass, muscle strength, physical activity, biochemical parameters, and serum cytokine levels of the patients were compared.

Results: Patients with CKD and malnutrition (CKD-MN) had higher serum phosphate, interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α levels and lower serum albumin levels and blood lymphocyte counts than those with CKD-NN independent from glomerular filtration rate. Regression analysis showed a relationship between MN and serum phosphate level, blood lymphocyte count, and serum IL-6 and TNF-α levels. Muscle strength and gait speed showed a positive relationship with nutritional status and negative relationship with inflammation.

Conclusion: An increased inflammatory environment in patients with non-dialysis-dependent CKD was significantly associated with MN and decreased physical activity. An increased serum phosphate level appears to contribute to this MN-inflammation environment.

Keywords: Cytokine, inflammation, kidney failure, malnutrition, predialysis

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Introduction

Chronic kidney disease (CKD) is an important public health problem. The Chronic REnal Disease In Turkey study showed that the prevalence of CKD in adults is 15.7% in Turkey, and that 1 out of every 666 persons has end-stage renal disease (1).

Markers of systemic inflammation are elevated in patients with CKD, which are associated with an increased prevalence of morbidity and mortality (2). Poor nutritional status, which is termed as malnutrition (MN), is also highly prevalent in patients with CKD. A number of evidence suggest that an increased inflammatory response with MN tends to coexist in patients undergoing chronic hemodialysis (3). Increased levels of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α are known to induce proteolysis and decreased protein synthesis, which can lead to decreased lean body mass (LBM) (3-5). In patients with CKD, an adverse consequence of MN is its potential detrimental effect on physical functioning. Since skeletal muscle mass, quality, and muscle strength are the main determinants of physical function, it is also possible that there is an interplay between exaggerated inflammatory response, MN, and physical functioning. In fact, Amparo et al. (6) showed a neg-

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ative correlation with muscle strength and MN-inflammation score in non-dialysis-dependent CKD.

The aim of the present study was to evaluate the relationship between nutritional status, as assessed by the Subjective Global Assessment (SGA), measurements of muscle mass, muscle strength, and physical activity, and inflammatory state, as assessed by serum proinflammatory cytokine concentrations, in patients with non-dialysis-dependent CKD.

Methods

Study population

The patients were recruited from the Nephrology Clinic in Istanbul University, Istanbul Medical Faculty Hospital, Turkey. Inclusion criterion was the presence of CKD with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 (CKD stages 3, 4, and 5). eGFR was calculated using the Modification of Diet in Renal Disease formula (7).

Exclusion criteria were malignant cancer, hospitalization within the last 3 months, any ongoing infection, chronic inflammatory diseases, such as inflammatory rheumatoid diseases, immunosuppressive drug use, and maintenance dialysis treatment.

The participants completed a questionnaire regarding their health status, current comorbidities, and drug use. The study was approved by the Istanbul University Istanbul School of Medicine Ethics Committee (25/02/2015-459). Informed consent was obtained from the patients.

Characteristics of the patients and nutritional status

Demographic characteristics, smoking habits, body mass index (BMI), blood pressure measurements, comorbidities (e.g., hypertension, diabetes mellitus, and cardiovascular disease), and medications were recorded. The nutritional status of the patients was evaluated using the SGA by the same doctor working within the Clinical Nutrition Team of the hospital (8).

Anthropometric measurements

Mid-upper arm circumference (MUAC) is measured from the middle point of the upper arm between the acromion of the scapula at the posterior part of the shoulder and the olecranon process of the ulna at the elbow. Calf circumference (CC) is measured from the widest point of the calf.

Muscle strength, LBM, and physical performance measurements

Muscle strength was measured using a standardized handheld dynamometer (Jamar Hydrolic Hand Dinamometer, Lafayette Instrument, Lafayette IN 47903 USA), which was determined as the best of three measurements made in the dominant hand. In patients who had only one upper extremity or who could use only one extremity, measurements were made with this extremity. Bioelectrical impedance analysis (BIA) was used to measure fat-free mass (FFM, kg) (BIA, Tanita, Japan). Physical performance was measured using the 10-meter walking speed. Anthropometric measurements, BIA, and physical performance measurements were completed by the same two nurses of the Clinical Nutrition Team.

Blood sample analysis

Blood sample analyses were performed after overnight fasting. The complete blood count was determined using a Beckman Coulter LH 780 (hemoglobin by photometry and others by impedance method). Blood urea nitrogen, creatinine, albumin, C-reactive protein (CRP), and glucose were determined using spectrophotometry with a Roche Cobas 8000 c702 analyzer.

Serum cytokine levels

Serum levels of TNF-α, IL-6, IL-8, IL-10, and IL-1β were measured using an enzyme-linked immunosorbent assay with commercially available kits (Diaclone Research, Besancon, France). Serum samples were separated, immediately centrifuged at 3000 RPM for 10 min, and stored at −80°C until assay.

All assays were conducted according to the manufacturer's protocols. These experiments were performed in duplicate, and the concentrations of cytokines in each sample were determined by extrapolating absorbance values to cytokine concentrations using the standard curve.

Statistical analysis

Statistical analysis was performed using IBM Statistical Packages for the Social Sciences 21.0 (IBM SPSS Statistics, Corp., Armonk, NY, USA) version 21. Data are expressed as mean±SD. Chi-square test was used for comparison of the distribution of variables. An analysis of variance (ANOVA) was used to assess the difference between the arithmetical averages adjusted for multiple comparisons. ANOVA or Mann-Whitney U test was used for comparisons between the groups when results were distributed non-parametrically depending on the normality of the distribution of variables. The coefficient of variation is defined as the standard deviation percentage of the mean. Spearman coefficient (r) was calculated to determine the correlation between inflammatory markers and biochemical parameters. Linear and logistic regression analyses were used with appropriate samples. Significance tests were two-sided. A p-value ≤ 0.05 was considered as statistically significant.

Results

The demographic characteristics of the participants are shown in Table 1. The two main causes of CKD in our patients were hypertension and diabetes (43.6% and 36.4%, respectively).

Table 1. Demographic characteristics of the participants

	CKD-NN (n=35)	CKD-MN (n=20)
Age (year)	63.06±13.117	59.3±20.59
Sex		
Male	22 (62.9%)	8 (40%)
Female	13 (37.1%)	12 (60%)
CKD stage		
3	13 (37.1%)	5 (25%)
4	16 (45.7%)	7 (35%)
5	6 (17.1%)	8 (40%)
CKD cause		
Hypertension	17 (48.6%)	7 (35%)
Diabetic nephropathy	13 (37.1%)	7 (35%)
PCKD	2 (5.7%)	1 (5%)
Others	3 (8.6%)	5 (25%)
ACEI/ARB usage	22 (62.9%)	8 (40%)
Ischemic heart disease	10 (28.6%)	7 (35%)
Statin usage	10 (28.6%)	7 (35%)
GFR (mL/min)	26.71±11.8	20.4±12.03
CKD duration (years)	7.8±8.5	6.43±8.36
Smoking (pack-year)	23.6±36.15	11.68±28.6
Height (m)	1.64±0.07	1.60±0.12
Weight (kg)	80.0±14.3	66.2±17.2§
BMI (kg/m^2)	29.66±5.96	26.02±7.71
SGA stage		
A (normal)	35 (100%)	0
B (moderate MN)	0	12 (60%)
C (severe MN)	0	8 (40%)

§Significant difference between patients with CKD with or without MN (p≤0.01). PCKD: polycystic kidney disease; CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; SGA: Subjective Global Assessment; BMI: body mass index; GFR: glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

According to the SGA, 20 (36%) patients had MN (CKD-MN), and 35 patients had normal nutritional status (CKD-NN). MN was more prevalent in the later stages of the disease. No significant difference was found between the two groups when GFR was taken into consideration (Table 1). The CKD-MN group had higher serum phosphate and parathyroid hormone levels and lower serum albumin levels and blood lymphocyte counts (Table 2).

Patients with CKD-MN had lower MUAC, CC, and muscle strength than those with CKD-NN. Although BIA-FFM was lower in the CKD-MN group, it did not reach statistical significance (Table 3).

The median cytokine levels of the patients in different CKD stages did not show any significant difference (Table 4). CKD-MN had higher serum IL-6, IL-10, and TNF-α

Table 2. Laboratory measurements of the patients according to nutritional status

	CKD-NN (n=35)	CKD-MN (n=20)
WBC (mm^3/mL)	8677±1773	7697±1703§
Lymphocytes (mm^3/mL)	2202±742	1719±390§§
Hemoglobin (g/dL)	12.1±1.4	10.19±1.57§§
Creatinine (mg/dL)	2.73±1.21	3.92±2.11§
GFR (mL/min)	26.7±11.9	20.5±12.0
Albumin (g/dL)	4.2 (2.8-4.7)	3.9 (2.4-4.5)§
CRP (mg/L)	3.95 (0.20-34.0)	2.25 (0.22-26.80)
Vitamin B12 (pmol/mL)	285 (171-2000)	475 (160-1023)
25-Hydroxyvitamin D (ng/mL)	15.5±8.47	24.36±18.9
Transferrin sat. (%)	27.75±15.94	30.5±16.67
Ferritin	117±117	142±141
Calcium (mg/dL)	9.2±0.49	8.59±0.73§§
Phosphate (mg/dL)	3.84±0.6	4.57±1.07§§
PTH (pg/mL)	164.4±156.2	330.8±288§
Proteinuria (g/day)	1.19±1.33	1.93±2.09

§Significant difference between patients with CKD with or without MN (p≤0.05). §§Significant difference between patients with CKD with or without MN (p≤0.01). CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; PTH: parathyroid hormone; WBC: white blood cell count; GFR: glomerular filtration rate; CRP: C-reactive protein

levels than CKD-NN (Table 5). Serum albumin showed a negative correlation with IL-6 and CRP. Proteinuria was positively correlated with TNF-α and IL-10. BIA-FFM, MUAC, and CC showed no correlation with serum cytokines (Table 6).

Table 3. Assessment of anthropometric measurements, muscle mass, muscle strength, and gait speed of patients with CKD according to their nutritional status

	CKD-NN (n=35)	CKD-MN (n=20)	p
Weight (kg)	80.0±14.3	66.2±17.2	0.006
BMI (kg/m^2)	29.66±5.97	26.02±7.71	0.085
MUAC (cm)	31.9±4.4	28.7±4.2	0.013
CC (cm)	38.2±3.1	34.3±5.2	0.006
BIA fat (%)	28.5±11.7	23.6±12.9	0.164
BIA-FFM (kg)	50.5±11.7	44.2±14.8	0.091
BIA visceral fat (%)	12.2±4.0	8.3±5.8	0.008
Handgrip (kg)	31.3±8.8	25.3±9.2	0.029
Gait speed (m/s)	1.16±0.38	1.12±0.48	0.274

BIA: bioelectrical impedance analysis; BMI: body mass index; CC: calf circumference; CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; FFM: fat-free mass; MUAC: mid-upper arm circumference

Serum phosphate showed a positive correlation with IL-1β, IL-8, TNF-α, and weight loss and a negative correlation with serum albumin. In the regression analysis, serum phosphate levels showed an independent relationship with serum IL-1β (R^2=0.340), TNF-α (R^2=0.240), and IL-8 (R2=0.240). Logistic regression analysis showed a relationship between MN and serum phosphate level (p=0.003), lymphocyte count (p=0.005), IL-6 level (p=0.044), and TNF-α level (p=0.035).

Gait speed had a positive correlation with muscle strength (p=0.019) and a negative correlation with age, BMI, proteinuria, and serum IL-6 (Table 7). Muscle strength showed a positive correlation with serum protein levels and BIA-FFM and a negative correlation with age and serum IL-6 (Table 7). Both gait speed and muscle strength did not show any correlation with GFR.

Discussion

The prevalence of MN is between 20% and 50% in CKD (9, 10). Anorexia and cachexia in CKD can be related with

Table 4. Median cytokine levels of the patients in different disease stages

CKD stage	Stage 3 (n=17)	Stage 4 (n=22)	Stage 5 (n=13)	p
IL-1β (pg/mL)	5.73 (4.7-172)	6.6 (4.4-131.8)	7.28 (5.4-85.8)	0.054
IL-6 (pg/mL)	3.45 (1.1-201)	4.32 (0.9-171.9)	5.5 (1.3-287)	0.435
IL-8 (pg/mL)	10.78 (5.8-691)	16.1 (1.96-1326)	14.7 (2.5-814)	0.638
IL-10 (pg/mL)	0.80 (0.27-3.3)	1.1 (0.23-3.3)	0.98 (0.44-33.8)	0.474

CKD: chronic kidney disease; IL: interleukin

Table 5. Median cytokine levels of the patients according to nutritional status

	CKD-NN (n=35)		CKD-MN (n=20)	
	Median	25th-75th percentile	Median	25th-75th percentile
IL-8 (pg/mL)	11.76	7.8-19.6	24.51	8.8-546
IL-6 (pg/mL)	2.91	1.36-6.86	5.43§	3.15-47.6
IL-1β (pg/mL)	6.5	5.48-7.23	7.28	5.53-26.4
TNF-α (pg/mL)	12.5	11.5-19.8	17.38§	13.6-23.6
IL-10 (pg/mL)	0.77	0.54-1.63	1.47§	0.8-2.15

§Significant difference between CKD-MN and CKD-NN (p≤0.05). CKD-NN: chronic kidney disease with normal nutritional status; CKD-MN: chronic kidney disease with malnutrition; IL: interleukin; TNF-α: tumor necrosis factor-α

uremia, metabolic acidosis, inflammation, decreased oral intake, inappropriate protein restrictions, polypharmacy, depression, dialysis complications, and comorbidities, such as diabetes and heart failure (11, 12). In the present study, 36% of patients with CKD had MN, and patients with MN showed no significant difference in GFR when

Table 6. Correlation analysis of serum cytokines and CRP with biochemical parameters and indirect measurement of muscle mass

	IL-1β		IL-6		IL-8		IL-10		TNF-α		CRP	
	r	p	r	p	r	p	r	p	r	p	r	p
Calcium	-0.30	0.030*	-0.326	0.018*	-0.172	0.223	-0.326	0.018*	-0.134	0.342	-0.170	0.239
Phosphate	0.386	0.005*	0.234	0.095	0.388	0.005*	0.265	0.057	0.378	0.006*	0.253	0.076
GFR	-0.238	0.089	-0.124	0.383	-0.180	0.200	-0.228	0.103	0.042	0.769	-0.255	0.074
Albumin	-0.262	0.060	-0.307	0.027*	-0.283	0.042*	-0.252	0.071	-0.093	0.511	-0.329	0.020*
Proteinuria	0.273	0.052	0.167	0.241	0.196	0.168	0.326	0.020*	0.319	0.022*	0.175	0.253
PTH	0.191	0.180	0.121	0.399	0.139	0.331	0.326	0.019*	-0.017	0.903	0.075	0.606
Lymphocytes	0.073	0.605	-0.195	0.166	-0.087	0.540	-0.085	0.547	0.022	0.874	-0.130	0.367
MUAC	0.076	0.598	0.126	0.378	-0.016	0.913	-0.063	0.663	0.057	0.590	0.158	0.277
CC	-0.035	0.809	-0.040	0.778	-0.145	0.309	-0.173	0.225	-0.056	0.694	0.095	0.516
BIA-FFM	0.078	0.587	0.001	0.995	-0.064	0.657	-0.030	0.837	0.033	0.816	-0.052	0.725

*p≤0.05. BIA-FFM: fat-free mass measurement according to bioelectrical impedance analysis; CC: calf circumference; GFR: glomerular filtration rate; MUAC: mid-upper arm circumference; PTH: parathyroid hormone; TNF-α: tumor necrosis factor-α; IL: interleukin; CRP: C-reactive protein

Table 7. Correlation analysis of gait speed and muscle strength with anthropometric measurements, BIA measurements, biochemical parameters, and cytokines

	Gait speed (m/s)		Muscle strength (kg)	
	r	p	r	p
Age (years)	−0.443	0.001*	−0.568	0.001*
GFR (mL/min)	0.188	0.174	−0.039	0.779
BMI (kg/m^2)	−0.279	0.047*	−0.213	0.126
MUAC (cm)	0.185	0.180	−0.016	0.908
CC (cm)	0.041	0.769	0.150	0.285
BIA-FFM (kg)	0.080	0.578	0.383	0.005*
Albumin (g/dL)	−0.008	0.956	0.289	0.036*
Prealbumin (g/dL)	0.472	0.056	0.531	0.023*
Calcium	0.066	0.647	0.094	0.501
Phosphate (mg/dL)	−0.006	0.967	−0.173	0.217
PTH (pg/mL)	−0.098	0.493	0.046	0.746
Proteinuria (g/day)	−0.304	0.027*	0.159	0.269
CRP (mg/L)	−0.160	0.288	−0.160	0.276
IL-6 (pg/mL)	−0.491	0.001*	−0.296	0.037*

*Significant relationship (p≤0.05). BIA-FFM: fat-free mass measurement with bioelectrical impedance analysis; BMI: body mass index; CC: calf circumference; GFR: glomerular filtration rate; MUAC: mid-upper arm circumference; PTH: parathyroid hormone; IL: interleukin; CRP: C-reactive protein

compared with those with NN. Serum phosphate levels were higher in CKD-MN.

In our patients, MN was associated with decreased MUAC, CC, muscle strength, and visceral fat. In patients with CKD, decreased muscle and/or fat revealed lower survival rates, which was related with age, uremia-related metabolic acidosis, systemic inflammation, decreased appetite, dietary restrictions, MN, dialysis-related factors, comorbidities, and increased insulin and insulin-like growth hormone resistance. CKD-related cachexia causes FFM loss (13-15). Muscle strength is also important for evaluation of sarcopenia in CKD. It was found to be correlated with muscle mass in patients undergoing hemodialysis and peritoneal dialysis (16). Although FFM was lower in our patients with CKD-MN, it did not reach statistical significance. This might be related with the low number of patients in the study groups.

TNF-α, IL-1β, IL-6, and IL-8 are proinflammatory cytokines, and IL-10 is an anti-inflammatory cytokine. In the current study, IL-6 was found to be significantly higher in patients with MN. TNF-α and IL-10 levels were also higher in patients with CKD-MN than in those with CKD-NN. We found no relationship between serum cytokines and CKD stage or GFR. In patients with CKD, inflammation can be related with underlying disease, cardiovascular diseases, comorbidities, dialysis complications, and infections; each disease is related with increased morbidity and mortality (17). An experimental study by Tsujinaka et al. (18) demonstrated that proinflammatory cytokines cause anorexia by directly affecting the satiety center. Giving TNF and IL-6 to rats resulted in muscle wasting that could be reversed by anti-IL-6 antibodies. A negative relationship was shown between GFR and serum cytokine levels (19, 20).

According to our data, serum albumin was found to be negatively correlated with IL-6 and IL-8, which was also reported in previous studies (3, 21). Decreased serum albumin levels result in a vicious cycle of MN and inflammation by triggering oxidative stress and inflammation. IL-10 is an anti-inflammatory cytokine, and its level increases together with proinflammatory cytokines in patients with CKD (22). In our study, IL-10 level was higher in patients with CKD-MN ($p<0.05$). Thus, an increased inflammation in patients with CKD-MN may trigger IL-10 production to control proinflammatory activity.

Leukocytes are mainly active during infectious diseases. Uremia can induce leukocytosis. Sela et al. (23) indicated a positive relationship between the degree of kidney failure and total blood leukocyte and neutrophil counts. Our patients with CKD-MN had lower leukocyte and lymphocyte counts than those with CKD-NN ($p<0.05$). As such, MN can cause lymphopenia. Patients with anorexia nervosa showed changes in bone marrow histology, such as hypoplasia and aplasia, which were found to be correlated with weight loss (24, 25). Accordingly, MN and weight loss can cause leukopenia and lymphopenia in CKD.

Serum phosphate levels showed an independent relationship with MN, lymphocyte count, IL-6, and TNF-α in our patients. A cell culture and animal study on phosphate and inflammation-MN showed diet phosphate load-induced MN and increased serum TNF-α levels (26). In addition, serum phosphate level was found to be correlated with each MN-inflammation-atherosclerosis component, such as phosphate load-induced inflammation, decreased albumin synthesis, increased albumin degradation, and muscle atrophy. All of these contribute to MN (26). Our results support the fact that serum phosphate level contributes to MN-inflammation. Our patients with CKD-MN had higher serum phosphate levels than those with CKD-NN.

Assessment of nutritional status in patients with CKD can be difficult. As GFR decreases, fluid retention causes edema; therefore, patients and physicians cannot realize their weight loss. The present study also showed some important clues about anthropometric measurements in the diagnosis of MN. Simple measurements during follow-up can be useful in determining patients at risk for MN, such as serum albumin with CRP, serum phosphate, MUAC, and CC.

Decreased GFR was found to be related with immobility, frailty, and increased mortality in CKD (27). Lower gait speed was related with increased all-cause mortality (13). Our results showed a negative correlation between 10-meter walking speed (m/s), age, BMI, fat mass, and IL-6 and a positive correlation with muscle strength, blood hemoglobin level, and serum transferrin saturation ($p<0.05$). An association between gait speed and muscle strength was shown in previous studies (28). Thus, the lower gait speed, MUAC, CC, muscle strength, and higher IL-6/TNF-α in our patients with CKD-MN indicate a possible relationship of MN, inflammation, and sarcopenia in these patients.

The present study had a few limitations. First, the study had a low number of patients in the study groups. MN is particularly seen in severe renal insufficiency on renal replacement therapy and occurs in patients with multiple comorbidities. Exclusion of such patients resulted in a reduced number of patients recruited to the study groups. Second, dual-energy X-ray absorptiometry and magnetic resonance imaging are the gold standards for evaluation of muscle mass; however, both cost and difficulty in appli-

cation forced the use of BIA in our patients, which is also used effectively in many studies.

In conclusion, to the best of our knowledge, this was the first study to evaluate inflammation in non-dialysis stage CKD according to nutritional status, muscle mass, muscle strength, and physical activity of the patients. As a result, patients with CKD showed increased inflammatory environment that was significantly aggravated with MN. Increased serum phosphate levels appear to contribute to this MN-inflammation environment. Serum albumin level, blood lymphocyte count, and anthropometric measurements can also be used to predict patients at increased risk for MN and sarcopenia. It appears that decreased muscle mass was mainly related with MN. Muscle strength and gait speed showed a relationship with MN and inflammation. Further studies are needed with more patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine (25/02/2015- 459).

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

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Retrospective evaluation of the effect of nutritional status of patients with left ventricular assist device on clinical results in the postoperative period

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ABSTRACT

Objective: Malnutrition in patients undergoing left ventricular assist device (LVAD) implantation has negative consequences, such as infection and limited functional capacity. The effects of nutritional status of patients with LVAD on their clinical outcomes were investigated.

Methods: Patients with LVAD implantation were retrospectively analyzed. For nutritional evaluation, nutrition risk score NRI score was calculated to divide the patients first into two groups with and without malnutrition risk (MR) then three subgroups (mild/moderate/severe) according to malnutrition risk. Demographic and clinical data before LVAD, early postoperative adverse events after LVAD, prognostic data, and laboratory findings were analyzed.

Results: Sixty patients (9 females) had a mean age of 46.1±14.3 years; mean NRI score was 99.6±10.2. Interagency Registry for Mechanically Assited Circulatory Support (INTERMACS) scores were determined as 1 (n=10), 2 (n=18), 3 (n=11), and 4 (n=21). Thirty-two patients (53.3%) (6 mild, 25 moderate, 1 severe) had MR. The MR was higher in patients with preoperative INTERMACS score 1, acute renal injury (AKI), emergency LVAD indication, mechanical ventilation (MV) and preoperative ICU requirement. The incidence of adverse events was found to be significantly higher in patients with low-grade NRI and early postoperative MR. Postoperatively, the duration of renal replacement therapy (RRT), MV, ICU and hospital stay and the need for heart transplantation and mortality did not differ between the two groups.

Conclusion: In the early postoperative period, a MR of 53.3% was detected in patients who underwent LVAD. Total 68.8% patients had adverse events. We found that the presence of MR was effective in predicting postoperative adverse events according to NRI score before LVAD treatment.

Keywords: Intensive care unit, left ventricular assist device treatment, malnutrition risk, NRI scoring system

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Introduction

Left ventricular assist device (LVAD) implantation is successfully applied all over the world and in our country for the treatment of end-stage heart failure with an aim to bridge decision making, bridge to candidacy, bridge to transplantation (BTT), and long-term destination therapy (DT) (1, 2). The assessment and support of nutrition is an integral part of LVAD treatment. Nutrition disorder and cardiac cachexia contribute toward a series of postoperative problems that have long-term negative effects such as infection and limited functional capacity (3-5). Therefore, body mass index (BMI) has become an important determinant of cardiac results in the selection of patients under LVAD implantation application.

Mortality in chronic heart failure patients is in close relation with classic markers such as BMI and albumin values. However, the reliabilities of both these parameters are insufficient when evaluated individually since they can be influenced by inflammation, fluid loading, hepatic impairment, kidney problems, and changes in blood volume (6). While the indirect calorimetry method is used for the detection of energy consumption

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of patients under LVAD therapy, bedside malnutrition risk evaluation is assisted by risk scoring systems, such as ESPEN-NRS 2002 and nutritional risk index (NRI).

In patients under LVAD treatment, NRI-a practical and fast applied nutrition evaluation tool-has been used during patients' application to cardiovascular surgery polyclinics and intensive care units. When technical equipment is present, the use of indirect calorimetric measurement methods for the detection of energy consumption measurement in daily applications has been suggested in patients with high malnutrition risk (7).

In our study, we aimed to evaluate the retrospective effects of nutrition on the clinical results in LVAD-applied patients during the early postoperative period using NRI.

Methods

After the approval from the Ethics Committee of Baskent University Medicine Faculty September 25, 2018 (KA18/278), patients accepted postoperatively after LVAD implantation in the cardiovascularw surgery's intensive care unit were included in this retrospective study. In order to calculate the NRI scores, patients with insufficient data on serum albumin and body weight were excluded.

The patients were divided into two groups: as malnutrition risk present (MRP) (NRI≤99) and no malnutrition risk (NMR) (NRI≥100) according to their NRI scores. In the next step, the MRP group was subdivided into three groups: severe (NRI<83.5), moderate (83.5≤NRI<97.5), and mild (97.5≤ NRI<100) according to their NRI scores.

The BMI (kg/m^2) values of the patients under investigation were calculated using their heights and weights.

The demographic data, including age, gender, height, current weight, BMI, ideal body weight (IBW), and maximum-minimum and average NRI scores, were recorded.

Clinical data prior to LVAD therapy, namely, the indication of LVAD treatment, bridge to decision making, bridge to candidacy, bridge to transplantation (BTT), long-term therapy (destination therapy (DT)), associated diseases (ischemic heart disease, hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, acute kidney injury (AKI), chronic kidney injury (CKI), and thyroid diseases), number of patients and their values in percentage, and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scoring system values for the scoring of cardiac impairment, were evaluated. Preoperative LVAD therapy urgency, needs for dialysis, intensive care, mechanical ventilator and dobutamine, values of tricuspid annular plane systolic excursion (TAPSE), left ventricular ejection fraction (EF, %), and pulmonary artery pressure (PAP) using transthoracic echocardiography were examined.

All these data were categorized into two groups: MRP and NMR. Adverse events after LVAD treatment (SVDC thrombus, wound debridement, AV groove rupture, tamponade, intracranial hemorrhage, arrest, and hemorrhages in all the other bodily regions except RVR, RVDC, RVAD requirement, and sepsis) were retrospectively analyzed and compared between the groups. The distribution of the prognostic clinical finding and comparison between the groups were studied after LVAD therapy.

In the biochemical tests performed in the biochemistry laboratory, creatinine, blood urea nitrogen (BUN), and albumin values on the preoperative and postoperative days 2 and 7 were evaluated. Their values between and within the MRP and NMR groups were analyzed.

Statistical analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. During data evaluation, besides the descriptive statistical methods (average, standard deviation, median, frequency, ratio, minimum, and maximum), the quantitative data of the two groups showing normal distribution were compared using the Student's t-test, while the Mann-Whitney U-test was used for data without normal distribution. Pearson's chi-squared test, Fisher-Freeman-Halton exact test, and Fisher's exact test were used for comparing the qualitative data. The follow-up of the variable without normal distribution was performed with the Friedman test, and Wilcoxon signed-rank test was used for the evaluation of the paired comparison. The in-group evaluation of data with normal distribution was performed with paired sample T-test. The significance was evaluated at $p<0.05$.

Results

A total of 60 cases, 51 M (85%) and 9 F (15%), with ages varying between 9 and 73 years, who were accepted to the intensive care unit after LVAD application, were included in this study. The age of the patients was 46.1±14.3 years; BMI was 24.9±4.9 kg/m^2; IBW was 64.4±6.8 kg. The distribution of clinical data before LVAD treatment is shown in Table 1.

The average NRI score in the patients was calculated to be 99.6±10.2. According to the NRI scoring system, a score of 32 (53.3%) shows the risk for malnutrition. Malnutrition risks were classified as mild, moderate, and severe in 6 (10%), 25 (41.6%), and 1 (1.7%) cases, respectively (Table 2).

Table 1. Data distribution before LVAD treatment		
Data before LVAD treatment		**n (%)**
LVAD treatment indications	DT	31 (51.7)
	BTT	23 (38.3)
	Bridge to candidacy	2 (3.3)
	Bridge to decision making	4 (6.7)
Associated diseases	Ischemic heart disease	27 (45.0)
	AKI	7 (11.7)
	CKI	3 (5.0)
	Diabetius Mellitus	20 (33.3)
	Hypertension	22 (36.7)
	COPD	12 (20.0)
	Thyroid diseases	8 (13.3)
INTERMACS Scores	Score 1	10 (16.6)
	Score 2	18 (30)
	Score 3	11 (18.3)
	Score 4	21 (35)
The presence of urgent need for LVAD treatment		14 (23.3)
Need of dialysis		12 (20.0)
Need of intensive care		36 (60.0)
Need of mechanical ventilation		5 (8.3)
Need of dobutamine		27 (45.0)
TAPSE (mm)	Min-Max (Median)	8-25 (13)
	Mean±SD	13.6±3.8
EF (%)	Min-Max (Median)	8-55 (18)
	Mean±SD	18.8±6.4
PAP (mmHg)	Min-Max (Median)	25-90 (55)
	Mean±SD	55.0±12.7

LVAD: left ventricular assist device; DT: destination therapy; BTT: bridge to transplantation; AKI: acute kidney injury; CKI: chronic kidney injury; COPD: chronic obstructive pulmonary disease; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support Scoring; TAPSE: tricuspid annular plane systolic excursion; EF: ejection fraction; PAP: pulmonary artery pressure; SD: standard deviation

A statistically significant difference was not detected between the ages of the patients in the presence of malnutrition (p>0.05). The frequency of malnutrition is higher in female patients (p=0.029). BMI values were lower in the MRP group in the presence of malnutrition (p=0.001). IBW measurements were similar in the MRP and NMR groups (p>0.05). Patients with MRP have lower NRI values (p=0.001) (Table 3).

Left ventricular assist device therapy indications do not exhibit a significant difference between the two groups (p>0.05). In the MRP group, while the frequencies of ischemic heart disease, CKI, diabetes mellitus, hypertension, COPD, and thyroid disease do not show a statistically significant difference, the elevated level of the AKI frequency was found to be statistically significant (p=0.012) (Table 4).

When the INTERMACS scores were 2, 3, and 4, no significant relation existed with the malnutrition frequency; MRP was statistically more common in patients with INTERMACS score of 1 (p=0.001). Patients with urgent LVAD therapy indications had statistically high MRP scores (n=11, 34.4%) (p=0.0). Between the groups, the patients with the need of dialysis and dobutamine support did not show a statistically significant difference (p>0.05). A statistically significant difference between the two groups was detected in terms of the intensive care unit ratios (p=0.011): patients with MRP had higher ratios (n=24, 75%). Further, a statistically significant difference was observed between the groups when the need for mechanical ventilation support prior to LVAD therapy was considered (p=0.029): the MRP group is in additional need of mechanical ventilation support (n=5, 15.6%) (Table 4).

After LVAD treatment, during CVS intensive care unit follow-up, adverse events were not observed in 43.3% (n=26) cases, while they were present in 56.7% (n=34) cases. Depending on the presence of malnutrition, the occurrence of adverse events after LVAD treatment shows statistically significant difference between the groups (p=0.043); adverse events after LVAD treatment are more frequent in the MRP groups (n=22, 68.8%). The need for dialysis (RRT), mortality, and heart transplantation therapy after LVAD treatment do not show a statistically significant difference between the two groups (MRV/MRY) (p>0.05). Depending on the presence of malnutrition, the duration at the intensive care unit, hospitalization, and mechanical ventilation support do not show a statistically significant difference between the two groups (p>0.05) (Table 5).

Depending on the presence of malnutrition, creatinine values on preoperative day (creatinine 1), postoperative day 2 (creatinine 2), and postoperative day 7 (creatinine 3) do not show a statistically significant difference (p>0.05). In the

NMR group, changes in the creatinine 1, 2, and 3 measurements were statistically significant (p=0.001). Comparative analyses have shown that there was an increase in creatinine at the second measurement as compared to that at the first measurement (p=0.013); there was a decrease in creatinine in the third measurement as compared to that at the first measurement (p=0.010); and there was a decrease in creatinine in the third measurement as compared to that at the second measurement (p=0.001); these were statistically significant (p<0.05) (Table 6). In the case of the MRP group, the preoperative (Albumin1) and postoperative (Albumin2) albumin values were significantly lower than those in the NMR group (p=0.001 and p=0.047, respectively). Further, the postoperative albumin values were statistically significantly and lower than the preoperative albumin values in the MRP cases (p=0.001) (Table 6).

Table 2. Classification of patients according to their malnutrition status using NRI scoring system

	n (%)
Malnutrition risk	
Absent (NMR)	28 (46.7)
Present (MRP)	32 (53.3)
MRP	
Mild	6 (10.0)
Moderate	25 (41.6)
Severe	1 (1.7)

MRP: presence of malnutrition risk; NMR: absence of malnutrition risk

Discussion

In this study, where the effects of the nutritional status in the LVAD during the early postoperative period were retrospectively evaluated using the NRI scores, the presence of malnutrition was detected in 53.3% cases in the early postoperative period. Patients who have AKI before LVAD treatment with an INTERMACS score of 1 and with urgent LVAD treatment indication and who are in need of treatment in the intensive care unit during the preoperative period have higher risks for malnutrition. When patients with higher risks for malnutrition were compared to those without such risks, 68.8% patients

Table 3. Evaluation of malnutrition risk according to demographic properties

Demographic properties	Malnutrition risk		p
	Absent (n=28) n (%)	Present (n=32) n (%)	
Age (year)			
Min-Max (Median)	31-68 (50.5)	9-73 (43.5)	[a]0.059
Mean±SD	49.7±9.1	43.0±17.2	
Gender			
Male	27 (96.4)	24 (75.0)	[b]0.029*
Female	1 (3.6)	8 (25.0)	
BMI (kg/m^2)			
Min-Max (Median)	20.4-36.5 (27.9)	13-31.8 (23)	[a]0.001**
Mean±SD	27.6±4.3	22.6±4.3	
IBW (kg)			
Min-Max (Median)	53-76.3 (65)	41-74 (65)	[a]0.243
Mean±SD	65.6±5.7	63.5±7.7	
NRI			
Min-Max (Median)	98.8-131.1 (105.4)	83.3-100 (92.8)	[a]0.001**
Mean±SD	108.2±7.6	92.1±5.0	

[a]Student's t-test, [b]Fisher's exact test, *p<0.05, **p<0.01. BKI: body mass index; IBW: ideal body weight; NRI: nutritional risk index; SD: standard deviation

Table 4. Comparison of clinical data before LVAD treatment in the presence of malnutrition			
	Malnutrition		
Clinical data before LVAD treatment	Absent (n=28) n (%)	Present (n=32) n (%)	p
LVAD treatment indications			
DT	17 (60.7)	14 (43.8)	[d]0.123
BTT	11 (39.3)	12 (37.5)	
Bridge to candidacy	0 (0)	2 (6.3)	
Bridge to decision making	0 (0)	4 (12.5)	
• Associated diseases			
Ischemic heart disease	15 (53.6)	12 (37.5)	[c]0.212
AKI	0 (0)	7 (21.9)	[b]0.012*
CKI	2 (7.1)	1 (3.1)	[b]0.594
Diabetes mellitus	12 (42.9)	8 (25)	[c]0.143
Hypertension	11 (39.3)	11 (34.4)	[c]0.694
COPD	5 (17.9)	7 (21.9)	[c]0.698
Thyroid diseases	2 (7.1)	6 (18.8)	[b]0.264
INTERMACS			
Score 1	0 (0)	10 (31.3)	[b]0.001**
Score 2	11 (39.3)	7 (21.9)	[c]0.142
Score 3	4 (14.3)	7 (21.9)	[c]0.448
Score 4	13 (46.4)	8 (25.0)	[c]0.083
The urgent need for LVAD treatment			
Absent	25 (89.3)	21 (65.6)	[c]0.031*
Present	3 (10)	11 (34.4)	
Need of dialysis			
Absent	24 (85.7)	24 (75.0)	[c]0.301
Present	4 (14.3)	8 (25.0)	
Need of intensive care			
Absent	16 (57.1)	8 (25.0)	[c]0.011*
Present	12 (42.9)	24 (75.0)	
Need of mechanical ventilation			
Absent	28 (100)	27 (84.4)	[c]0.029*
Present	0 (0)	5 (15.6)	
Need of dobutamine			
Absent	17 (60.7)	16 (50)	[c]0.405
Present	11 (39.3)	16 (50)	
TAPSE (mm)			
Min-Max (Median)	8-19 (14)	8-25 (12)	[a]0.343
Mean±SD	14.1±3.1	13.1±4.4	
EF (%)			
Min-Max (Median)	10-25 (18)	8-55 (18)	[a]0.564
Mean±SD	18.3±4.3	19.2±7.9	
PAP (mmHg)			
Min-Max (Median)	30-75 (52.5)	25-90 (55)	[a]0.184
Mean±SD	52.6±12.0	57.0±13.1	

•More than one disease is observed. [a]Student's t-test, [b]Fisher's exact test, [c]Pearson's chi-squared test, [d]Fisher-Freeman-Halton exact test, [e]Mann-Whitney U test, *p<0.05. LVAD: left ventricular assist device; DT: destination therapy; BTT: bridge to transplantation; AKI: acute kidney injury; CKI: chronic kidney injury; COPD: chronic obstructive pulmonary disease; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support Scoring; TAPSE: tricuspid annular plane systolic excursion; EF: ejection fraction; PAP: pulmonary artery pressure; SD: standard deviation

Table 5. Adverse events after LVAD treatment in the presence of malnutrition and evaluation of prognosis features			
	Malnutrition		
Adverse events after LVAD treatment	Absent (n=28) n (%)	Present (n=32) n (%)	p
Absent	16 (57.1)	10 (31.3)	[c]0.043*
Present	12 (42.9)	22 (68.8)	
LVAD trombus	1 (3.6)	5 (15.6)	
Wound debridement	3 (10.7)	6 (18.8)	
AV Groove rupture	0 (0)	1 (3.1)	
Cardiac tamponade	0 (0)	1 (3.1)	
Intracranial hemorrhage	0 (0)	1 (3.1)	
Arrest	1 (3.6)	2 (6.3)	
hemorrhage (other)	2 (7.1)	3 (9.4)	
RVDC RVAD	0 (0)	1 (3.1)	
Sepsis	4 (14.3)	1 (3.1)	
Wound debridement+Intracranial hemorrhage	0 (0)	1 (3.1)	
Cardiac tamponade+ Intracranial hemorrhage	1 (36)	0 (0)	
Prognosis after LVAD treatment			
Need for dialysis (RRT)			
Absent	21 (75.0)	22 (68.8)	[c]0.592
Present	7 (25.0)	10 (31.3)	
Duration at ICU (day)			
Min-Max (Median)	4-95 (11)	1-82 (16.5)	[e]0.161
Mean±SD	18.9±21.2	22,8±19,2	
Hospitalization duration (day)			
Min-Max (Median)	6-98 (30)	2-155 (36.5)	[e]0.150
Mean±SD	33.8±21.6	46.0±36.1	
Mechanical ventilation duration (hour)			
Min-Max (Median)	10-564 (24)	5-600 (40.5)	[e]0.265
Mean±SD	59.2±105.9	75.6±116.7	
Mortality			
Absent	18 (64.3)	16 (50.0)	[c]0.235
Present	10 (35.7)	16 (50.0)	
Heart Tx after LVAD treatment			
Absent	25 (89.3)	27 (84.4)	[b]0.712
Present	3 (10.7)	5 (15.6)	

[b]Fisher's exact test, [c]Pearson's chi-squared test, [e]Mann-Whitney U test, *p<0.05.

LVAD: left ventricular assist device; AV: atrioventricular; RVDC RVAD: Right ventricular assist device; ICU: Intensive care unit; RRT: renal replacement theraphy; SD: standard deviation

Table 6. Evaluation of creatinine, BUN, and albumin in follow-ups in the presence of malnutrition			
	Malnutrition		
	Absent (n=28)	Present (n=32)	p
Creatinine1			
Min-Max (Median)	0.6-3.9 (1)	0.6-3.2 (0.8)	0.073
Mean±SD	1.2±0.6	1.0±0.6	
Creatinine2			
Min-Max (Median)	0.6-4.8 (1.2)	0.5-3.4 (1.2)	0.084
Mean±SD	1.5±0.9	1.5±0.8	
Creatinine3			
Min-Max (Median)	0.5-4.6 (0.8)	0.4-3.8 (0.7)	0.700
Mean±SD	1.0±0.8	1.1±0.8	
[f]p	0.001**	0.001**	
[g]C1-C2	0.013*	0.001**	
[g]C1-C3	0.010*	0.388	
[g]C2-C3	0.001**	0.001**	
BUN1			
Min-Max (Median)	10-68.9 (20.5)	10-110 (22.7)	0.882
Mean±SD	27.2±16.3	26.7±18.6	
BUN2			
Min-Max (Median)	13-78.3 (28,3)	12-100 (40.5)	0.063
Mean±SD	33.1±16.8	42,1±20,9	
BUN3			
Min-Max (Median)	9-79.7 (20)	6-56 (19.1)	0.558
Mean±SD	28.7±20.4	23.6±13.7	
[f]p	0.002**	0.001**	
[g]B1-B2	0.004**	0.001**	
[g]B1-B3	0.639	0.507	
[g]B2-B3	0.060	0.001**	
Albumin1			
Min-Max (Median)	26-42 (38)	25-40,2 (32,9)	[a]0.001**
Mean±SD	37.5±4.0	32.9±4.1	
Albumin2			
Min-Max (Median)	25-39 (33)	24-38.7 (31)	[a]0.047*
Mean±SD	33±3.6	31±3.9	
[h]p	0.001**	0.004**	

[a]Student's t-test, *p<0.05, **p<0.01, [f]Friedman test, [g]Wilcoxon signed-rank test, [h]paired sample t-test.
Creatinine1: Preoperative creatinine; Creatinine2: Postoperative day 2 creatinine; Creatinine3: Postoperative day 7 creatinine; BUN1: Preoperative blood urea nitrogen; BUN2: Postoperative day 2 blood urea nitrogen; BUN3: Postoperative day 7 blood urea nitrogen; Albumin1: Preoperative albumin; Albumin2: Postoperative albumin; SD: standard deviation

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Clinical evaluation of the effectiveness of different nutritional support techniques in the intensive care unit

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ABSTRACT

Objective: Malnutrition is a common condition in patients admitted to intensive care units (ICUs). Proper nutritional support is essential to reduce malnutrition-associated morbidity and mortality. The aim of this study was to evaluate the effectiveness of different nutritional support techniques in ICUs on some nutritional and inflammatory biochemical parameters.

Methods: In this retrospective study, 143 patients with a history of admission to ICUs were divided into three groups according to form of nutritional therapy: oral nutritional supplementation (ONS), enteral tube feeding (ETF), and parenteral nutrition (PN). Patients' demographic characteristics, length of stay in the ICU, length of nutritional support, serum prealbumin levels, C-reactive protein (CRP) levels, and transferrin levels at the time of nutritional supplementation initiation and treatment discontinuation were evaluated.

Results: The change in median serum prealbumin, CRP, and transferrin levels measured on days when nutritional therapy was initiated and terminated was not statistically significant (p=0.537, p=0.635, and p=0.073; respectively) in patients with ONS. Median prealbumin (0.14 vs. 0.21 mg/dL; p<0.001) and transferrin saturation (1.55% vs. 1.87%; p=0.001) levels significantly increased in patients who received ETF. In addition, median CRP (85.5 vs. 30.8 mg/L; p=0.001) levels significantly decreased. In patients with PN, only a significant increase in prealbumin level (0.10 vs. 0.13 mg/dL; p=0.003) was observed. The increases in CRP and transferrin saturation levels were not statistically significant (p=0.730 and p=0.243; respectively).

Conclusion: In the present study, a significant improvement was observed in the prealbumin, CRP, and transferrin levels in patients supported with ETF. However, similar improvement was not observed in patients with ONS.

Keywords: Enteral nutrition, intensive care units, nutritional support, parenteral nutrition

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Introduction

Malnutrition is an extremely common condition observed in critically ill patients treated in intensive care units (ICUs). Studies have shown that the prevalence of malnutrition among patients in ICU is between 13% and 78% (1, 2). Moreover, malnutrition associated with an increased risk of infection, prolonged mechanical ventilation requirement, and delayed recovery period in these patients (3). Therefore, several studies investigating the factors causing malnutrition and the prevention of this condition are ongoing.

Nutritional support is the most important step in the prevention of malnutrition. Most patients in ICU are unable to receive sufficient energy and protein via oral intake; therefore, enteral (EN) or parenteral nutrition (PN) support is necessary in these patients (1-5). For conducting the meta-analysis of studies to compare the enteral and parenteral approaches in these patients, interpretation of the results is challenging because of the small and heterogeneous patient groups (4, 5). However, it is always recommended that the use of EN over PN in patients with an intact gastrointestinal tract. PN also should not be started until all strategies to maximize EN tolerance have been attempted; and lastly, PN could be considered as the primary approach for special situations wherein enteral nutrition cannot be applied (5).

Appropriate parameters are required for assessing nutritional status, determining the presence of malnutrition, and assessing the effectiveness of the nutritional support. Albumin, transferrin, prealbumin, and retinol-binding protein plasma levels are the biochemical parameters frequently used for the evaluation of nutrition and

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monitoring the response to this support. However, the fact that these parameters could be affected by factors other than nutrition, such as infection, excess hydration, corticosteroid consumption, liver and renal failure, or inflammatory conditions, should be considered (6, 7).

Enteral assists the continuation of the barrier function of the gastrointestinal system, prevention of mucosal atrophy, and inhibition of bacterial translocation (8). However, it has been reported that achieving desired nutrition levels via EN, particularly at the early stages of ICU, is difficult; there is a definite increase in morbidity and mortality due to energy deficit occurring at the long term (9). It is also considered to increase the risk of bacterial colonization and aspiration pneumonia in patients with high gastric residual volume (8, 10, 11). Meanwhile, PN is a nutritional support method that enables the nourishment of patients who have limited absorption capacity or nonfunctional gastrointestinal system or an issue causing an obstacle for EN. However, the time and the conditions for initiation, the duration of the support, and the timepoint of switching to EN are being discussed in patients in ICU receiving PN because in this patient group, although positive effect could be observed on the clinical course when appropriately applied, inappropriate use could result in metabolic or infectious complications, such as overnutrition, hyperglycemia, fatty liver, or sepsis (12, 13). Although it is recommended to meet the energy requirements during the early and late period, large prospective randomized controlled studies are warranted in this field (14, 15).

In the present study, we aimed to determine the effectiveness of different approaches used on patients in ICU receiving nutritional support via some biochemical markers and investigate the severity of the inflammatory response in patients.

Methods

The study was performed in accordance with the principles of the Helsinki Declaration, and written informed consents were obtained from the patients and/or their relatives. This study included patients aged ≥18 years who were supported with nutritional support for ≥3 days in the surgical ICU between March 2015 and June 2015. Patients from whom informed consents could not be obtained; those who were connected to mechanical ventilators for >48 hours or those with enteral or parenteral support for <3 days; hemodynamically instable patients who were treated with inotropic or vasopressor agents due to long-term uncontrollable sepsis; and patients with renal or kidney failure were excluded from this study. The calorie needs of a patient was calculated as 25-35 kcal/kg/day, and the protein support target was determined to be 1.2-1.5 g/kg/day depending on state of catabolism.

Within the indicated time interval, data of 143 patients who were followed at the "Nutrition Department" were obtained from the hospital database, ICU database, and patient files. The patients were divided and analyzed in three groups: those under oral nutrition supplementation (ONS), enteral tube feeding (ETF), and parenteral nutrition (PN). The demographic characteristics of the patients; diagnoses; length of stay in the ICU; nutritional support durations; and serum prealbumin, C-reactive protein (CRP), and transferrin levels at the time of initiation and termination of the nutritional support were recorded.

Statistical analysis

Statistical Package for the Social Sciences programme 15.0 version (SPSS Inc.; Chicago, IL, USA) was used for the evaluation of the data obtained from this study. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), where appropriate. Categorical variables were expressed as a percentage (%). The Chi-square test was used to compare categorical variables, whereas the Kruskal-Wallis test was used for the parameters not distributed normally in triple-group analyzes, and the Wilcoxon test was used for the evaluation of the differences among dependent groups. The significance level was accepted as $p<0.05$ in all statistical analyses.

Results

This study included a total of 143 patients. Of the 34 patients who underwent ONS, 9 (26.5%) were followed up for benign reasons and 25 (73.5%) for malignant reasons. Of the 54 patients who underwent ETF, 16 (29.6%) were benign and 38 (70.4%) were malignant. Additionally, of 55 patients who were treated with PN, 20 (36.4%) were followed up for benign and 35 (63.6%) for malignant reasons. No statistically significant difference was detected between patient groups in terms of age, gender, diagnosis, and length of stay in the ICU ($p>0.05$). However, nutritional support duration was significantly higher in patients under ETF support compared with others (8.01 days; $p=0.026$). The demographic and clinical features of the patients are presented in Table 1.

When the measurements were performed at the initiation and termination of the nutritional support in patients with ONS, the median prealbumin levels were 0.15 (0.03-0.41) and 0.16 (0.05-0.38) mg/dL, CRP values were 40.0 (0.8-166.0) and 23.1 (0.8-176.0) mg/L, and transferrin saturation levels were 1.65% (0.59-3.69) and 1.82% (0.61-3.17),

Table 1. Demographic and clinical features of the patients				
	ONS (n=34)	ETF (n=54)	PN (n=55)	p
Age	61.7±15.1	56.0±13.6	56.7±15.8	0.181
Gender (F/M)	9/25	12/42	21/34	0.169
Primary disease				
Benign	9 (26.5%)	16 (29.6%)	20 (36.4%)	0.216
Malignant	25 (73.5%)	38 (70.4%)	35 (63.6%)	
Nutritional support duration (day)	6.38±3.11	8.01±3.26	7.32±3.06	0.026*
Length of stay in the ICU (day)	7.76±3.37	8.68±3.50	9.38±3.33	0.062

* The statistical significance was obtained from the comparison of ONS and ETF. ONS: oral nutritional supplementation; ETF: enteral tube feeding; PN: parenteral nutrition; F: female; M: male; ICU: intensive care unit

Table 2. Median prealbumin, CRP, and transferrin saturation levels of the patients at the initiation and termination of the nutritional support						
	ONS (n=34)	ETF (n=54)	PN (n=55)	p^1	p^2	p^3
Prealbumin (mg/dL)						
Initiation	0.15 (0.03-0.41)	0.14 (0.03-0.31)	0.10 (0.02-0.29)	0.537	<0.001	0.003
Termination	0.16 (0.05-0.38)	0.21 (0.03-0.37)	0.13 (0.02-0.32)			
CRP (mg/L)						
Initiation	40.0 (0.8-166.0)	85.5 (4.5-296.0)	74.1 (1.5-323.0)	0.635	0.001	0.730
Termination	23.1 (0.8-176.0)	30.8 (0.9-321.0)	66.3 (2.0-209.0)			
Transferrin (%)						
Initiation	1.65 (0.59-3.69)	1.55 (0.63-2.43)	1.26 (0.47-2.48)	0.073	0.001	0.243
Termination	1.82 (0.61-3.17)	1.87 (0.60-3.25)	1.30 (0.11-2.06)			

p^1, The comparison of laboratory values of ONS measured at the initiation and termination, p^2, The comparison of laboratory values of ETF measured at the initiation and termination, p^3, The comparison of laboratory values of PN measured at the initiation and termination. ONS: oral nutritional supplementation; ETF: enteral tube feeding; PN: parenteral nutrition; CRP: C-reactive protein

respectively. However, there was no significant difference between the laboratory parameters of these patients on the days the nutritional support was initiated and terminated (p=0.537, p=0.635, and p=0.073 for prealbumin, CRP, and transferrin, respectively). Patients with ETF support had significantly increased levels of median prealbumin (0.14 vs. 0.21 mg/dL; p<0.001) and transferrin saturation (1.55% vs. 1.87%; p=0.001) at termination of nutritional support when compared with baseline levels; there was a definite decrease in CRP levels (85.5 vs. 30.8 mg/L; p=0.001). However, decrease in CRP levels (74.1 vs. 66.3 mg/L; p=0.730) and increase in transferrin saturation levels (1.26% vs. 1.30%; p=0.243) were not found to be significant (Table 2).

Discussion

Today, supplemental nutritional support for ICU patients is an integral part of routine treatment (1, 4, 16). Although a pragmatic approach remains to consider EN as the first choice for nutrition support, parenteral approach stands out at some special conditions where EN cannot be performed. In a recent multicenter randomized controlled study, it was reported that there is no difference in terms of the clinical results (30-day mortality, complications, hospitalization duration) between patients supported with EN or PN (1). Although the combined use of enteral and parenteral nutrition is the most commonly used method in clinical practice, the benefits of supplementary PN use are

still controversial in patients who are well tolerated and can be nourished to the targeted dose at a good level (5).

Another controversial point is the evaluation of nutritional status. Clinical evaluation, anthropometric measurements, score-based evaluation indexes, and physical functionality tests are the most common methods; however, there is no gold standard parameter. In addition, a marker which can show malnutrition precisely and definitely have not been defined in biochemical tests. In spite the fact that plasma proteins have limited validity, parameters such as prealbumin (transthyretin), retinol binding protein, fibronectin or CRP are frequently being used. The half-life of prealbumin which is among the most commonly used biochemical markers is two days. Measuring CRP at the same time is necessary since prealbumin is affected from inflammatory conditions because the decrease in prealbumin levels in cases where CRP remains constant is related to a poor nutritional status. The half-life of transferrin is eight days, but it is believed to reflect the recent nutrient intake more accurately (1, 2, 6, 14).

Despite the definite benefits of early enteral nutritional support, the use of oral nutrition in ICU patients is often limited and not effective due to mechanical ventilation, changes in patients' vital functions, and frequent surgical interventions (4, 5, 15). The guidelines recommend early initiation of enteral feeding in patients with functional gastrointestinal tract (14, 17). However, studies show that EN alone results in insufficient energy and protein intake (9).

In our study, as a result of the evaluation of 34 patients who did not need mechanical ventilation and who received ONS in ICU for various reasons, decrease in CRP and increase in the levels of prealbumin and transferrin saturation were found between the initiation and termination of nutritional support, but these changes were not statistically significant. Patients with ETF support were found to have significantly decreased serum CRP values at termination of nutritional support when compared with baseline levels, while serum prealbumin levels and transferrin saturation were significantly increased. In this study, there were significant changes in the levels of biochemical markers measured in patients with ETF which might be suggestive of positive clinical results. Although there were similar changes in the markers of ONS patients, no statistically significant difference was found. While this may be due to the patients in the ONS group having a better general clinical condition than the patients in the ETF group, it can also be due to the fact that nutritional support is administered at longer periods in the ETF group than in other groups. Another possible reason may be that the caloric requirement calculated in patients with ETF support can be reached at desired levels, while patients with ONS are not able to achieve a sufficient nutritional support for various reasons (failure to comply, inability to use the nutrition product effectively, vomiting).

The optimal energy balance in ICU patients is an important target. The inability of reaching the desired targets in enteral nutrition is common due to especially gastrointestinal dysmotility or hemodynamic conditions. In 2018, ESPEN (European Society for Clinical Nutrition and Metabolism) published a guideline on clinical nutrition in the ICU and stated that every patient staying in ICU for more than 48 hours had a risk of malnutrition. It is emphasized in the guideline that oral feeding is superior to all supportive therapies and that all patients who are not expected to receive oral nutrition should be supported early with EN (within 48 hours). The guideline also recommends that PN should be implemented within 3 to 7 days, in case of contraindications to oral and EN (14). In the present study, there was a statistically significant improvement in prealbumin level in patients with PN, but the decrease in CRP and the increase in transferrin saturation were not statistically significant.

The meta-analyzes of EN and PN performed in recent years have been shown that PN does not have a significant relationship with clinical adverse outcomes (16). Furthermore, reduced infection incidence due to a better understanding of the importance of central venous catheter care and adequate nutritional support with PN have reduced negative prejudices, regarding PN in ICU patients (1, 4, 5, 14, 16).

The main limitation of the study was that patients included in the study were not from a single ICU in the hospital but gathered from several units and the fact that the calories and protein requirements calculated for each patient were excluded from the evaluation. Another limitation is that the underlying pathologies and complications have not been evaluated. Our future studies should include nutritional assessments, risk classifications, complications during treatment, and clinical outcomes. However, the evaluation of the nutritional status of the patients by a single team and the application of the standardized nutrition plan were the strengths of this study.

In conclusion, a significant improvement was observed in the prealbumin, CRP and transferrin levels of the patients supported with ETF, in the present study. Only prealbumin level was significantly increased with PN support, while similar improvements were not observed in the biochemical markers of patients with ONS. This may be due to the inability of the ONS to reach the desired targets.

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: Written informed consent was obtained from the patients and/or their relatives who participated in this study.

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that exhibited adverse events, need for renal replacement therapy, mortality, heart transplantation, intensive care unit and hospitalization needs, as well as mechanical ventilation duration did not show a statistically significant difference.

Today, survival has reached up to 80% with long-term LVAD treatment (8). For success and survival, patients who benefit with high probability from this treatment should be carefully selected. The one-year survival ratio of advanced-stage cardiac failure has been stated as 80% in cases with INTERMACS scores of 2 and 3 (9, 10). Uribarri et al. (11) retrospectively analyzed 279 patients in terms of the malnutrition risk using NRI scoring with three groups (severe, moderate, and mild); the one-year survival ratios after LVAD treatment were determined to be 53.3%, 31.7%, and 23.1%, respectively. In the same study, while patients with mild malnutrition according to NRI scoring were more prevalent in the group with the INTERMACS score of 1 (n=7, 26.9%), the number of cases with severe malnutrition was high in the group with INTERMACS score of 2 (n=3, 20%). The NRI scoring system was discovered by the Veterans Affairs Total Parenteral Nutrition Cooperative Study Group that could be used during the preoperative period; it is reported to be a simple and reliable method for the inhibition of complications that might occur as a result of malnutrition after LVAD treatment (7, 12). In our study, malnutrition was detected in all the patients with an INTERMACS score of 1. There was no difference in the presence of malnutrition in the patient groups with INTERMACS scores of 2, 3, and 4. In our research, although we initially subcategorized the MRP group into three (mild, moderate, and severe), since only one patient was detected in the severe malnutrition group, comparisons were performed for two groups, namely, MRP and NMR. Eduardo Barge-Caballero et al. (7) showed that low scores in the NRI system are related to increased mortality, longer hospitalization durations, and hospitalization; since isolated criteria are used during the estimation of the malnutrition risk, it might have limitations in the reflection of nutrition status after heart transplantation. In our study, mechanical ventilation duration, mortality, and intensive care unit and hospitalization durations of patients with 53.3% malnutrition risk according to the NRI scores did not show a significant difference as compared to the NMR group, which is in contrast to the findings of Aziz et al. (12). The presence of malnutrition in our study was significantly higher in females as compared to males. These results may be attributed to the limited number of cases and this being a single-centered study.

In our study, while BMI is low in patients with malnutrition, there was no significant difference in the terms of IBW between the MRP and NMR groups. Al-Najjar and Clark (13) stated that calculating the BMI is easy in patients with advanced heart failure, but it is difficult to associate it with prognosis since mortality and VKA have a "U-shaped" relation. Meanwhile, Cowger et al. (14) emphasized that a low albumin level is an important indicator in the prediction of mortality. We have also detected that albumin levels in the MRP group during both preoperative and postoperative periods are significantly lower as compared to those in the NMR group. Critsinelis et al. (15) showed that the prealbumin levels are more specific and sensitive in the evaluation of protein malnutrition as compared to albumin, but the prealbumin concentration can be rapidly influenced by infections and inflammations, since it is an acute-phase reactant. One of the limitations of our study is the inability to retrospectively obtain the prealbumin levels of all the patients.

Thomas et al. (16) stated that deficits in malnutrition delay wound healing due to an impaired immune system, increase in postoperative complication ratios, and local and systemic infection risks. The same authors emphasized that the ideal time for the evaluation of nutrition in patients who are taken to an elective operation is from the first application to the hospital. In our study, in the MRP group, both the need for urgent LVAD and some adverse events occurring after LVAD have been found to be significantly higher. In our study series, the need for mechanical ventilation was found to be higher in the MRP than the NMR group before LVAD treatment.

Sandner et al. (17) found that in an 86-case cohort under continuous current LVAD treatment, mortality was increased in patients with AKI as compared to individuals with normal kidney functions. Meanwhile, the ratio of these AKI patients in need of cardiac transplantation is lower (18, 19). In our study, while no significant difference was observed in the occurring frequencies of ischemic heart disease, CKI, diabetes mellitus, hypertension, COPD, and thyroid diseases between the MRP and NMR groups, the AKI frequency was significantly higher in the MRP group. There was no significant difference between the groups in terms of the need for RRT after LVAD treatment.

Among the limitations of our study, being retrospective, single-centered, using a single parameter in the evaluation of nutritional status, and numerical imbalance between the groups due to a large patient cohort can be considered.

In our study, according to the NRI scores, the malnutrition risk during the postoperative period was shown to be present in one out of two patients who were subjected to LVAD. The early- and late-period complication frequencies were found to be higher in patients with malnutrition

risks. Considering these data, we believe that patients with planned LVAD treatment should be evaluated with easily applicable and effective tests (e.g., NRI scoring system) to determine detailed nutrition at the initial arrival to the hospital and nutrition support should be initiated according to these results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Baskent University School of Medicine (No: 25, Date: 2018).

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

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Assessment of the nutritional status with the nutritional risk screening-2002 in surgical patients: Single-center, descriptive study

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ABSTRACT

Objective: Malnutrition is common among surgical patients. It decreases surgical treatment, leads to poor clinical outcome, and especially substantially affects morbidity and mortality. This study aimed to assess nutritional risk in surgical patients.

Methods: This study was prospectively conducted in general surgery clinic. Patients aged above 18 years or more were included. Post-admission, data collection also included information on nutritional support and diagnosis of patients. A nutritional risk screening system (NRS-2002) was applied to all patients, and it was weekly repeated in patients with hospital stays more than one week.

Results: We enrolled 624 patients. Among them, 296 were male (47.4%), and 328 were female (52.6%). The mean age was 53.13±16.63 years. The route for nutrition was oral in 59.6% and enteral/parenteral in 4.8%. However, 35.6% of the patients received no nutritional support. Nutritional risk was recorded for 304 patients (73.4%) in first week and 46 patients (22.1%) in second week. Nutritional risk increased with age ($p<0.05$). There was nutritional risk in 193 patients (62.7%) with major abdominal surgery and 50 patients (46.7%) with hypertension. Additionally, there was nutritional risk in 162 patients (54.9%) who received oral diet.

Conclusions: Nutritional risk in the first week was very high in the patients. High nutritional risk was related to age, major abdominal surgery, and hypertension.

Keywords: Major abdominal surgery, malnutrition, minor abdominal surgery, nutritional risk screening

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Introduction

Malnutrition is defined as the structural deficiencies and organ dysfunctions related to deprivation of macronutrients and micronutrients that are the main requirement of tissues (1, 2). It is directly related to clinical outcomes such as delayed wound healing, impaired immune system, regression in cognitive functions, and reduced functional capacity. Depending on these, it can be seen that the healing period is prolonged, which causes an increase in health costs (long-term hospital stay, re-hospitalizations, primary care visits etc.) (3, 4).

The surgical patients from the groups at nutritional risk are noteworthy. Despite the favorable improvements in anesthesia and pre-operative care, malnutrition negatively affects 27-50% of patients. In surgical patients, hypermetabolism caused by surgical stress, failure to pay attention to increasing nutritional requirements due to catabolic status and insufficient nutritional support, the belief that the patient should be fasted for operation in the pre-operative period, and that oral intake in the post-operative period is longer than seven days are important factors in the development of malnutrition. Malnutrition is an independent negative predictive factor in the outcome of surgery and complications. It directly affects the success of surgical treatment, and leads to complications such as increased risk of infection in post-operative period, delay in wound healing, hypoproteinemic edema, decreased intestinal motility, susceptibility to hemorrhagic shock, bone marrow depression, and multiple organ failure. Thus, malnutrition prolongs hospital stay and increases morbidity and mortality (5-11).

The success of the surgical treatment depends on knowledge and experience of the surgeon, as well as on adequate nutri-

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tion of the patient during the pre-operative and post-operative periods. In particular, there is evidence that adequate nutritional support can avoid post-operative complications. Therefore, the nutritional status of the patient should be closely monitored and evaluated in terms of nutritional risk. Many screening methods have been developed. However, there is no consensus on the best screening tool to determine the nutritional risk in surgical patients. A retrospective analysis of 128 randomized controlled trials of nutritional support documented in the nutritional risk screening-2002 method (NRS-2002) method is more reliable and useful than other methods to determine patients with increased risk of post-operative complications of surgical patients, with more weight loss in the hospital, and length of hospital stay due to malnutrition (12-16).

Although malnutrition directly affects mortality and morbidity in patients undergoing surgical intervention, most clinics ignore it. Complete assessment of nutritional status is important to prevent adverse events before and after surgery. Efforts should be made to minimize malnutrition to minimize hospital stay and to ensure a better quality of life for the patient after surgery.

Methods

This study was prospectively performed in general surgery clinic. The study included 624 patients aged 18 years and above in the general surgery clinic. Patients were included in the study within 48 hours after admission. Pregnant-breastfeeding and transplanted patients were excluded. All patients were informed about the purpose of the study, and their consent was obtained.

Age, gender, and body mass index (BMI) of the patients were recorded. Diagnosis, comorbidity, major/minor operation, and nutritional route (oral, enteral, parenteral) were recorded. Major abdominal surgeries were gastric cancer, colon cancer, rectal cancer, pancreatic cancer, esophageal cancer, choledochus tumor, and pyloric stenosis. And minor surgery was accepted as Crohn's disease, pancreatitis, Fournier gangrene, cholelithiasis, diaphragmatic hernia, appendicitis, liver cyst hydatid, gastroesophageal reflux, umblical hernia, splenomegaly, anal fistula, hemorrhoid, bridectomy, and diverticulosis. Mass in the breast, granulomatous, morbid obesity, and adrenal mass surgeries were accepted as other surgical diseases.

The oral diet types of the patients included in the study were also examined, and the regimen 1 diet with the clear liquid diet was determined only as water. Combined diet was considered that regimen 2 and parenteral nutrition or regimen 2 and enteral nutrition.

For nutritional risk during hospital stay, patients were screened using the NRS-2002 form. First step of NRS-2002 form contains BMI>20.5, weight loss in the last three months, decreased food intake in the previous week, and presence of a severe disease. Patients with changes in at least these criteria were included in the study in the following weeks. In assessment, if at least one of first step is yes, then the second stage is passed. Three points and above is mean nutritional risk in second step of NRS-2002. Patients with nutritional risk were repeatedly screened during their hospitalization period.

Statistical analysis

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences Statistics (IBM SPSS Statistics Corp.; Armonk, NY, USA) 22 program. Student t-test was used for comparison of means, and chi-square test was used for categorical data. A value of $p<0.05$ was considered significant.

Results

In this study, 624 patients were included. There were 296 (47.4%) male and 328 (52.6%) female patients. The mean age of the patients was 53.13±16.63 years. A total of 414 patients (66.3%) in the first week and 208 patients (33.4%) in the second week were screened for nutritional risk. The patients were hospitalized with minor abdominal surgery (36.7%), major abdominal surgery (33.8%), and other surgical diseases (29.5%). The most common comorbidity disease was hypertension (47.3%), diabetes mellitus (29.6%), and coronary artery disease (11.3%) (Table 1).

The route for nutrition was oral diet in 59.6% and enteral/parenteral nutrition in 4.8%. However, 35.6% of the patients received no nutritional support. In the first week, 54.8% of the patients received oral diet, and 39.4% received no nutritional support. Of the 210 patients screened in the second week, 69.0% (145 patients) received oral diet, 28.1% (59 patients) received no nutritional support, and 2.9% (6 patients) received enteral/parenteral nutrition. (Table 2). Table 3 shows the oral diet types of patients. The majority of patients (44.9%) who received oral diet received regimen 3 normal diet.

In the first week, 73.4% of patients had nutritional risk; and in the second week, 22.1% (46 patients) had nutritional risk. The NRS-2002 scores of the patients in weeks are shown in detail in Table 4. Nutritional risk of patients according to various variables (age, diet, diagnosis, comorbidity) is shown in Table 5. It was observed that the nutritional risk increases with age.

Among the patients with nutritional risk, 62.7% (193 patients) had major abdominal surgery, and 36.7% (113 patients) had minor abdominal surgery ($p<0.05$). A rate of 32.5% of the patients had comorbidity. The highest nutritional risk was seen in patients with hypertension (46.7%). Also, 35.5% of the patients with diabetes mellitus, 7.5% of the patients with asthma, bronchitis or chronic obstructive pulmonary disease (COPD) had nutritional risk ($p<0.05$).

A total of 54.9% (162 patients) of patients who received oral diet, 42.1% of patients who received no nutritional support, and 27.6% (8 patients) of patients who parenteral nutrition had nutritional risk.

Table 1. Demographic characteristics of patients

Variable	Value
Age, mean±SD	53.13±16.63
Gender, n (%)	
Male	296 (47.4)
Female	328 (52.6)
BMI, mean±SD	23.68±5.30
Weeks, n (%)	
Week 1	414 (66.3)
Week 2	208 (33.4)
Diagnosis, n (%)	
Major abdominal surgery	211 (33.8)
Minor abdominal surgery	229 (36.7)
Other surgical disease	184 (29.5)
Comorbidity, n (%)	
Diabetes mellitus	60 (29.6)
Hypertension	96 (47.3)
Coronary artery diseases	23 (11.3)
Pulmonary diseases (COPD, bronchitis, asthma, etc.)	14 (6.8)
Neurological diseases (Epilepsy, cerebrovascular disease, etc.)	4 (2.0)
Other (gastritis, etc.)	6 (3.0)

*Mean±SD stands for Mean±Standard Deviation. BMI: body mass index; COPD: chronic obstructive pulmonary disease

Discussion

Malnutrition is a common clinical problem, and it is associated with high mortality and morbidity in surgical patients. In our study, nutritional risk was determined as 73.4% in the first week and 22.1% in the second week after hospitalization. The prevalence of nutritional risk rate in general surgery ranges from 6% to 30% (17-21).

As per KEPAN (Turkish Society of Clinical Enteral and Parenteral Nutrition), using the NRS-2002 scoring system, in our

Table 3. Oral diet type of patients

Diet	n	%
Clear liquid diet (regimen 1)	11	3
Full liquid diet (regimen 2)	94	25.3
Regimen 3 normal diet	167	44.9
Regimen 3 saltless diet	34	9.1
Diabetic diet	48	12.9
High potassium diet	4	1.1
Combined diet*	14	3.8
Total	372	100.0

*Stand for regimen 2 and parenteral nutrition or regimen 2 and enteral nutrition.

Table 2. Nutritional support of patients in screening weeks

	Weeks					
	Week 1		Week 2		Total	
Variable Route for nutrition	**n**	**%**	**n**	**%**	**n**	**%**
Oral	227	54.8	145	69.0	372	59.6
Enteral/parenteral	24	5.8	6	2.9	30	4.8
No nutritional support	163	39.4	59	28.1	222	35.6
Total	414	100.0	210	100.0	624	100.0

country, a multicenter study of 29,139 general surgery patients, nutritional risk was found to be 8.6% in 2005-2006 (22). Since the diagnosis of the patients is differently classified, the rate of nutritional risk obtained in other studies is different.

Jia et al. (23) evaluated the nutritional risk in 5042 surgical patients with NRS-2002. In the study, 10 kcal/kg/day energy intake was considered sufficient for the patients, and patients were followed in the general surgery clinic during their hospitalization. Nutritional risk was found in 19.2% of the patients. Although the patient groups included in the study were similar to those in our study, the nutritional requirements suggested in this study were lower than those predicted in our study. Therefore, different rates of nutritional risk were found. Among the factors affecting the incidence of malnutrition, the characteristics and age of the disease are important. Elderly patients are reported to have a high nutritional risk, especially due to physiological factors (23-25). In our study, nutritional risk was higher in elderly patients than in other age groups.

A total of 33.8% of patients who underwent major abdominal surgery had nutritional risk. Also, this group had a higher nutritional risk than other surgical patients. In multicenter prospective study, Sorensen et al. (20) screened 5052 patients in terms of nutritional risk in accordance with the classification of major and minor abdominal sur-

Table 4. NRS-2002 score of patients in screening week

	Week 1		Week 2	
NRS-2002 Score	**n**	**%**	**n**	**%**
0	1	0.2	90	43.3
1	42	10.1	50	24.0
2	67	16.2	64	30.8
3	177	42.8	4	1.9
4	91	22.0	0	0.0
5	31	7.5	0	0.0
6	5	1.2	0	0.0
Total	414	100.0	208	100.0
Total score				
NRS≤2	110	26.6	162	77.9
NRS≥3	304	73.4	46	22.1
Total	414	100.0	208	100.0

NRS-2002 nutritional risk screening-2002.

Table 5. Nutritional risk of patients characteristic

	No Nutritional risk		Nutritional risk		Total	
Variable	**n**	**%**	**n**	**%**	**n**	**%**
Age						
19-28	31	9.8	19	6.2	50	8.0
29-38	57	18.0	29	9.4	86	13.8
39-48	63	19.9	47	15.3	110	17.6
49-58	66	20.9	52	16.9	118	18.9
59-68	70	22.2	64	20.7	134	21.5
69+	29	9.2	97	31.5	126	20.2
Diagnosis						
Major abdominal surgery	18	5.7	193	62.7	211	33.8
Minor abdominal surgery	116	36.7	113	36.7	229	36.7
Other surgical disease	182	57.6	2	0.6	184	29.5
Comorbidity						
Diabetes mellitus	22	22.9	38	35.5	60	29.6
Hypertension	46	47.9	50	46.7	96	47.4
Coronary artery diseases	14	14.6	9	8.4	23	11.3
Pulmonary diseases (COPD, bronchitis, asthma, etc.)	6	6.3	8	7.5	14	6.9
Neurological diseases (Epilepsy, cerebrovascular disease, etc.)	2	2.0	2	1.9	4	1.9
Other (gastritis, etc.)	6	6.3	0	0.0	6	2.9
Route for nutrition						
Oral	210	63.8	162	54.9	372	59.6
Enteral	0	0.0	1	0.3	1	0.2
Parenteral	21	6.4	8	2.7	29	4.6
No nutritional support	98	29.8	124	42.1	222	35.6

COPD: chronic obstructive pulmonary disease

geries in NRS-2002. In 44% of patients who underwent major abdominal surgery, 22% of patients who underwent minor abdominal surgery were detected with nutritional risk. Nutritional risk was reported in 44%-50% of patients in most studies that evaluated the nutritional risk in patients with major abdominal surgery (26, 27).

Surgical patients who received nutritional support had lower nutritional risk than those who did not receive nutritional support. And it is stated that the rates range from 14.7% to 25%. However, in our study, patients who received nutritional support were at a higher nutritional risk (28, 29).

There were some limitations in our study. According to NRS-2002, it did not contain sufficient and detailed information to classify diseases. In addition, nutritional risk above three points may not be considered as standard, and may be adapted to the disease.

Due to the existing disease of the patient and the complications that may arise due to this disease, malnutrition is a common condition among hospitalized patients. Nutritional deficiency has a significant effect on treatment and survival. All surgical patients who have had an operation and will undergo the operation are patients with high risk of malnutrition. In such patients, care should be exercised more carefully during nutritional assessment, and should be frequently repeated during hospitalization. The nutritional status of the patient should be first determined by using an effective and reliable method for the application of a proper nutrition program. The effective and reliable method depends on the high sensitivity and sensitivity of the evaluation method. The method to be used should be insightful in terms of criteria such as the patient's condition, disease severity, previous nutritional status, weight loss, anthropometric measurements, and comorbidities. It is thought that NRS-2002, which is an evaluation method that includes all these parameters, can give good results in evaluating nutritional status in all hospitalized patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine (Date: 02.06.2009; No: 09/299).

Informed Consent: Verbal informed consent was obtained from all patients who participated in this study.

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CLINICAL SCIENCE OF NUTRITION

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Factors affecting the postoperative morbidity in patients who underwent gastric or colorectal resection due to cancer: Does preoperative nutritional status affect postoperative morbidity?

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ABSTRACT

Objective: The aim of the present study is to detect the factors affecting the postoperative morbidity of gastric or colorectal resection due to cancer and to evaluate the predictive value of the preoperative Nutritional Risk Screening 2002 (NRS-2002) score on postoperative morbidity.

Methods: Patients who underwent gastric and colorectal resection due to malignancy were included in the study. The effects of age, gender, the malignancy origin, preoperative NRS-2002 score, blood transfusion size during operation, stage of the disease, length of the operation, body mass index (BMI), and preoperative blood albumin levels on morbidity were statistically evaluated.

Results: A total of 418 patients between January 2012 and December 2014 were included in the study. Ninety-nine of them (23.6%) showed postoperative morbidity. Postoperative morbidity developed in 50 (19.3%) patients with a good nutritional score. The morbidity rate was 30.8% (n=49) in patients with a poor nutritional score ($p<0.05$).

Conclusion: The preoperative evaluation of the nutritional status with NRS-2002 in surgery clinics can be used as a method to predict postoperative morbidity in patients who underwent resection due to gastric or colorectal cancer.

Keywords: Colon cancer, gastric cancer, NRS-2002, nutrition

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Introduction

Malnutrition is common in patients with cancer. This is an important factor affecting postoperative morbidity and mortality (1). The incidence of malnutrition is 40%-80% in patients with cancer (2). The rate of malnutrition depends on the tumor type, location, stage of disease, treatment received, and nutritional assessment method (3). A poor nutritional status is correlated with a poor quality of life, high postoperative morbidity and mortality, and low tolerance to chemotherapy for gastrointestinal cancer (4, 5). In addition, Cause of death in as many as 20% of patients with cancer is associated with malnutrition (6).

Operations for gastric cancer and colorectal cancer are common in general surgery clinics. Preoperative nutritional status must be evaluated in patients with gastrointestinal cancer. There are several methods to evaluate preoperative nutritional status in patients. Anthropometric measurements such as the weight change, arm muscle circumference, triceps skin-fold thickness, and biochemical parameters are commonly used methods (7). Other methods are the Subjective Global Assessment (SGA), Patient-Generated SGA (8), and Nutritional Risk Screening (NRS-2002). The NRS-2002, which has demonstrated a high sensitivity and specificity at hospital admission, has been recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN). The NRS-2002 was developed by Kondrup in 2003 (9). This is a useful and easy method for general surgeons in patients with colorectal and gastric cancer.

In this retrospective study, we aimed to determine the effect of preoperative nutrition on the postoperative morbidity and mortality of patients with gastrointestinal cancer.

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Methods

The approval for non-invasive investigations was obtained from the Ethics Committee of Katip Çelebi University (No: 53,24.03.2016). The patients who underwent gastric and colorectal resection due to malignancy between January 2012 and December 2014 were included in the study. The patients with rectal cancer, Stage 4 (metastatic disease) tumors and non-adenocarcinoma tumors were excluded from the study. Patient file charts were recorded. A decision about the operation type was made by consensus in the clinic. The operations were performed by four surgical teams. Age, gender, the origin of the cancer, stage of the disease, preoperative albumin level (g/dL), preoperative BMI (kg/m^2), operation time (hours), the number of blood transfusion, preoperative nutritional status according to NRS-2002 (Table 1), the length of hospital stay (days), and the morbidity rates were recorded. The nutritional status is accepted as poor if the NRS-2002 score was ≥3 points. The effect of parameters on morbidity were statistically evaluated.

Table 1. Nutritional risk screening 2002

Step 1. Initial screening		**Yes**	**No**
1. Is BMI <20.5 kg/m^2?			
2. Has the patient lost weight within the last 3 months?			
3. Has the patient had a reduced dietary intake in the last week?			
4. Is the patient severely ill? (e.g., in intensive therapy)			
Yes: If the answer is yes to any question, the screening in Step 2 is performed.			
No: If the answers is no to all questions, the patient is re-screened at weekly intervals. If the patient, for example, is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			
Step 2. Final screening			
Impaired Nutritional Status		Severity of Disease (≈ increase in requirements)	
Absent, Score 0	Normal nutritional status	Absent, Score 0	Normal nutritional requirements
Mild, Score 1	Weight loss >5% in 3 months or food intake below 50%-75% of normal requirements in proceeding week	Mild, Score 1	Hip fracture, chronic pulmonary disease, oncology, chronic hemodialysis, diabetes
Moderate, Score 2	Weight loss >5% in 2 months or BMI 18.5-20.5 + impaired general condition or food intake below 25%-60% of normal requirements in the proceeding week.	Moderate, Score 2	Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy
Severe, Score 3	Weight loss >5% in 1 month (15% in 3 months) or BMI <18.5 + impaired general condition or food intake below 0%-25% of normal requirements in proceeding week	Severe, Score 3	Head injury, bone marrow transplantation, intensive care patients (APACHE>10)
score	+	score	= total score
Age	If >70 years, add 1 to total score		= age-adjusted total score

Score ≥3: The patient is nutritionally at risk, and a nutritional care plan is initiated.
Score <3: Weekly rescreening of the patient. If the patient, for example, is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.
APACHE: Acute Physiology and Chronic Health Evaluation

Statistical analysis

The Mann-Whitney U test and one-way analysis of variance were used for numeric parameters. A chi-squared test and Fisher's exacts test were used for other parameters. A p-value <0.05 was accepted as statistically significant. The Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) version 16.0 was used for the statistical analysis.

Results

A total of 418 patients who met the study criteria were included in the study. Gastric resection was performed in 196 (46.8%) patients, and colon resection was performed in 222 (53.2%) patients. The nutritional status was poor in 61.2% (120) of patients with gastric cancer and 17.5% (39) of patients with colorectal cancer. There were 170 patients (76.5%) with left-side and sigmoid colon cancer, 42 patients with right-side colon cancer (18.9%), and 10 transverse colon cancer cases (4.6%). Totally gastrectomy and D2 lymphatic dissection were performed in 108 patients (55.1%), and subtotally gastrectomy with D2 lymphatic dissection were performed in 88 patients (44.9%). The 64.1% (268 patients) of the patients were male, and the overall age was 61.1±12.3 (24-88) years. The characteristics of the patients were shown in Table 2.

Table 2. Patient characteristics

	n (%)	Morbidity	%	p
Gender				
Male	268 (64.1)	71	26.5	NS
Female	150 (35.9)	28	18.7	
Origin of the cancer				
Gastric	196 (46.9)	42	21.4	NS
Colorectal	222 (53.1)	57	25.7	
Stage of cancer				
1	47 (11.2)	24	51.1	0.001
2	335 (80.1)	54	16.1	
3	36 (8.7)	21	58.3	
NRS-2002 score				
1	99 (23.7)			
2	160 (38.2)			
3	17 (4.1)			
4	139 (33.3)			
5	2 (0.5)			
6	1 (0.2)			
Nutritional status				
Poor	159 (38.0)	49	30.8	0.001
Good	259 (62.0)	50	19.3	

There were 99 patients with morbidity (23.6%). A total of 89 patients had minor complications, such as minor pulmonary infection and wound infection, and the remaining 10 patients had major complications. Anastomotic leakage was observed in 8 patients (6 in total gastrectomy and 2 in right hemicolectomy). One patient had pulmonary emboli, and 1 patient had postoperative gastrointestinal bleeding. While total morbidity rates were found to be 21.4% and 25.7% in patients who underwent gastrectomy and colectomy, respectively, 8 of 10 patients who were developed major complications were gastrectomy patients. Postoperative morbidity developed in 50 (19.3 %) of patients with a good nutritional score. The morbidity rate was 30.8% (n=49) in patients with poor nutritional performance. The statistical analysis showed that a poor nutritional status is a factor affecting morbidity (p<0.05). In addition, an increasing number of blood transfusions, duration of the operation, and an advanced stage of the disease were morbidity-increasing factors (p<0.05). Results of the statistical analysis are shown in Table 3.

Mortality was observed in only 3 patients from the study group, and all of them underwent gastrectomy. Therefore, mortality was not statistically evaluated. Two of the 3 patients died for cardiac reasons, and 1 died due to the anastomosis leak and septicemia.

Discussion

Approximately 30%-40% of patients with cancer suffer from weight loss and malnutrition (10, 11), which is particularly high in patients with gastrointestinal or head and neck cancer (12).

The Joint Commission International recommended a nutritional assessment within 24 hours to diagnose malnutrition and to treat nutritional problems as early as possible. Nutritional screening tools vary according to the risk parameters used and the ability to determine nutritional risk. The Nutrition Risk Index, Malnutrition Universal Scan Tool, NRS-2002, and Mini Nutritional Assessment are the most commonly used nutritional screening tools that have proven reliability (13). Poulia et al. (14) and Kyle et al. (15) reported differences in the prevalence of malnutrition in nutrition screening tools when the tools were applied to the same patients. A good nutritional screening tool should

be simple, fast, non-invasive, standard, and cost-effective. In our study, we used the NRS-2002 screening tool recommended by ESPEN (16). The NRS-2002 is based on anthropometrics measurements, intakes of the patient, age, and metabolic stress, applying it to the identification of nutrition risk groups for all hospitalized patients (17).

We found that 38.0% of patients had a poor nutritional status after the NRS-2002 assessment in our study. Not surprisingly, the nutritional status was poorer in patients with gastric cancer than patients with colorectal cancer. The morbidity rate was higher in the malnourished patients than in well-nourished patients in the present study.

The postoperative morbidity did not only depend on the nutritional status, but also the tumor stage, the operation duration, and the number of blood transfusions were also important factors in the present study. Age, gender, and the origin of the cancer did not affect the morbidity.

Ryu et al. (18) studied several parameters that can be linked with the postoperative morbidity in patients with gastric

Table 3. Factors affecting morbidity

	N	Mean	Standard Deviation	Minimum	Maximum	p
Age (year)						
Group 1	319	60.77	12.304	24	88	NS
Group 2	99	62.48	12.449	36	87	
Total	418	61.17	12.345	24	88	
Length of hospital stay (day)						
Group 1	319	7.01	0.647	3	14	0.0001†
Group 2	99	11.75	3.234	8	35	
Total	418	8.13	2.616	3	35	
Duration of the operation (minutes)						
Group 1	319	159.92	34.353	120	478	0.032†
Group 2	99	167.86	22.689	123	218	
Total	418	161.80	32.131	120	478	
BMI (kg/m²)						
Group 1	319	23.79	3.648	17	36	NS
Group 2	99	23.62	3.036	18	34	
Total	418	23.75	3.510	17	36	
Albumin (g/dL)						
Group 1	319	2.8	0.5	2.0	4.0	NS
Group 2	99	2.8	0.6	2.0	4.0	
Total	418	2.8	0.58	2.0	4.0	
Blood transfusion (unit)						
Group 1	319	0.18	0.5	0	3	0.0001†
Group 2	99	0.56	1.0	0	3	
Total	418	0.27	0.7	0	3	

Group 1, patients without morbidity, Group 2, patients with morbidity, †Statistically significant. NS: nonsignificant; BMI: body mass index

cancer. They showed that the nutritional status is an important factor to predict postoperative morbidity. They used the NRS-2002 and SGA to evaluate preoperative nutritional status. Although the preoperative anthropometric parameters of patients with gastric cancer were found to be within the normal range of mean BMI, malnutrition scores were significantly correlated with the weight loss according to SGA and NRS-2002 (18). Aydin et al. (19) reported that even patients with a normal BMI may be malnourished and that the SGA may detect malnutrition before BMI falls below 20 kg/m^2. For this reason, it is very important to combine several methods to evaluate a patient's nutritional status. In the present study, we did not compare the nutritional status with BMI, but we detected that BMI was not a factor affecting morbidity. Data show that BMI is not sufficient when evaluating a preoperative nutritional status.

Albumin and prealbumin are common biochemical parameters in the nutritional status assessment. Prealbumin has a plasma half-life of 2 days, much shorter than albumin and more sensitive to changes in the protein-energy state than albumin. The prealbumin test is not routinely studied in our hospital, and therefore, it was not used in our study. Ryu et al. (18) also examined the preoperative albumin levels in patients. They found that the albumin level was not affecting the preoperative morbidity in patients with gastric cancer, as in our study.

The ESPEN guidelines define that preoperative parenteral nutrition is indicated in severely undernourished patients in whom enteral nutrition cannot be adequately administered either orally or enterally (20). On the contrary, its use in well-nourished patients has no benefit. Therefore, preoperative detecting of the nutritional status in patients with cancer is a tool to plan postoperative nutritional support.

The preoperative nutritional status of the patients who underwent elective colorectal resection induced the postoperative morbidity, length of hospital stay, and back to the normal gastrointestinal functions in a recent study (21). Chen et al. (22) reported that malnutrition occurs in more than 25% of the colorectal cancer patients, and morbidity is frequent in these patients. Because of that, the preoperative NRS-2002 score can be used to predict postoperative morbidity in patients with colorectal cancer. In compliance with the literature, in our study, the morbidity increased after colon resection in malnourished patients.

There are several studies that evaluated the factors affecting the postoperative morbidity or fatigue rates following gastrointestinal surgery. Old age, the NRS-2002 score ≥3, and gastrectomy were risk factors for postoperative fatigue (23). The original study in 2014 showed that there were nutritional risks in patients with gastrointestinal cancer. The study also detected that old age is a risk factor for nutritional risk (24).

Lohsiriwat assessed the effect of preoperative nutritional status on postoperative morbidity after colorectal surgery. The author found that malnourished patients were at risk of increased postoperative morbidity, delayed recovery of gastrointestinal function, and prolonged hospital stay (21). The results of our study were similar with the literature. Malnourished patients showed a higher risk of postoperative morbidity and prolonged hospital stay.

In our study, blood transfusion was found to be a factor affecting the morbidity. In the literature, it is observed that blood transfusion increases morbidity and mortality in patients undergoing gastrointestinal surgery. Blood transfusion was performed in 27% of our patients in accordance with the literature (25).

The factors that could affect mortality were not studied in our research because there was only 1 patient with postoperative early mortality in our study.

In conclusion, the NRS-2002 is an easy, rapid, and noninvasive tool to detect preoperative nutritional status in patients with gastrointestinal cancer. Postoperative morbidity in patients undergoing gastrectomy and colectomy is more frequent in malnourished patients according to the NRS-2002 score. BMI and blood albumin levels are important parameters, but they are not correlated with the nutritional status and postoperative morbidity. Patients with advanced-stage gastrointestinal cancer and a poor nutritional status should receive nutritional support.

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Original Article

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Enteral nutrition; uncomplicated? Can we achieve the target?

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ABSTRACT

Objective: Enteral nutrition (EN) is safe, well tolerated and efficient nutritional support for patients with functional gastrointestinal (GI) tract. The major problems of EN are intolerance of the nutrition products and problems of achieving the targeted dose. This is a prospective observational study investigating the nutrition related problems, solutions to those problems, and the time for achieving the targeted dose in patients who received EN in our inpatient clinic and intensive care unit.

Methods: This prospective study was made between 11/01/2015-11/01/2016. This study evaluated patients demographic findings, nutrition status, daily calculated calories (25 kcal/kg/day), daily calculated protein dose (1.5 gr/kg/day), daily delivered calories, daily delivered protein dose, whether or not additional parenteral nutrition applied, biochemical parameters (blood sugar, Na, K, Ca, Mg, cholesterol, liver function tests, urea, CRP, albumin, prealbumin), intolerance issues, complications and EN termination reasons.

Results: Considering 2258 patients hospitalized during this period, a total of 70 patients (3.1%) were applied EN (Female/Male: 30/40, The mean age of the patients was 60±16.5 years). The average application time is 11.5 (2-42) days. Among these patients, 26 had an NRS-2002 score ≥3, and only 6 had a BMI<18.8. The rate of calorie and protein application was lower than the calculated, respectively, 37.14% and 52.8% of the cases. It was observed that 40.54% of total malignant patients were subjected to immunonutrition. There were GI tract related problems in 20 patients. Diarrhea was the most important problem during enteral support. Oral supplementation intolerance problem was observed in 20% of the population. Hyperglycemia was detected in 35.7% of the patients, and more than half of them were between 200-300 mg/dL levels. Almost 53% of the patients had malignancy, however, only 5 of them had prescription for oral supplementation during discharge.

Conclusion: EN was performed less than required with inaccurate calories and protein intake, and immunonutrition protocols in malignant patients are not properly complied and oral supplement prescription for those patients is rarely given after hospital discharge. Additionally, product intolerance is seriously frequent, and product and dosage changes should be done more actively.

Keywords: Complication, enteral route, nutrition

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Introduction

It has been known for many years that malnutrition resulting from the imbalance between food intake and requirements has led to an increase in morbidity and mortality, prolongation of hospital stay, and an increase in costs (1-3). Malnutrition is observed in 20%-40% of general surgery clinics, especially in oncologic surgery (4-6). Nutritional support (NS) plays an important role in pre- and postoperative care of these patients and decreases postoperative complications and hospitalization duration (7). In addition, it is known that in patients undergoing major oncologic surgery, postoperative immunonutrition reduces infectious complications (8). The preferred method for NS is enteral nutrition (EN) (8).

EN is a physiologic, safe, and effective NS method for patients with normal bowel function, and complications are less common than parenteral nutrition (PN) (9, 10). However, gastrointestinal complications, which are more common in EN, may make the products difficult to be tolerated, resulting in a failure to reach the desired target dose during NS or termination of EN. The most common complication of EN is diarrhea, and this problem is more severe in intensive care units (may exceed 50%) (11, 12). Nausea and vomiting are seen in 20%-30% of EN patients. Other gastrointestinal problems include constipation, abdominal distention, regurgitation due to gastric emptying problems, and aspiration. Displacement and clogging of the tube that may occur in patients fed via tube are the mechanical problems that may cause EN termination. These prob-

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lems, which are more frequently encountered in EN, especially in intensive care patients, raise the differences in patients' time to reach the targeted calorie and the implementation of additional PN (13). In addition, difficulties in toleration due to taste-odor, among others, encountered in patients with oral nutritional supplement are another important problem. Patients are unwilling to use these products (14). The most critical point is to implement the correct application to achieve the goal of EN, which is thought to be more physiological, cheaper, and associated with less complications compared with PN.

The aim of the present study was to determine the frequency of EN use in patients hospitalized in Uludag University Department of General Surgery Clinic and Intensive Care Unit, to determine whether the requirements were met correctly, to determine the duration of reaching the target dose, and to evaluate the problems encountered in this process.

Methods

This was a prospective observational study planned between 11/01/2015 and 11/01/2016 Ethical approval for the audit was obtained from the Uludag University Ethics Committee, and written informed consent was obtained from the study subjects [no.: 2015-21/15 (28.12.2015)]. All data were recorded by an experienced clinical dietician (Figure 1).

First, a follow-up form was created for all EN-treated patients. Nutritional status was assessed by Nutrition Risk Screening-2002 (NRS-2002 score ≥3), body mass index (BMI <18.5 kg/m^2), weight loss percentage in the last 3 months (>10%), and prealbumin (<13 mg/dL). The daily energy and protein targets of the patients were calculated as 20-25 kcal/kg/day and 1.2-1.5 g/kg/day (15, 16). The daily calories and protein content of the patients were calculated and recorded by the dietician. The type, dose, calorie, and protein contents of the enteral/oral nutritional product were recorded. In the patient follow-up, disruptions related to the consumption of the product (bad taste, excess amount, no appetite, increased blood sugar, very sweet, and nausea when used) were determined. Gastrointestinal complications [vomiting, diarrhea (aqueous/soft stool >200-250 g/day or >250 mL/day and fecal frequency ≥3-5 times/day), constipation (absence of excretion for >3 days), distension, and abdominal pain] and what was done against these problems (the dose was reduced, the product was changed, the fiber product was added, and EN was discontinued) were recorded. Mechanical complications related to the tube (obstruction, displacement, and removal) and procedures for the solution (opened with the guide, irrigation with pressurized water or soda, opened, and withdrawn) were determined. Laboratory parameters, total protein, albumin, prealbumin, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, total cholesterol, sodium, potassium, calcium, zinc, magnesium, abnormal results in C-reactive protein values, and daily applied exogenous insulin amount, as well as blood sugar levels, were recorded. It was questioned whether residual control was performed in patients fed via gastric tube, whether the patient and/or relative were given near-tube maintenance training, and whether there was a compliance problem. The reason for termination of EN during the treatment period (patient rejected, patient could not tolerate, oral intake was adequate, complications, hemodynamic instability, operation, discharge, and died) and whether or not oral supplement was given during discharge were also recorded. As standard EN product, isosmolar products are used according to the hospital purchase policy. Oral impact was used as an immunization product (17).

Statistical analysis

Chi-square test was used to compare the groups. A p value <0.05 was considered statistically significant.

Results

A total of 70 patients were applied to the EN. The female-to-male ratio was 30/40. The mean age of the patients was 60±16.5 years. Considering 2258 patients hospitalized during this period, the rate of EN use was 3.1%. The average application time is 11.5 (2-42) days.

A total of 37 patients had malignant causes; 19 of them had periampullary region tumor, 5 had gastric malignant neoplasia, 6 had colorectal malignancy, 4 had intra-abdominal neoplasia, and 3 had malignant neoplasia. Among the patients admitted and hospitalized with benign causes, 18 had pancreatitis, 4 had trauma, 2 had liver hydatid cyst, and 9 had surgical site infection and biliary diseases.

Among these patients, 44 had an NRS-2002 score ≥3, and only 6 had a BMI <18.5 kg/m^2 (Table 1). The majority of the patients with an NRS-2002 <3 were those who used oral supplement because of inadequate oral intake. Eight patients were receiving support for immunonutrition. Of the 70 patients, 37 were malignant. Malnutrition was present in 78.3% (29 cases) of malignant patients, and hypocaloric support was applied in 33.3%. Of the 16 patients who underwent immunonutrition, 93.75% were malignant. It was observed that 40.54% of total malignant patients were subjected to immunonutrition.

1. Age:	2. Height:	3. Weight:	4. Body mass index:	5. NRS:
6. Daily calorie need:…….kcal/day		7. Protein need:……..g/day		
8. Daily intake				
a. Caloric amount (24 h):…….kcal		b. Protein amount (24 days):……..g		
9. Blood sugar (highest value):				
10. Daily stool number:				
11. Daily stool character				
a. Fluid/soft		b. Solid		
12. Product consumption				
a. Bad taste	b. Excess amount	c. No appetite	d. Very sweet	e. Nausea when used
13. Complications				
a. Vomiting	b. Diarrhea	c. Constipation	d. Distention	e. Stomachache
14. Nutritional supplement given while being discharged				
a. Yes		b. No		

Figure 1. Follow-up form in patients receiving nutritional support

Table 1. General characteristics of the patients using enteral nutrition

	Patient number (n)
Gender (M/F)	30 (42.9%)/40 (57.1%)
Average age (mean±SD)	60±16.5
Day NS was taken (median/min-max)	11.5 (2-42)
NRS-2002 score ≥3	44 (62.8%)
NRS-2002 score <3	26 (37.2%)
Diagnosis	
Benign	33 (47.2%)
Malignant	37 (52.8%)

As summarized in Table 2, only 9 (12.85%) of the 70 patients were given support for daily calorie target, whereas 50% had a hypercaloric dose. Target calories were achieved in the patients at an average of 3.2 (1-12) days. While 12 of the 44 patients who had reached the target calories and above used EN alone, it was seen that a large proportion of the patients (32 patients) had additional PN support. A total of 32 patients underwent additional PN. When all patients were taken into consideration, 32 (76.1%) of 42 patients who had additional PN were found to have hypercaloric dose.

The calculated protein dose was met in 33 cases, whereas the protein dose given in 21 (30%) of these patients was above the calculated dose. In addition, insufficient protein was given in more than half of the cases (37 cases, 52.85%). Three-fourths of the patients who received low-dose protein (52.85%) and low-dose calories (37.14%) were patients with an NRS-2002 ≥3.

Twenty (28.5%) patients had problems during NS (Table 3). It was observed that 13 of these patients were hypercaloric, 4 were hypocaloric, and 3 received daily caloric support. In 8 of 13 patients who received hypercaloric NS, the dose was reduced due to gastrointestinal system complications, such as diarrhea, abdominal pain, distention, and swelling. Two patients had been discontinued due to the development of vomiting and diarrhea, whereas the formula of enteral supplement was changed in three patients due to hyperglycemia that was difficult to control. There were no changes in enteral product in three patients who developed abdominal pain and distention. Additional PN supplementation was performed in eight patients who were administered dose reduction. Half of these patients were seen to have sufficient caloric support by enteral route at the end of 3 days.

Among the four patients with gastrointestinal problems who received hypocaloric support, two had changes in the enteral product due to the development of diarrhea and vomiting; in one of the two patients with only vomiting, NS was terminated, and the dose was reduced in the

Table 2. Calorie and protein values			
	No. of cases (%)	NRS-2002<3 (n=26)	NRS-2002≥3 (n=40)
Energy requirement			
Hypercaloric (>25 kcal/kg/day)	35 (50)	17	18
Hypocaloric (<20 kcal/kg/day)	26 (37.14)	6	20
Isocaloric (20-25 kcal/kg/day)	9 (12.85)	3	6
Protein requirement			
High-dose protein (>1.5 g/kg/day)	21 (30)	13	8
Low-dose protein (<1.2 g/kg/day)	37 (52.85)	9	28
Normal dose protein (1.2-1.5 g/kg/day)	12 (17.15)	4	8

Table 3. Complications in patients with enteral nutrition	
Complications	**Case number (n=70)**
Gastrointestinal	
Distention	11 (15.7%)
Stomachache	5 (7.1%)
Vomiting	4 (5.7%)
Diarrhea	15 (20%)
Problem of tolerating oral supplements (taste-smell-discomfort)	15 (20%)
Metabolic	
Hyperglycemia	25 (35.7)
Hypopotassemia	3 (4.2%)
Hyperpotassemia	2 (2.8%)
Mechanic	
Tube clogging	5 (7.1%)

other case. EN was discontinued in one patient who was fed isocaloric due to vomiting and in two because of uncontrolled hyperglycemia even though diabetic product was given.

The patients with hypercaloric feeding (13 of 35 patients) had more gastrointestinal system complications than hypoisocaloric patients (7 of 35 patients), but this difference was not statistically significant (p=0.11).

While 48.5% of the patients had aqueous/soft stool (9: aqueous), the number of defecation was >2/day in all cases. In 15 of these patients, the number of stools was >4 (21.4% of 70 patients). No constipation was detected in any of the cases.

Twenty percent of the patients had additional problems with oral supplement toleration. In 42% of these patients, the amount of oral supplements was high, 35.7% of them had poor taste, and 28% of them refused to use it because of mild nausea after ingestion. In one of these patients, while the product was changed, temporary dose reduction was performed in six of them.

A total of 42 patients were applied to the tube with EN. All of these patients were postoperatively enteral-fed patients. Thirty of them were given additional PN. There were 5 (11.9%) mechanical complications related to the tube. While the two blocked nasojejunal tubes were reopened, EN was discontinued in three patients. Although all of the relatives of the patients were given trainings related to tube maintenance, problems related to the change of the patients were observed. Five patients who had tube problems experienced the event during the night shift.

In nine patients (four patients had gastrointestinal intolerance despite of the precautions, two patients had metabolic problems (difficulty in glycemic control), and three patients had nasojejunal tube problems), EN had to be discontinued (12.8% of all patients). Hyperglycemia (>150 mg/dL) was observed in 35.7% of the cases (25 cases); among these, blood glucose in 2% was between 200 and 300 mg/dL. Intravenous insulin infusion was used in all hyperglycemic cases. In seven patients, 110-148 U was found to be regulated with insulin at a level of >300 mg/dl. Twenty-three of these patients were hypercaloric feeding cases and product change and dose reduction enabled glycemic control. No significant problems were found in liver function tests and electrolyte values during

the follow-up period. Only three cases showed hypopotassemia, and two hyperkalemia.

Although 52.85% (37 patients) of the patients were patients with cancer, only 5 patients were supplement prescribed while being discharged.

Discussion

Although EN is recommended for NS, it is noteworthy that the EN application rate was 3.1%. This rate is much less than expected because the need for NS patients in general surgery clinics is much higher. In this context, in a study published in 2009 and reflecting the situation in our country, it is seen that the rate of total malnutrition risk is 15% when data of 29,139 patients from 38 different centers (19 different cities) are taken into consideration. This rate increases to 40% in clinics dealing with cancer. Considering all standard surgical procedures in the general surgery clinics, the rate of malnutrition in the 8% level is approximately three times higher in the clinics applying only the gastrointestinal (6). In our study, malnutrition was present in 62.8% of the patients. This rate increased to 78.37% in malignant patients. The reason for administration of NS to other patients is not understood considering that only one-quarter of the patients without malnutrition uses immunonutrition. It is also noteworthy that only 40.54% of total malignant patients were immunonutritized.

It is interesting that only 12.85% of the patients were fed at the calculated caloric support dose, whereas 37.14% have hypocaloric, and 50% have hypercaloric support. The rate of hypocaloric patients varies in the literature. Reid stated that the calculated caloric dose is reached in 81% of the patients, and De Jonghe et al. showed that 63.5% of the total energy can be reached enterally (18, 19). In another study, this rate was found to be 51.6% (20). However, in 50% of the cases, hypercaloric support was provided, suggesting that the NS protocol was not adequately evaluated, and the follow-up was not effective. At this point, it is seen that the implementation of additional PN is an important factor. With regard to protein support, the condition is worse, and the rate of patients receiving low protein is 52.85%. This was observed in even 20% of the patients who were hypercaloric.

Although EN is a recommended method, various causes may prevent the target dose from being reached. Nutrition intolerance due to motility and absorption disorders, especially in intensive care, trauma, and gastrointestinal patients undergoing surgery, were observed as high gastric residual volumes, distension, vomiting, and diarrhea. In the present study, gastrointestinal problems were observed in 28.5% of EN patients. Of these 20 patients, 13 were hypercaloric, and 4 were hypocaloric. The incidence of gastrointestinal complications increased to 37.1% in hypercaloric patients and decreased to 20% in hypoisocaloric patients. On the other hand, it is noteworthy that 33.3% of the patients who received isocaloric nutrition had problems. The lack of statistically significant difference could be related to the low number of cases (p=0.11).

For management of gastrointestinal complications emerging during the use of enteral products, methods, such as prokinetic agent use, dose reduction, elimination of other factors that may result in diarrhea, use of antiemetic, and gradual dose increment during administration, are widely used (21, 22). The studies in particular on the presence or absence of fibrils in the products did not differ with regard to gastrointestinal complications (23). In our study, our approach to gastrointestinal complications is generally in the form of dose adjustment. However, if the problem persists, the product has been changed. Mentec et al. (24) reported a 46% intolerance incidence in a study on 153 enteral-fed patients. In a 44 case study by McClave et al. (20), 51.6% of the targeted calorie was accessed enterally, and 52.3% of them developed diarrhea. Similarly, in another study consisting of 60 cases by Engel et al. (13), >80% of the calculated energy requirements were reached in only 35% of the patients. In the same study, the cause of >50% of the insufficient EN is shown as gastrointestinal causes. Low-dose EN is usually attributed to patient-related factors, especially in patients after trauma and surgery. Diarrhea is observed between 15% and 50% among gastrointestinal complications. Especially in the study by Jakob et al. (25) in 2017, high dose and hyperosmolar were found to be associated with EN diarrhea. Similarly, in their study, no significant effect of other features of enteral product on diarrhea and intolerance was found. In our study, diarrhea was found in 15 of 20 patients who developed gastrointestinal complications. In fact, in approximately half (48.5%) of the patients receiving EN, stool change was detected. Among the patients with diarrhea, 83.3% were hypercaloric patients, and the rate of administration was >70 ml/h. In all patients who developed diarrhea, the first step was to reduce the dose or stop enteral feeding. However, the time to reach the targeted daily calorie was prolonged in dose-reduced patients.

An important cause of EN cutting is the problems in the tube. The most effective method to prevent tube clogging is education (26, 27). Although it was understood from the records that this education was given to the relatives of all patients who applied EN in the study, the fact that five patients who had tube problems experienced the

event during the night shift suggested problems related to patient relative changes.

The most prominent metabolic complication in the study was hyperglycemia (35.7%) and was controlled by high-dose insulin infusion in 7 of these patients. Almost all of the cases were hypercaloric fed, and dose reduction and product change were applied. It is noteworthy that this problem is seen, especially in patients using immunonutrition products.

It is interesting to note that only 5 (7.3%) patients underwent oral NS after discharge. This rate was found to be 14% in the presence of 37 patients with ND. However, significant weight loss and reductions in muscle mass and muscle strength were defined even 180 days after major surgery (28). Gastrointestinal symptoms, such as dietary restrictions, anorexia and nausea, vomiting, abdominal pain, and diarrhea, may persist for a long time after a major surgery and endanger adequate nutrition. Beattie et al. (29) and Jensen et al. (30) showed that oral supplements performed after discharge at home make positive changes in weight and body composition. No approach strategy was observed to be followed in our clinic.

In conclusion, the EN application in the surgical clinic is much lower than expected. The measurements of protein and energy requirements are not calculated sufficiently sensitive enough in EN patients. The rate of patients undergoing hypercaloric nutrition was significantly higher. The number of hypoproteinemic patients is significant. In malignant patients, immunonutritional support is not adequately administered. Although the metabolic and catheter complications are low, symptoms affecting the quality of life due to product tolerance are severe, and product changes and dosing should be performed more actively. The use of supplement during discharge is also as low as to be neglected.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Uludag University (Date: 28.12.2015; Decision no.: 2015-21/15).

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

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CLINICAL SCIENCE OF NUTRITION

Case Report

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The medication management in a patient with resistant hypertension with percutaneous endoscopic gastrostomy tube: The role of the clinical pharmacist

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ABSTRACT

Resistant hypertension (RH) is characterized as a clinical condition in which the patient needs three antihypertensive medications including diuretic for uncontrolled blood pressure (BP). Treatment of RH involves improving medication adherence and correct administration. Medication administration may be the key point when the patients' clinical conditions are not applicable for oral drug administration. Thus, comprehensive investigation of the patient is extremely important to identify the right medication, administration route, and time. In this case report, BP control was not achieved despite consulting several related medical services/departments for the patient with gastrostomy and uncontrolled RH. Thereafter, BP was gradually decreased with the intervention of the clinical pharmacists based on detailed research about the appropriateness of drug administration through percutaneous endoscopic gastrostomy (PEG) tube and timing. Drug administration via a PEG tube or feeding tube can be challenging at some points. Although drug–drug interactions can be recognized easily, potential drug–nutrient interactions should be also considered.

Keywords: Clinical nutrition, clinical pharmacy, drug administration, percutaneous endoscopic gastrostomy, resistant hypertension

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Introduction

Resistant hypertension (RH) is defined as a clinical condition in which the patient is prescribed ≥3 antihypertensive medications including diuretic for uncontrolled blood pressure (BP) or the patient requires ≥4 antihypertensive medications to achieve target BP levels (1).

The prevalence of RH is unclear, but the reported prevalence is approximately 13% in the adult population and appears to be a relatively common problem in many countries (1, 2). However, the prevalence would be almost 4% higher with the implementation of the new BP target levels of <130/80 mm Hg (3, 4).

The prognosis of RH has not been sufficiently determined compared with that of those who more eagerly achieve control; however, the risk of myocardial infarction, stroke, end-stage renal disease, and congestive heart disease may be two to sixfold higher in adults with RH than in those with controlled hypertension (HT) (5, 6).

Medication administration may be the key point when the patients' clinical conditions are not applicable for oral drug administration. Thus, comprehensive investigation of the patient is extremely important to identify the right medication, administration route, and time. Patients' medication adherence is also important as well as correct administration method and timing. Here, we report a patient with gastrostomy and uncontrolled RH whose BP control was not achieved despite consulting several related medical services/departments but not clinical pharmacy department.

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Table 1. Medication-related recommendations and changings		
Medication	Information provided by the clinical pharmacist	Physicians' intervention
Carvedilol	Tablet can be crushed. Absorption will be delayed with nutrients. All beta-blockers will reduce the bioavailability of lercanidipine with a 50% reduction in hepatic blood flow	Switched to nebivolol treatment because absorption is unaffected by food. About the interaction with lercanidipine, no action is taken
Valsartan	Tablet can be crushed. Bioavailability reduces 40% with nutrients	Administration time changed from 08:00 a.m. to 06:00 a.m. before feeding starts
Furosemide	Bioavailability reduces 30% with nutrients	Administration time changed from 08:00 a.m. to 02:00 p.m
Lercanidipine	Tablet can be crushed. The drug–nutrient interaction was reported. Oral availability of lercanidipine increased fourfold when ingested 2 h after a high-fat meal	Dose and administration time changed from 05:00 p.m. to 10:00 a.m. and 09:00 p.m
Acetylsalicylic acid	With pharmacodynamics antagonism, the activity of furosemide, carvedilol, and valsartan will be reduced (recommendation: monitor closely)	No action is taken

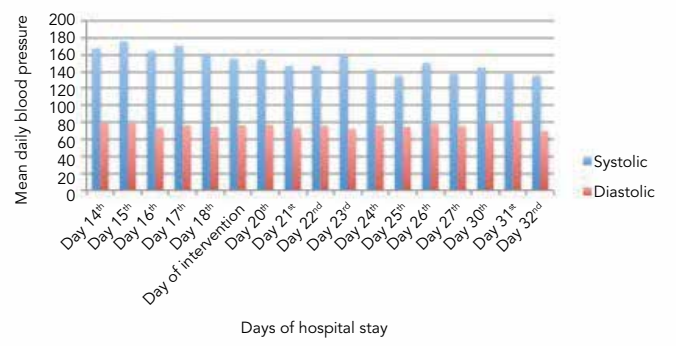

Figure 1. Daily blood pressure before and after intervention

Case Presentation

We present a case of a 62-year-old Caucasian woman who has an oxygen concentrator and gastrostomy with a medical history of essential HT (25 years), diabetes mellitus (DM) (25 years), dyslipidemia (3 years), chronic obstructive pulmonary disease (7 years), and chronic kidney disease (10 years). The patient's relatives provided verbal consent for this case report. Approximately 1 year ago, percutaneous endoscopic gastrostomy (PEG) tube was placed for feeding as well as for oral drug administration. Continuous enteral feeding was provided through a PEG tube with 230 mL Glucerna SR (Abbott, IL, USA). The only information about her family history was a brother with DM. She has a history of 10 pack-years of cigarette smoking, but no alcohol.

She was taking amlodipine (Norvasc; Pfizer, NY, USA) (10 mg daily), nebivolol (Vasoxen; Ulagay Ilac, Istanbul, Turkey) (5 mg daily), diltiazem (Diltiazem; Mustafa Nevzat Ilac, Istanbul, Turkey) (90 mg daily), and doxazosin mesylate (Cardura; Pfizer, NY, USA) (16 mg daily) for HT. Her BP was approximately 140/80 mmHg while she was adherent to her medication treatment; if not, it would increase up to 180/90–190/95 mmHg. In her medication history, she used different antihypertensive combinations with different doses at different periods of her life.

She was admitted to the intensive care unit (ICU) with chest pain, shortness of breath, and headache. On admission at the ICU, her physical examination was as follows: body temperature 36.4°C, pulse rate 70 beats/min, BP 140/80 mm Hg, and body mass index 33.2 kg/m^2. Her laboratory test results were also as follows: serum creatinine 1.21 mg/dL, sodium 139 mEq/dL, potassium 4 mEq/dL, blood urea nitrogen (BUN) 42 mg/dL, hemoglobin 9 g/dL, B-type natriuretic peptide (BNP) 154 pg/mL, and pCO_2 53 mmHg.

While the patient was stable, she was transferred to the internal medicine service on day 4. Owing to uncon-

trolled BP, several departments, such as nephrology, geriatric medicine, and cardiology departments, were consulted for managing her RH treatment. However, all interventions of these consultations failed (Figure 1), unless the administration of antihypertensive medications intravenously.

Thereafter, BP was gradually decreased with the intervention of the clinical pharmacists and geriatricians based on detailed research about the appropriateness of drug administration through PEG tube and timing and drug–nutrient and drug–drug interactions (Table 1). Some of the recommendations of the clinical pharmacists have not been accepted by the physicians. Then, her BP was controlled with spironolactone (Aldactone; Ali Raif Ilac, Istanbul, Turkey) (100 mg daily), alpha methyldopa (Alfamed; Ulagay Ilac, Istanbul, Turkey) (250 mg three times daily), valsartan (Diovan; Novartis, Basel, Switzerland) (320 mg daily), furosemide (Lasix; Sanofi Aventis, Paris, France) (40 mg daily), nebivolol (Nexivol; Abdi Ibrahim Ilac, Istanbul, Turkey) (10 mg daily), and lercanidipine (Lercadip; Actavis, NJ, USA) (20 mg twice daily).

The patient was discharged on day 39, with BUN 63 mg/dL, serum creatinine 1.46 mg/dL, sodium 137 mEq/dL, potassium 4.5 mEq/dL, hemoglobin 10.1 g/dL, BNP 42 pg/mL, and BP 140/80 mm Hg. Her nutritional therapy plan was rearranged according to the current medication administration through PEG tube. Intermittent enteral feeding was provided after intervention day at 12:00 p.m., 6:00 p.m., 12 a.m., and 6 a.m. with Glucerna Select (Abbott) (450 mL four times daily).

Discussion

Frequent usage of feeding tubes and ostomy is increasing in both hospital settings and other care facilities. Feeding tubes are used not only for nutrients but also for medication administration (7).

Medication administration may be challenging with regard to pharmaceutical, legal, and technical issues. From the pharmaceutical aspect, some variables should be taken into account, such as interactions, stability, and effectiveness. From the legal aspect, it should be noted that medication administration via a feeding tube is an off-label procedure. Therefore, all aspects of appropriate medication administration through a feeding tube should be considered for better patient outcomes and safety.

Conclusion

There are many components to consider for RH, such as BP measuring technique, white coat HT, secondary causes of HT, and medication compliance. This case report indicated that the medication administration method also needs to be evaluated especially for patients with PEG tubes. An appropriate treatment should include the right antihypertensive drugs and their right administration information.

Uncontrolled HT may cause many complications including cardiovascular diseases, stroke, and organ damages. Therefore, it is important to achieve BP control. Although previous studies mentioned many other factors involved in HT, to the best of our knowledge, no study was found that indicates clinical nutrition and RH relationship. More clinical research and special consideration may be needed to obtain optimal treatment strategies for this particular group of patients.

Informed Consent: Verbal informed consent was obtained from the patient's relatives who participated in this case.

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