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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.

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Editor in Chief: Sadık Kılıçturgay
Address: Department of General Surgery, Uludağ University School of Medicine, Bursa, Turkey
E-mail: skturgay@gmail.com

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

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Tables

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

Figures and Figure Legends

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

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

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

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

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

References

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

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Review Article	6000	300	60	6	10 or total of 20 images
Case Report	2500	250	20	No tables	10 or total of 20 images
Letter to the Editor	1000	No abstract	5	No tables	No media
Editorial	1000	No abstract	5	No tables	No media

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

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

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

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

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

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

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

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

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

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

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Editor in Chief: Sadık Kılıçturgay
Address: Department of General Surgery, Uludağ University School of Medicine, Bursa, Turkey
E-mail: skturgay@gmail.com

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
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CONTENTS

CLINICAL SCIENCE OF NUTRITION

Review

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Drug-induced nutritional disorders

Nadir Yalçın, Merve Armut, Burcu Kelleci Çakır, Kutay Demirkan

Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara, Turkey

ORCID ID of the author: N.Y. 0000-0002-2280-8727; M.A. 0000-0002-4089-8172; B.K.Ç. 0000-0003-2547-8919; K.D. 0000-0002-6427-5826

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ABSTRACT

Nutritional disorders include malnutrition and inadequate nutrition, overweight and obesity, micronutrient disorders and refeeding syndrome. According to the European Society for Clinical Nutrition and Metabolism, sarcopenia and fragility are nutrition-related conditions with complex and multiple pathogenic infrastructure. Inadequate nutrition is also considered as protein-energy malnutrition and is often accompanied by micronutrient as well as macronutrient deficiencies. Macronutrients such as carbohydrates, proteins, and fats are essential nutrients that provide energy to the body and aid in growth. Micronutrients such as vitamins, minerals, and trace elements are necessary for many special functions in the body. Meanwhile, drug intake can lead to increased morbidity and mortality and decreased quality of life by causing malnutrition through various mechanisms. The pharmacological and pharmaceutical properties of drugs can affect the intake, digestion, absorption, storage, metabolism, and elimination of nutrients, causing imbalance in the amount of nutrients required in the body. Polypharmacy makes this situation even more risky. Many of the patients' symptoms or complaints received by physicians in their daily practice are associated with drug-induced nutritional disorders. When evaluating symptoms, physicians should also assess whether the symptoms are related to the disease, drug side effects, or drug-induced nutritional disorders. Instead of thinking that the resulting symptoms are simply "part of the disease" or "old age" and starting to take additional medication to resolve them, physicians should focus thoroughly on the event and examine what problems that the drugs used may cause in patients and the underlying reasons for deciding what they can do to eliminate them. This intervention should be investigated. Hence, this review aimed to explore the importance of the subject by mentioning the mechanisms of the negative effects of drugs on nutrition and providing examples of commonly used drugs.

Keywords: Clinical nutrition, drug, malnutrition, nutritional disorder

Introduction

Malnutrition is defined as a nutritional disorder that causes a loss of energy, protein, and other nutrients resulting from decreased food intake or digestive disorders, changes in body composition, and loss in functions, which may be accompanied by inflammation and worsen the clinical course of existing diseases (1). According to the European Society for Clinical Nutrition and Metabolism, nutritional disorders and nutrition-related conditions can be categorized as malnutrition, sarcopenia and fragility, overweight and obesity, micronutrient disorders, and refeeding syndrome (2).

Drugs affect the intake, digestion, absorption, storage, metabolism, and elimination of nutrients (3). They can disrupt food intake by causing gastrointestinal system (GIS) disorders (GIS irritation, increased acidity, endogenous digestive disorder, and gastroparesis) and digestive disorders (achlorhydria, digestive enzyme and enterocyte dysfunction, and malabsorption introduction) and affecting the intestinal system (dehydration, hypercalcemia, and hypokalemia) and the central nervous system (CNS) (CNS depression, dementia, hand tremor, and coordination disorders) (4). Moreover, the metabolism and elimination of nutrients are affected by increased energy requirements, catabolism (thyroidal and sympathomimetic drugs), organ dysfunction (hepatopathy and nephropathy), and lack of building blocks for metabolism (hypovitaminosis) (5, 6). However, anorexia can cause premature saturation, malnutrition, dysphagia, constipation, and diarrhea, affecting the sense of taste and leading to weight loss and malnutrition (5). These effects can also exacerbate subclinical malnutrition or low energy intake, especially in the elderly (7).

In this review, the effects of drugs that can cause weight loss and anorexia, nausea and vomiting, decreased GIS motility, diarrhea, dry mouth, taste and smell disorders, and obesity on nutrition disorders will be examined.

Corresponding Author: Nadir Yalçın; nadir.yalcin@hotmail.com

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Drugs that May Cause Weight Loss and Anorexia

Weight loss and anorexia are common side effects of many commonly prescribed drugs. For example, weight loss in patients with Parkinson's disease has been associated with levodopa treatment. However, this weight loss can also be attributed to the severity of the disease and the effect of movement disorders on the inability to prepare and consume food. The therapeutic use of amantadine in the treatment of patients with weight gain associated with antipsychotic drugs also causes weight loss (8).

Other drugs associated with weight loss are felbamate, topiramate, and zonisamide (9). Topiramate, which causes an increase in energy metabolism, helps prevent or treat weight gain caused by psychotropic drugs. In the United States, topiramate-phentermine combination therapy has been approved as an anti-obesity drug (8, 9). Imipramine and methylphenidate are associated with decreased appetite and are the most commonly prescribed psychotropic drugs by pediatric mental health physicians.

Another drug associated with anorexia and weight loss is sibutramine, which has been approved for weight control in adolescents and adults (3). However, considering its cardiovascular side effects (increased blood pressure and heart rate), the European Medicine Agency has suspended the licenses of sibutramine-containing drugs (10).

Furthermore, cardiac glycosides, biguanides, thiazide diuretics, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, potassium-sparing diuretics, acetylcholine esterase inhibitors, metformin, and penicillamine are associated with weight loss and anorexia (7, 8, 11). Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucose-like peptide-1 (GLP-1) receptor analogues also cause weight loss (11). Meanwhile, GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, which are alternative drugs to insulin and insulin secretagogues, have positive effects on weight when achieving glycemic targets (12).

Bupropion is used as the sole antidepressant for continuous weight loss in the treatment of depression and smoking cessation because of its effect on appetite reduction. Together with naltrexone, bupropion has been approved as an anti-obesity drug in the US and Europe (9). Selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine, and sertraline) and selective noradrenaline reuptake inhibitors (SNRIs) (venlafaxine and duloxetine) have been associated with mild weight loss. However, this effect is temporary, and the weight increases in long-term treatment (9).

Drugs that May Cause Nausea and Vomiting

Nausea and vomiting are two of the most common side effects of drug therapy. Although they are generally observed in the early period of treatment, these symptoms may improve despite the continued treatment. Nausea and vomiting have important effects on food intake. Drug treatment may cause vomiting by a direct effect on the chemoreceptors or chemoreceptor trigger zone in the gastrointestinal tract or by joining of both pathways at the vomiting center in the medulla (8).

Cytotoxics, potassium, iron preparations, and antibiotics affect the chemoreceptors in the gastrointestinal tract, causing nausea and vomiting. However, cytotoxics, anesthetics, opiates, SSRIs, nicotine, and levodopa affect the chemoreceptor trigger zone, also causing nausea and vomiting (8). Cardiac glycosides can also cause nausea. Sulfonylureas may cause epigastric pain, heartburn, and nausea. Beta blockers may cause a decrease in gastric motility. Biguanides cause vomiting in patients with inadequate renal function (11). Nausea is also the most common side effect of acetylcholinesterase inhibitors used for treating Alzheimer's disease (13). Gastritis, peptic ulcer, and nausea associated with anorexia can also be manifested in patients with long-term high doses of aspirin (7). Drug-induced nausea, as in the case of digoxin or theophylline, may be indicate drug toxicity, which is a condition to be considered (8).

Drugs that May Reduce Gastrointestinal Motility

Decrease in gastrointestinal motility is associated with gas, bloating, and constipation, affecting oral nutrition. Drugs that stimulate anticholinergic and opiate receptors in the intestines cause slow passage and bloating. In many drugs, these symptoms are dose-dependent effects and can be minimized by reducing the dose or switching to another drug. Abdominal distension, pain, constipation, nausea, and vomiting are well-known side effects of opiate (morphine and codeine) treatment, affecting more than 50% of patients (8). In addition, tricyclic antidepressants (TCAs) and oxybutynin can reduce gastrointestinal motility, whereas beta blockers can cause constipation (11).

Drugs that May Cause Diarrhea

Diarrhea, which is one of the most common side effects of medications, occurs in cases with increased gastrointestinal motility, altered intestinal flora, and deteriorated mucosal surface. More than 25% of antimicrobial drugs are responsible for drug-induced diarrhea, which ranges from mild diarrhea to severe pseudomembranous colitis. Pen-

icillin and cephalosporins constitute the majority of cases of pseudomembranous colitis. Erythromycin increases gastrointestinal motility by acting directly on motilin receptors. Especially, lopinavir-ritonavir-combined antiretroviral therapy is also associated with diarrhea (8). Further, drugs such as irinotecan and 5-fluorouracil, which are used especially in the treatment of gastric and colorectal cancers, cause more diarrhea than other chemotherapeutics, and loperamide is routinely used to treat such diarrhea (8, 14).

Attention should also be paid to the excipients used in drugs in the form of suspension. For example, intake of sorbitol with these drugs can cause diarrhea, and intake of maltitol can cause bloating (15). Diarrhea typically ends by discontinuing these drugs. Taking the drug with food or increasing the dose may gradually reduce symptoms. This method is especially effective in diarrhea associated with metformin and iron preparations (8).

Alpha-glucosidase inhibitors used for treating diabetes can cause diarrhea and gas (11). Nauseas and vomiting are also the common side effects of acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease (13). Proton pump inhibitors (PPIs) may also cause diarrhea when used for a long time (>6 weeks) (7). Biguanides, which are one of the oral antidiabetic drugs, also cause diarrhea (11).

Metoclopramide and domperidone, broad-spectrum antibiotics, misoprostol, antivirals (adefovir, tenofovir, and lamivudine), magnesium salts, acarbose, and sevelamer also cause diarrhea. Of note, the occurrence of diarrhea in patients treated with narrow therapeutic intermittent lithium, digoxin, and colchicine indicates toxicity (8).

Drugs that May Cause Dry Mouth

Saliva has many functions, such as increasing the sense of taste, facilitating speech, and protecting the mucosa. The parasympathetic pathway increases the volume of saliva produced, whereas the sympathetic pathway decreases such volume and increases the viscosity. Many drugs cause an effect on receptors affecting the saliva production, thereby causing a dry mouth and ultimately affecting the perception of flavor (8). The most common causes of dry mouth are the parasympathetic blockade by drugs with anticholinergic or antimuscarinic activity and the sympathetic stimulation caused by alpha-agonists (8).

Drugs that May Cause Taste Disorders

Disorders in taste due to drug treatment may affect patients' drug compliance and impair their food intake. Taste disorders can be classified into the following four main types: ageusia, hypogeusia, dysgeusia, and parageusia. Ageusia and parageusia are rare, whereas hypogeusia and dysgeusia are commonly associated with drug treatment (8).

Drugs that May Cause Olfactory Impairment

Odor is associated with appetite and saturation and is the first part of the cephalic phase. Food odor triggers an increase in saliva, gastrin, and insulin secretion. Decrease or change in the sense of smell affects food intake. Studies involving patients with cancer have shown that chemotherapy causes a temporary decrease in taste and smell, especially in older patients (8).

Drugs that May Cause Obesity

Obesity is one of the most important public health problems worldwide. According to WHO, approximately more than 600 million adults were obese in 2014, and 39% of them were overweight (9). Drug-induced weight gain may cause morbidity and mortality due to glucose intolerance, lipid profile deterioration, and increased blood pressure. Drugs that can cause overweight and obesity are categorized as follows:

Antidepressant drugs

Excessive weight gain during antidepressant treatment varies significantly between different classes, and it is associated with treatment duration. The use of TCA is associated with weight gain and obesity in the acute and maintenance phases of treatment. However, weight gain is not associated with the efficacy of antidepressant therapy, and it is observed when TCA is used for other indications, such as neuropathic pain or anxiety disorders. The highest weight gain is associated with amitriptyline, nortriptyline, and mirtazapine (9). Furthermore, TCAs affect the neurotransmitter pathways in the brain and exhibit antihistaminic activity that increases appetite and causes weight gain (16).

SSRIs are expected to have a weight-loss effect because of their effects on serotonin, which aids in the control of carbohydrate and food intake. In fact, in acute treatment, some SSRIs (citalopram, fluoxetine, and sertraline) and SNRIs (venlafaxine and duloxetine) are associated with mild weight loss. However, this effect is temporary, and weight gain is expected in long-term maintenance treatment (9). Although citalopram, which is an SSRI, does not show a significant weight gain, SNRIs, especially duloxetine, cause less weight gain (17). The SSRI paroxetine causes the most weight gain in long-term use, probably because of its affinity for the cholinergic receptor (9). Non-

reversible monoamine oxidase (MAO) inhibitors, such as phenelzine and tranylcypromine, also increase weight (18). Traditional antidepressants, including TCAs and MAO inhibitors, cause more weight gain than SSRIs and other recent antidepressants (17).

Antipsychotic drugs

While antipsychotic drug-induced weight gain and other metabolic effects are common side effects that increase the risk of comorbidity and mortality, the pathophysiology of antipsychotic-induced weight gain remains poorly understood. However, many studies have found a positive correlation between weight gain and therapeutic efficacy of antipsychotic drugs (19). The number of individuals taking antipsychotic drugs is relatively high. Second-generation antipsychotic drugs are often prescribed in adults as well as in children for nonpsychotic disorders, such as bipolar affective disorder, attention deficit hyperactivity disorder, and dementia in the elderly. However, 80% of the patients using this group of drugs are exposed to weight gain of 20% or more of their ideal body weight (9). Second-generation antipsychotics are the cornerstone of schizophrenia treatment. Numerous studies have linked these drugs with weight gain, dyslipidemia, insulin resistance, and type 2 diabetes (19). Drugs with high antihistaminic effects, such as clozapine and olanzapine, are the most common antipsychotics that cause weight gain (19). Nonetheless, aripiprazole, amisulpride, and ziprasidone induce minimal weight gain. Recently approved asenapine, iloperidone, lurasidone, and paliperidone cause less metabolic side effects than other antipsychotics (9). Some typical antipsychotics, such as chlorpromazine and thioridazine, may also cause weight gain, but these drugs are less commonly used due to extrapyramidal side effects (16).

Weight gain caused by antipsychotic drugs depends on the dose and duration of the drug (9). In the study of Raben et al. (19) examining patients treated with clozapine, a significant relationship was found between antipsychotic drug-induced weight gain and therapeutic efficacy after 10 weeks of treatment. Conversely, in the study conducted by Hermes et al. on patients treated with risperidone, quetiapine, and ziprasidone, no significant relationship was found on weight gain at the end of 12 weeks but appeared on the 72nd week. The relationship between antipsychotic drug-induced weight gain and therapeutic efficacy depends on the duration of treatment, but this relationship may be due to the drug treatment received by the patients in the study (19).

Lithium

In 60% of patients receiving lithium treatment for bipolar affective disorder, weight gain of more than 5% of initial body weight was detected. Risk factors for weight gain are high basal weight, younger age, gender (higher risk for women), and combined therapy with antidepressants. The mechanism of action of lithium on weight gain is unclear. Reportedly, appetite is increased due to hypothalamic effects, increased thirst and high calorie drink intake, changes in food consumption, and hypothyroidism (9).

Antidiabetic drugs

Among the antidiabetic agents, insulin, sulfonylurea, and thiazolidinediones cause significant weight gain compared with placebo. Sulfonylurea-induced weight gain is approximately 4 kg in the first year of treatment; it is apparent in the first months of treatment and then plateaus (9). In a 27-week study of 845 patients with type 2 diabetes who received gliclazide or glimepiride once a day, body weight increased by approximately 0.6 kg in both groups. Similarly, weight gain was observed in patients treated with repaglinide and nateglinide. A randomized, multicenter, 16-week clinical trial study compared the efficacy and safety of repaglinide and nateglinide monotherapy in patients with type 2 diabetes who were previously treated with diet and exercise. The study found that the average weight gain was 1.8 kg in the repaglinide group, whereas it was 0.7 kg in the nateglinide group. These studies show that insulin secretagogues are associated with weight gain in patients with diabetes. Meanwhile, glyburide is a sulfonylurea drug that causes the most weight gain (12).

Thiazolidinediones are insulin-sensitizing drugs that reduce insulin resistance in peripheral tissues and minimize hepatic blood glucose production. Weight gain was observed more in patients who responded better to thiazolidinedione treatment (12). This drug causes 1.5-4 kg weight gain in the first year of treatment, depending on the dose and duration of use (9). In a clinical trial study of pioglitazone, which included 5238 patients with type 2 diabetes, an average of 3.8 kg weight gain was observed over a three-year period with the use of pioglitazone. According to a clinical study of 4360 patients who were first treated with rosiglitazone, metformin, and glyburide for newly diagnosed type 2 diabetes, those who received rosiglitazone gained an average weight of 4.8 kg. Weight gain caused by thiazolidinedione use may result from the renal excretion of sodium and fluid retention. When rosiglitazone is used in combination with metformin, weight can be reduced or remained unchanged (12).

Some patients with type 2 diabetes may require insulin therapy for a period of time to achieve glycemic control (9). One study found a significantly higher weight gain in patients receiving insulin (4 kg) compared with those receiving chlorpropamide (2.6 kg) or glibenclamide (1.7

kg). Patients receiving insulin therapy generally gain 2-3 kg over a period of 6-12 months. This weight gain is less common in metformin-combined therapy than in insulin monotherapy, due to the insulin dose and/or the attenuating effects of metformin. The anabolic properties of insulin can lead to weight gain by increasing protein synthesis and inhibiting lipolysis and proteolysis, resulting in increased lean body mass. In some studies, insulin detemir causes less weight gain than neutral protamine Hagedorn (NPH) insulin. For example, in a 26-week multicenter randomized study of 504 patients with type 2 diabetes from 91 centers in the US and Europe, patients receiving insulin detemir (1.0 kg) gained significantly less weight than those receiving NPH insulin (1.8 kg). The weight difference between insulin detemir and NPH insulin appears more pronounced when insulin detemir is administered at night. The evidence suggests that insulin detemir and insulin glargine have a similar effect on glycemic control and that insulin detemir does not provide weight gain (12).

In conclusion, drug-induced weight gain should be monitored in patients with diabetes using oral antidiabetic agents and insulin to increase compliance with treatment and reduce metabolic side effects.

Antihypertensive drugs

Hypertension is one of the common comorbidities of obesity and type 2 diabetes. Therefore, drugs that increase weight gain or have other metabolic side effects are a significant concern in hypertensive patients with obesity (9). Thiazide diuretics are generally recommended as first-line agents for treating hypertension but are not recommended for patients who are overweight or obese and at risk of metabolic syndrome and type 2 diabetes, due to dose-related side effects such as dyslipidemia and insulin resistance (20). Patients receiving beta blockers generally tend to increase in weight. At the end of the first year of beta-blocker treatment, a 4 kg increase was detected (9). Beta blockers may either increase weight gain or prevent weight loss, especially in patients with both hypertension and diabetes. Hence, beta blockers should not be the first-line treatment for hypertension in patients with overweight or obesity, considering that weight control is more difficult in patients with hypertension treated with beta blockers (20). Given the effects of beta blockers on body weight, around 4%-9% is reduced in total energy expenditure of patients. Beta-blocking agents reduce the basal metabolic rate by 12% in hypertensive patients with obesity compared with other antihypertensive drugs. Beta blockade also prevents lipolysis in response to adrenergic stimulation, making weight loss difficult for patients. It can also cause fatigue and tiredness in patients, thereby preventing exercise (9). Selective agents such as carvedilol and nebivolol are recommended for patients who require beta blockers; such patients include those with coronary artery disease, heart failure, or arrhythmia. These drugs have less potential for weight gain and have minimal effect on lipid-glucose metabolism. In a study involving 1106 patients with hypertension, weight gain of patients receiving metoprolol significantly increased compared with that of patients receiving carvedilol. While 4.5% of the metoprolol group gained more than 7% of their weight, such weight gain percentage was only found in 1.1% of carvedilol users. Therefore, weight gain can be minimized by selecting a different drug in the same group (20).

ACE inhibitors, ARBs, and calcium channel blockers are not associated with weight gain and insulin resistance. Considering that angiotensin is overexpressed in obesity, ACE inhibitors and ARBs have positive effects on obesity-related hypertension. These drugs become targeted options for the treatment of patients with obesity. Furthermore, given that many of these patients suffer from type 2 diabetes or prediabetes, they are likely to benefit from kidney protection through ACE inhibitors and ARBs (20). In conclusion, when controlling hypertension, physicians should select the most suitable antihypertensive drug, especially in patients at risk for obesity.

Steroid hormone drugs

Glucocorticoids stimulate appetite by altering the activity of protein kinase activated by adenosine monophosphate in the hypothalamus, and they affect dietary intake by increasing dietary fat requirement (9). Secondary to long-term glucocorticoid treatment, Cushing's syndrome occurs when body fat accumulates to cause truncal obesity, buffalo hump, and a moon face. The risk of these complications varies depending on both the dose and the duration of treatment. In patients with rheumatoid arthritis, the use of prednisone at 5-10 mg/day for two years is associated with an increase in the average body weight of 4%-8% (21). Weight gain caused by glucocorticoid treatment may be more than 10 kg in approximately 20% of patients in the first treatment year (9). Corticosteroids injected locally into the knee joint or spinal column for inflammation and inhaled corticosteroids used for asthma are not associated with weight gain (16). Synthetic anabolic steroids, such as oxandrolone, are increasingly used to reduce catabolism and weight loss experienced by critically ill patients (8, 22). In conclusion, metabolic side effects should be monitored in patients receiving long-term high-dose steroid therapy to minimize weight gain.

Synthetic progestins

Only progestin-containing birth control pills are used by women who cannot take estrogen to prevent pregnancy (23).

Although weight gain is generally known as a side effect of hormonal contraception, combined contraceptives are not associated with weight gain. However, while weight generally increases among patients using depot medroxyprogesterone acetate, information about other progestins is limited (24).

In a study conducted in the USA, more women gained weight when using depot medroxyprogesterone acetate than when using low-dose oral contraceptives (23). Medroxyprogesterone acetate is an approved drug for treating anorexia, cachexia, or unexplained weight loss in patients with acquired immunodeficiency syndrome in the USA (24). However, data supporting its use in cancer cachexia are also available. This drug has significant effects on appetite, weight gain, and health-related quality of life (8). When synthetic progestins are used, especially in adolescents, some weight gain may be regarded as developmentally normal and appropriate. Therefore, the possible causal relationship between contraceptives and weight gain is difficult to examine (24).

Antiepileptic Drugs

Most weight changes associated with antiepileptic drug therapy occur in the first 3 months after onset (25). Among the antiepileptic drugs, valproate and carbamazepine exhibited the most significant weight gain. Weight gain is observed in 71% of patients using valproate and 43% of patients using carbamazepine. Pregabalin and gabapentin can also cause weight gain. Antiepileptic drugs that have no effect on weight change are lamotrigine, levetiracetam, and phenytoin. Weight gain caused by valproate intake is the highest in the first year of treatment, with a higher incidence in women than in men. In addition, weight gain is higher in patients who are overweight before the start of treatment (9).

Histamine-1 (H1) receptor blockers

H1 receptor blockers are widely used as sedative and antiallergenic, and weight gain is one of their possible side effects. According to the 2005-2006 National Health and Nutrition Examination Survey, patients using H1 receptor blockers (cetirizine, fexofenadine, and desloratadine) had significantly higher weight, waist circumference, and insulin levels. However, further research is needed to determine the role of histamine in energy metabolism (26).

Drugs that May Cause Micronutrient Disorders

Micronutrients are indispensable for vital functions but are a global problem for two billion people worldwide. The effects of drugs on nutrients may lead to a reduction or depletion of micronutrients in various ways (27). In a study on 390 geriatric patients with drug-induced micronutrient deficiency, antacids caused phosphate deficiency (32.8%); digoxin potassium, calcium, and magnesium deficiency (29.5%); and bisacodyl vitamin D, vitamin K, potassium, and calcium deficiency (29%) (28). Drugs with effects such as inducing micronutrient metabolizing enzymes, inactivating digestion-related enzymes, complex formation, oral mucosal and intestinal flora damages, impaired gastrointestinal motility, changes in pH, loss of appetite, nausea, vomiting, diarrhea, and constipation can disrupt the absorption, distribution, and metabolism of micronutrients and can increase intestinal and renal excretions (29).

Acid-suppressing drugs

H2 receptor antagonists and PPIs are commonly prescribed for treating gastroesophageal reflux disease and peptic ulcer. These drugs cause various nutritional deficiencies (30). They can block histamine and reduce acid secretion, thereby reducing the absorption of calcium, iron, zinc, folic acid, vitamins D, and vitamin B12 and ultimately resulting in micronutrient deficiencies (29, 31).

PPIs reduce gastric acid production by up to 99% by decreasing the effect of proton pumps, which are a part of the stomach acid production mechanism. This action causes micronutrient deficiencies by decreasing the absorption of vitamin B12 and magnesium (29). Sufficient gastric acid is required for vitamin B12 absorption. Both PPI and H2 blockers significantly increase the risk of vitamin B12 deficiency in elderly patients, especially because these patients do not have sufficient gastric pH for B12 absorption (30). Thiazide-induced hypercalcemia may be significant enough to mask PPI-induced hypocalcemia and hypomagnesemia. Therefore, physicians should remember that long-term concomitant use of PPI and H2 blockers may lead to electrolyte imbalance (32).

Antibiotics

Antibiotics can reduce the absorption of micronutrients, form complexes, induce enzymes, cause mucosal damage, chelate, and reduce the endogenous production of micronutrients (29). Thus, deficiency in antibiotic-induced vitamins B1, B2, B3, B5, B6, B12, A, D, and K; folic acid; iron; calcium; magnesium; and potassium may occur (29, 30, 33). While fluoroquinolones cause calcium and iron deficiencies, tetracyclines can inhibit the absorption of vitamin B6, calcium, magnesium, iron, and zinc in the gastrointestinal tract when they bind to this type of drug (30, 34). Moreover, trimethoprim causes folic acid deficiency; penicillin and cephalosporins cause B and K vitamin deficiencies; and aminoglycosides, such as gentamicin, neomycin, and streptomycin, cause magnesium, calcium and potassium imbalance, and vitamin B and K deficiencies (30, 34).

Cardiovascular drugs

Beta blockers reduce the blood pressure by decreasing the effects of catecholamines, thereby reducing the heart rate. Beta blockers interfere with the production of this essential enzyme for energy production, leading to CoQ10 deficiency. Given that the target condition is a cardiovascular disease, the lack of CoQ10 is particularly dangerous. The presence of CoQ10 deficiency, which is needed in high amounts by mitochondria in the heart, increases the risk of heart failure (30). Digoxin, which is used for treating arrhythmias, increases renal elimination and causes magnesium, potassium, calcium, phosphorus, and vitamin B1 deficiencies (29).

Some antihypertensive drugs cause micronutrient deficiencies by increasing the renal elimination of micronutrients or by decreasing the functionality of cell work (29). Loop and thiazide diuretics cause deficiency in sodium; potassium; magnesium; vitamins B1, B6, and C; zinc; and CoQ10. Meanwhile, thiazide diuretics increase calcium, whereas loop diuretics reduce calcium content in the body. While potassium-sparing diuretics increase the amount of potassium, they also cause calcium, folic acid, and zinc deficiencies (34). ACE inhibitors also increase potassium levels while causing zinc deficiency (34, 35). Routine electrolyte monitoring is recommended in high-risk patient groups (pediatric and geriatric patients with renal failure), especially when using antihypertensive drugs that cause electrolyte imbalance.

Oral antidiabetic drugs

Vitamin B12 absorption decreases in patients with diabetes using metformin (29, 36). Metformin causes vitamin B12 deficiency in a dose- and time-dependent manner. According to the American Diabetes Association, vitamin B12 levels should be routinely checked in patients taking metformin, considering that B12 deficiency is associated with significant side effects, such as anemia and cognitive impairment (7, 37). Serum folic acid levels also decrease in patients with type 2 diabetes on metformin therapy. Vitamin B12 and folic acid depletion increase the homocysteine levels. In addition, metformin can reduce the CoQ10 levels, increasing the risk of heart disease (30). According to a cross-sectional study, a significantly higher rate of malnutrition was found in patients receiving two or more antidiabetic medication (38).

Statins

Commonly prescribed statins cause CoQ10 and vitamin D deficiencies (29, 30). Statins block the activity of 3-hydroxy 3-methylglutaryl coenzyme-A (HMG-CoA), which is an enzyme necessary for cholesterol production in the body. This blockade leads to the lack of CoQ10, which requires HMG-CoA for its production. Thus, harmful effects on muscle and heart health may occur. Therefore, daily supplementation of 100-200 mg of CoQ10 is recommended for patients using statins (30).

Anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs cause iron and folic acid deficiencies, whereas salicylates cause iron, folic acid, potassium, sodium, vitamin C, and vitamin B5 deficiencies. These drugs reduce the absorption and function of micronutrients in the cell (29). Prolonged use of high doses of aspirin is associated with gastric mucosa irritation, gastritis, peptic ulcer disease, nausea, anorexia, malnutrition, and decreased vitamin C levels. However, evidence of vitamin C reduction or that vitamin C supplementation is needed in patients receiving chronic low-dose aspirin is unavailable (7). Furthermore, patients using steroids (prednisone, methylprednisolone, triamcinolone, and dexamethasone) can experience deficiency in calcium; magnesium; zinc; vitamins B6, B12, C, and D; folic acid; selenium; and chromium (34).

Psychotropic drugs

For antidepressant drugs to work best, vitamin B must be present as sufficient cofactors to help produce the necessary neurotransmitters, such as serotonin and dopamine. Therefore, these drugs may not directly reduce the level of vitamin B, but patients should be known whether they have vitamin B deficiency (30). SSRIs can cause folic acid deficiency, TCAs and phenothiazines can cause CoQ10 and B2 vitamin deficiencies, benzodiazepines can cause calcium deficiency, and haloperidol can cause CoQ10 deficiency (29). In addition, lithium carbonate used for treating bipolar affective disorder can cause folic acid and inositol deficiencies (30).

Antiepileptic drugs

Antiepileptic drugs cause micronutrient deficiencies by reducing their absorption and increasing their metabolism, enzyme induction, and chelation. Barbiturates cause calcium, folic acid, vitamin D, and vitamin K deficiencies. Phenytoin also causes deficiency in calcium, folic acid, vitamins B1, B2, and D, and carbamazepine causes folic acid and vitamin D deficiencies. Meanwhile, valproic acid is associated with L-carnitine deficiency (29). In a study conducted by Mintzer et al. on 33 patients, enzyme-inducing antiepileptic drugs (phenytoin and carbamazepine) caused more vitamin B deficiency than non-enzyme-inducing antiepileptic drugs (levetiracetam, lamotrigine, and topiramate) ($p<0.05$) (39).

Hormone replacement therapy and oral contraceptives

Hormone replacement therapy and oral contraceptives lead to deficiencies by decreasing the absorption of mi-

cronutrients and increasing their metabolism and elimination (29). These drugs may cause deficiency in folic acid; vitamins B1, B2, B3, B6, B12, and C; magnesium; selenium; and zinc (34).

Other drugs

Methotrexate causes folic acid deficiency by reducing the functionality of secondary folate required for pyrimethamine, pentamidine, triamterene, and dihydrofolate reductase inhibition. Methotrexate also causes vitamin D deficiency, resulting in oral mucositis (40). Meanwhile, sulfasalazine causes folic acid deficiency by disrupting the absorption and metabolism of intestinal folate (3).

Isoniazid forms a complex with pyridoxine, causing increased urinary excretion of pyridoxine and leading to the lack of pyridoxine. Niacin synthesis is impaired due to pyridoxine deficiency; patients using isoniazid were found to have both pyridoxine and niacin deficiencies (3).

Cholestyramine induces cytochrome P 450 enzyme, resulting in the deficiencies of vitamins D, E, and K. This drug also causes folic acid deficiency (3).

Amphotericin causes potassium deficiency by increasing the renal loss of potassium, accompanied with magnesium deficiency (3, 35). In addition, foscarnet, which is a nephrotoxic drug, causes calcium, magnesium, and potassium deficiencies (34).

Vitamin B12 deficiency, which elevates the risk of chemotherapy-induced peripheral neuropathy, is increased especially when using the taxol-containing chemotherapeutic agents, leading to neurotoxic effects (41).

Effect of Drugs on Clinical Nutrition

Parenteral nutrition (PN) is generally administered as an intravenous infusion with the simultaneous administration of medications; thus, PN may be a suitable carrier. Adding a drug into the PN bag is a common practice because it does not need additional fluid in patients with fluid restriction, requires less venous catheters, and reduces the administration time. However, adding drugs into parenteral and enteral nutrition mixtures is not recommended because of the high risk of stability and incompatibility problems (35).

Feeding can often be frequently interrupted because of the administration of medication through the feeding tube. In this case, the infusion rate must be increased appropriately to meet the required caloric requirement; otherwise, this event results in malnutrition. For high-dose catecholamine users with hemodynamic instability, enteral nutrition should be interrupted until their hemodynamics stabilizes; meanwhile, caution should be exercised in enteral nutrition for low-dose catecholamine users (35). Adequate gastrointestinal blood flow is required for proper absorption and use of nutritional products. Considering that patients are not hemodynamically stable in cases such as sepsis, hemorrhage, hypovolemia, polytrauma, and cardiogenic shock, vasoactive agents, such as norepinephrine, epinephrine, phenylephrine, dopamine, and dobutamine, are needed to reserve blood flow to vital organs, including the heart and the brain. Hence, gastrointestinal blood flow decreases. If increased oxygen demand in the intestine cannot be met due to enteral nutrition, intestinal ischemia and rarely, small intestine necrosis with high mortality risk may occur. Given that ischemia in the intestine and necrosis in the small intestine are feared complications, application of enteral nutrition should be avoided as much as possible in patients requiring vasoactive substances (35).

Management of Drug-Induced Malnutrition

Patients with malnutrition should be monitored closely when initiating a medication and regularly reviewed to ensure that any weight loss can be detected quickly and corrective measures are taken. When attempting to increase weight gain, a multimodal approach is necessary, the dietician should be consulted, and healthy dietary recommendations should be given (8).

For drugs that may cause nausea and vomiting, an appropriate antiemetic drug can be selected to determine possible receptor stimulation. In a study conducted by Davidson et al. on 121 patients with cancer who had chemotherapy, chemotherapy-induced nausea and vomiting, which require urgent intervention, were detected in 26% of patients (42). Drug-induced nausea and vomiting should be closely monitored in such patients who are highly at risk. However, of note, drug-induced nausea and vomiting may indicate drug toxicity, such as digoxin or theophylline toxicity. The choice of antiemetic should not destroy the desired therapeutic effect of the targeted treatment. For example, the use of metoclopramide in nausea associated with levodopa treatment worsens Parkinson's symptoms due to central dopamine blockade (8).

For many drugs, reduced gastrointestinal motility is a dose-dependent effect, which can be minimized by lowering the dose or changing the preparation. The diet plan includes adequate oral or enteral fluid therapy and fiber supplementation. A multidisciplinary approach is needed to manage constipation, which may adversely affect

the quality of life of patients (8). Diarrhea spontaneously passes for most drugs or ends with drug discontinuation. Taking drugs with food and re-adjusting the dose of drugs may gradually reduce the symptoms (8).

In dry mouth, the severity of symptoms can be reduced by using a modified release preparation of the drug or by dividing the dose. If an alternative drug in the same class can achieve the desired therapeutic effect with fewer symptoms, then drug change is necessary. If discontinuing the drug that reduces patient compliance is not an option, the timing of drug administration should be adjusted to minimize the effect on oral intake and mealtime. In severe cases, the use of saliva stimulants and artificial saliva products may be appropriate (8).

Drug-induced taste disorders may be managed by researching for other reasons, such as dry mouth or depression, and when identified, taking corrective measures. Discontinuation of this drug should be considered when a clear association with a particular drug is identified. If discontinuing the responsible drug is not possible, using lozenges containing oral spray and local anesthetics may be beneficial (8).

Weight gain in the first month after treatment is a strong indicator of long-term weight gain. Therefore, patients should be monitored before and shortly after starting weight-gaining medications, and an increase of 5% above the baseline weight after the first month should encourage physicians to reconsider treatment options or initiate weight control strategies (9). Given that insulin, sulfonylurea, and thiazolidinediones are antidiabetic agents that cause significant weight gain, metformin and DPP-4 inhibitors can be used as alternatives because they do not cause weight gain. Furthermore, SGLT-2 inhibitors and GLP-1 receptor analogues cause weight loss. The effects of insulin on body weight can be reduced by adding metformin. With the new pharmacological classes, the effects of drugs on weight can be reduced, and even weight loss can be achieved (9).

Appropriate dietary strategies specific to the patient should be developed in drug-induced micronutrient disorders. In addition, considering that antibiotics affect the beneficial bacterial flora, including *Lactobacillus acidophilus* and *Bifidobacterium bifidum* in the digestive tract, probiotic intake is recommended in patients using antibiotics (30).

Conclusion

For preventing drug-induced nutritional disorders and the undesirable effects of these disorders, physicians and other healthcare providers need to accomplish the following: diagnose the disease properly, re-evaluate the selected treatment frequently, identify the treatments and disease stages necessary to minimize the number of drugs given, make a rational nutritional assessment, and if necessary, plan the optimal nutrition therapy to avoid adverse effects of drug-induced nutritional disorders.

The entire multidisciplinary team should be aware of the possible effects of drug treatment on nutritional status. Any nutritional assessment should include observation and intervention regarding the patient's medication. At this point, clinicians' should identify and analyze drug-induced nutritional disorders and minimize risk factors at the most appropriate time with the most appropriate way.

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Nutritional support practices among intensive care units in Turkey: One-day cross-sectional study

Kubilay Demirağ[1], Sadık Kılıçturgay[2], Derya Hopancı Bıçaklı[3], Hülya Sungurtekin[4], Kutay Demirkan[5], Murat Gündüz[6], Özgür Canoler[7], Tülay Erkan[8], Zekeriya Ülger[9], Osman Abbasoğlu[10]

[1]Department of Anesthesiology and Intensive Care, Ege University School of Medicine, İzmir, Turkey
[2]Department of General Surgery, Uludağ University School of Medicine, Bursa, Turkey
[3]Department of Oncology, Ege University School of Medicine, İzmir, Turkey
[4]Department of Anesthesiology and Intensive Care, Pamukkale University School of Medicine, Denizli, Turkey
[5]Department of Clinical Pharmacology, Hacettepe University School of Pharmacology, Ankara, Turkey
[6]Department of Anesthesiology and Intensive Care, Çukurova University School of Medicine, Adana, Turkey
[7]Department of Anesthesiology, Acıbadem Hospital, Ankara, Turkey
[8]Department of Pediatrics, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey
[9]Department of Internal Medicine, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[10]Department of General Surgery, Hacettepe University School of Medicine, Ankara, Turkey

ORCID IDs of the authors: K.D. 0000-0003-1311-7972; S.K. 0000-0002-2427-8344; D.H.B. 0000-0003-1594-3266; H.S. 0000-0002-9453-5625; K.D. 0000-0002-6427-5826; M.G. 0000-0002-0373-892X; Ö.C. 0000-0002-6697-7055; T.E. 0000-0002-8924-2799; Z.Ü. 0000-0002-6325-496X; O.A. 0000-0001-7069-929X

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ABSTRACT

Objective: Malnutrition is a significant problem among critically ill patients and is closely associated with poorer patient outcomes. With this study, we aimed to assess nutritional support practices and to evaluate the associated patient outcomes in intensive care units (ICU) in Turkey.

Methods: This one-day, cross-sectional study was conducted in November 2015. A total of 1140 patients from 120 ICUs in 46 hospitals across Turkey were included. The general characteristics of the ICUs and patients, clinical data regarding nutritional support, hospitalization courses of the patients, and patient outcomes were recorded. The study questionnaire was prepared by the investigators and was completed by health care professionals from various hospital departments.

Results: The mean age of the patients (55.7% were men) was 66.8±18.0 years. The median duration of the ICU stay was 17 days. Enteral tubes were present in 649 patients, of whom 79.4% had nasogastric tubes, 15.3% had percutaneous endoscopic gastrostomy (PEG) tubes, 4% had nasojejunal tubes, and 1.4% had surgical gastrostomy/jejunostomy tubes. 68.1% of ICUs had a nutritional support team. Nutritional support applied included enteral nutrition (44.1%), oral nutrition (25.9%), parenteral nutrition (18.5%), and enteral + parenteral nutrition (11.5%). On the 60th day, the mortality rate was 39.5%. Mortality rates were significantly lower in the oral nutrition group compared with the other groups, and were significantly higher in the parenteral nutrition group compared with the other groups.

Conclusion: Our findings confirm the importance of nutritional support teams to provide timely and adequate administration of nutritional support and its association with better patient outcomes. Additionally, better outcomes were obtained with enteral nutrition compared with parenteral nutrition.

Keywords: Enteral nutrition, intensive care unit, parenteral nutrition, Turkey

Introduction

Malnutrition is a generic term used to describe any imbalance in nutrition. Malnutrition is associated with several factors, including reduced food intake, increased metabolic demands, disease conditions, and pathologic features such as poor absorption or excess loss or a combination of these factors (1, 2). The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines define malnutrition as "a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, or other nutrients causes measurable, adverse effects on tissues or body form (body shape, size, or composition) and function, and clinical outcome" (3). Timely and appropriate interventions for malnutrition during the hospital stay are a key factor leading to better patient outcomes, given previous studies have reported that malnutrition prevalence in hospitalized critically ill patients can reach up to 50% (4-7).

Corresponding Author: Kubilay Demirağ; kubilaydemirag@gmail.com

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Course of intensive care unit (ICU) has many challenges for patients including their nutritional status (8). Advances in nutritional technology and support in recent decades have led to nutritional support becoming an integral part of routine patient care (9). Currently, nutritional support is considered a *sine qua non* in the ICU (10).

Adequate nutritional support to critically ill patients is associated with improved outcomes. Inadequate nutrition can result in complications including decreased and delayed wound healing, an increased risk of infection, poorer cardiac function, increased muscle loss, and impaired renal function (11). Moreover, seriously ill ICU patients, who have a particularly increased risk of malnutrition prior to hospitalization in the ICU, require more attention to existing nutritional deficits (8). If nutritional support is provided according to the guidelines and best practices in the ICU, complications, the need for ventilators, and the excess risk of mortality can be reduced (12, 13).

Therefore, determining the current status of nutritional interventions in ICUs and an evaluation of patient outcomes are critical for making reliable assessments and recommendations. Nevertheless, national data on these issues in Turkey are limited. The only national study to date was conducted by the Turkish Society of Clinical Enteral and Parenteral Nutrition (*Klinik Enteral Parenteral Nütrisyon Derneği* - KEPAN) between June 2005 and January 2006, results of which were published by Korfali et al. in 2009 (14). That study evaluated data from 19 cities, 34 hospitals, and 29,139 patients and reported an overall nutritional risk prevalence of 15% in all patients at first admission and of 52% for patients in ICUs. Ten years later, the present study was conducted with the aims of determining the current status of nutritional assessments, interventions, and methods applied in ICUs in Turkey and evaluating the associated patient outcomes.

Methods

The present study was a one-day, national cross-sectional study evaluating the nutritional support practices in ICUs in Turkey. It was conducted under the supervision of KEPAN in November 2015. The study questionnaire was prepared by the investigators and was completed by health care professionals (physicians, dietitians, or nurses) within a one-week period. Patients ≥18 years of age were included. Participation in the study was voluntary for both patients and health care professionals. The study protocol was approved by the Çukurova University Hospital Ethics Committee.

For obtaining an overall country-wide inference, 120 ICUs of 46 major hospitals (20 university hospitals, 24 state hospitals, and 2 private hospitals) were identified among 20 provinces in Turkey (Figure 1). For the determination of the participating hospitals, a balance between academic and non-academic centers and those providing services to various patient groups was considered. After determining the participating centers, a full-day training meeting was organised before the initiation of the study. This training was arranged and carried out participation of 2 health care personnel (physicians, dietitians, or nurses) from the study team who organized the procedures in the centers. During this training, all details about the study were explained and all forms were completed.

Figure 1. Geographical distribution of the study centers

Table 1. Demographic characteristics of the patients			
	Total	Females (n=505)	Males (n=635)
Age (years)	66.8±18.0	69.0±17.8	65.0±18.0
Weight (kg)	73.2±15.3	71.5±16.8	74.6±14.0
Height (cm)	166.9±9.1	162.4±8.4	170.5±7.9
BMI (kg/m^2)	25.7 (11.7-64.5)	26.2 (14.2-64.5)	25.2 (11.7-49.9)

Data are presented as mean±standard deviation or median (interquartile rage), where appropriate. BMI: body mass index

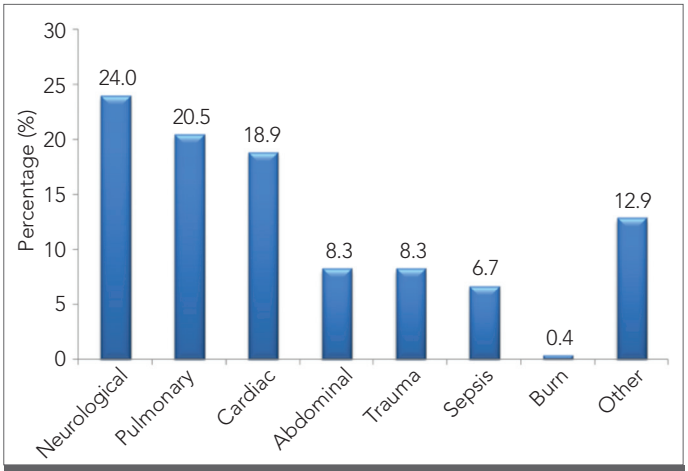

Figure 2. Reasons for hospitalization in intensive care units

A questionnaire was prepared to assess the general characteristics of the ICUs, health care personnel, and patients, as well as to evaluate clinical data regarding nutritional support, hospitalization courses of patients, and patient outcomes including mortality, discharges, and referrals to departments other than the ICU.

Statistical analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences Statistics for Windows software package, Version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive data were expressed as mean and standard deviation, median and interquartile range (IQR), or frequency and percentage. Statistical comparisons between independent groups were conducted using the Mann-Whitney U test for two groups and using the Kruskal-Wallis test for more than two groups. The Bonferroni correction was used for post-hoc pairwise comparisons. A type-I error level of 5% was considered statistically significant.

Results

We included 1140 patients (55.7% men) with the mean age of 66.8±18.0 years. Demographic features of the patients are shown in Table 1. About 73.1% of the patients had an underlying medical disorder and neurological (24.0%), pulmonary (20.5%), and cardiac (18.9%) diagnoses were the most frequent reasons for hospitalization (Figure 2). The most frequent comorbidities were diabetes (22.9%), congestive heart failure (17.5%), and cancer (13.6%). On the day of data collection in the ICUs, the median duration of hospitalization for all patients was 7 days (IQR: 2-19 days). The mean APACHE-II score was 18.9±8.2 (median, 18, IQR: 13-24). Regarding the types of catheters present during the day of the study, 78.3% were urinary catheters, 60.1% were peripheral venous catheters, 48% were central venous catheters, and 24.6% were arterial catheters. Enteral tubes were present in 649 patients, of whom 79.4% had nasogastric tubes, 15.3% had a percutaneous endoscopic gastrostomy (PEG) tubes, 4% had nasojejunal tubes, and 1.4% had surgical gastrostomy/jejunostomy tubes.

68.1% of ICUs had a nutritional support team (NST) at their facilities. Among the ICUs, 30.4% were using national/international nutrition guidelines, 29.5% had individualized nutrition treatment plans, 6.3% had their own nutrition protocol and 33.9% had no written procedures on nutrition. Types of nutritional support provided in the ICUs were enteral nutrition (44.1%), oral nutrition (25.9%), parenteral nutrition (18.5%), and enteral+parenteral nutrition (11.5%). The median duration of enteral and parenteral nutrition was 10 days (IQR: 4-30 days) and 4 days (IQR: 2-9 days), respectively. The most frequent reasons for not starting oral nutrition were intubation (64%), a risk of aspiration (52.7%), and being unable to swallow (42.7%). Nutritional support was interrupted in 248 patients due to surgical reasons (36.7%), intolerance (27%), and transportation (4%). The most commonly used products for enteral nutrition were polymeric standard products (31.5%), hypercaloric products (20.9%), and diabetic products (20.2%).

Parenteral nutrition was delivered through central venous access in 60.7% of the patients and through peripheral access in 39.3% of the patients. 63.5% of the parenteral nutrition solutions were all-in-one products, 35% were prepared as compounder solutions and multiple bottles were used for 1.5% of the patients. The most frequently used all-in-one parenteral nutrition products were soy-based products (37.3%), olive oil based products (34.6%), and soy/olive/fish oil based products (16%). The most frequent adjuncts used were glutamine (n=110), omega-3 fatty acids (n=91), trace elements (n=133), and vitamin-E (n=59), which were administered to 265 patients in various combinations. The ratio of given/planned calorie and protein supplementation was 87.2% and 86.7%, respectively. The products used for oral, enteral, and parenteral nutrition are shown in Figure 3.

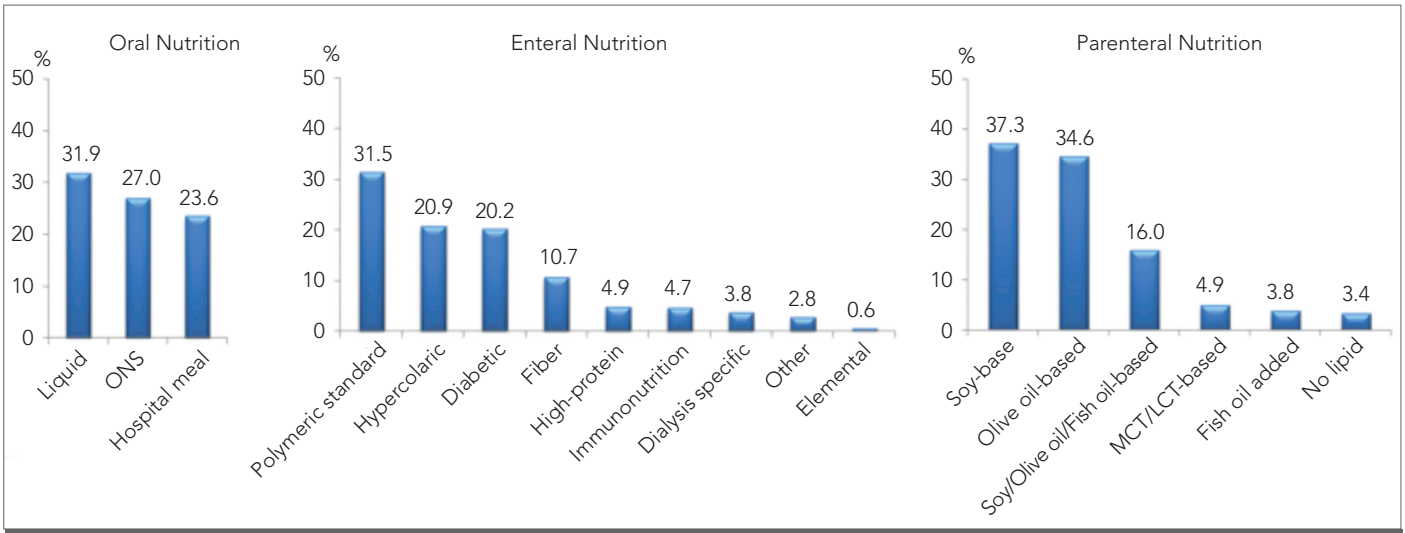

Figure 3. Products used for oral, enteral, and parenteral nutrition
ONS: oral nutritional supplement; MCT: medium-chain triglyceride; LCT: long-chain triglyceride

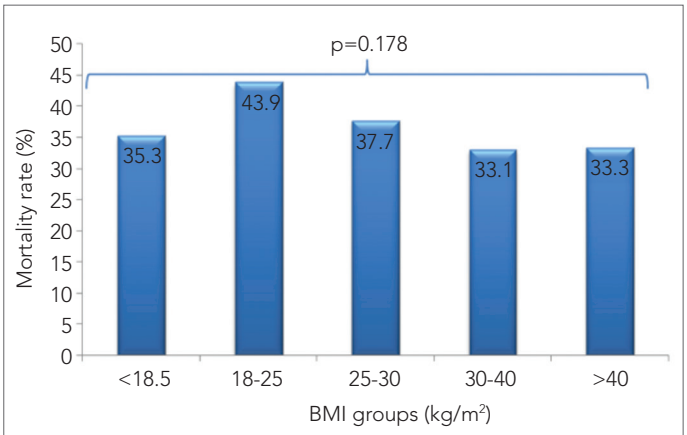

Figure 4. Mortality rates according to body mass index groups

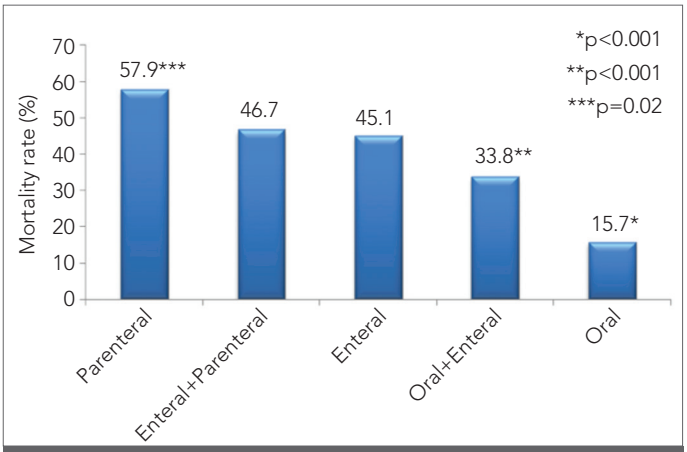

Figure 5. Mortality rates according to modes of nutritional support
(Mortality rate: * significantly lower in the oral nutrition group compared to those in other groups; ** significantly lower in the oral + enteral group than in the parenteral and enteral + parenteral groups; and *** significantly higher in the parenteral nutrition group than in the parenteral and enteral + parenteral groups)

The median duration of the ICU stay was 17 days (IQR: 6-42 days) and the median duration of the total hospital stay was 23.5 days (IQR: 11-48 days). On the 60th day, the mortality rate was 39.5%, the discharge rate was 44.1%, and the hospitalization rate was 16.4%. When the mortality rates were evaluated with regard to body mass index (BMI), no statistically significant differences were found among the BMI groups (p=0.178, Figure 4). In terms of mortality and the modes of nutritional support, mortality rates were significantly lower in the oral nutrition group than in the other groups (p<0.001). When oral and enteral nutrition were considered together, the mortality rate was again significantly lower in the oral+enteral group than the rates in the parenteral and enteral+parenteral groups (p<0.001). On the other hand, the mortality rate in the parenteral nutrition group was significantly higher than those in the enteral and enteral+parenteral groups (p=0.02) (Figure 5).

Discussion

Assessing nutritional status and performing appropriate nutritional interventions for patients in ICUs is critical for enhanced treatment responses, better recovery, and improved patient outcomes. Based on these facts and the high prevalence of malnutrition in ICUs, the present study was designed to evaluate the current status of nutritional approaches used in ICUs and to investigate associated patient outcomes in Turkey. Our results revealed that about 2/3 of the ICUs in Turkey had an NST in their facilities. The importance of an NST for patients hospitalized in ICUs has been emphasized in previous studies, including a recent

study by Jo et al. (15) who reported that the involvement of a multidisciplinary nutrition team significantly improved the proportion of enteral nutrition provision and nutritional goal achievement. These authors also reported that the presence of a multidisciplinary nutrition team in ICUs was associated with better patient outcomes during discharge from the units. These findings have been supported by other studies, such as a recent study from Turkey by Yilmaz et al. (16), which reported that the presence of a nutrition team directly affected the clinical outcomes of the patients undergoing treatment in ICUs. Another study by Mo et al. (17) reported that the activities of an NST comprised of doctors, pharmacists, and nutritionists decreased medical costs as well as improved the outcomes of the patients in ICUs. Similar results have also been reported in other studies (18, 19). In addition, in our study, about 2/3 of ICUs had national/international nutrition guidelines, individualized nutrition treatment plans or their own nutrition protocol, and this percentage reflected the ICUs with an NST. All of this evidence suggests that the contribution of an NST is important and effective in improving outcomes.

Another finding of the present study was that oral and enteral nutritional support were administered to a majority of the patients and that nasogastric and PEG were the most frequently used routes for enteral nutrition. Additionally, all-in-one solutions were the most frequently used products for parenteral nutrition and trace elements were not adequately used for supplementation. Currently available data suggest that enteral nutrition is preferable to parenteral nutrition for several reasons. First, enteral nutrition has been suggested to be associated with immune-enhancing properties as well as with a reduced incidence of infections (20, 21). Immunological changes associated with nutritional status include impairment of the gut-associated lymphatic system in cases of decreased oral and enteral nutrition. Patients who are shifted from an oral/enteral regimen to parenteral feeding despite the presence of a functional intestinal system encounter increased activated cells and proinflammatory stimulants during gut starvation (22). The secondary mechanisms include permeability changes and bacterial translocation (8). Nevertheless, there is an ongoing debate on these topics in the literature (23, 24). A meta-analysis of 27 nutrition studies conducted on 1828 patients concluded that enteral nutrition was associated with a lower risk of infections (relative risk: 0.66; 95% Confidence Interval [CI] 0.56-0.79) but had no advantage regarding mortality (RR: 0.96; 95% CI 0.55-1.65) (25). Our study revealed that enteral nutrition and oral nutrition were administered to the majority of patients, showing that NSTs and health professionals in the ICUs in Turkey followed the updated guidelines in accordance with recent research on nutrition. Moreover, our results regarding the comparisons between subgroups revealed that the duration of hospitalization in ICUs or other departments were not correlated with BMI or mortality rates. However, the mortality rates were significantly lower in the patients in the oral nutrition group and significantly higher in the patients in the parenteral nutrition group as compared with the patients in the enteral nutrition and enteral +parenteral nutrition groups. These findings are also in accordance with the literature data that favor enteral nutrition over parenteral nutrition.

In the present study, about 87% and 86% of the planned calories and protein were delivered to the patients. The median duration of hospitalization in the ICUs was 7 days, whereas the median duration of enteral nutrition was 10 days, suggesting that some patients were taking enteral nutrition during hospitalization in other non-ICU departments. According to the current guidelines of the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine, and ESPEN guidelines on clinical nutrition in the intensive care unit, initiation of enteral nutrition during the first 48 hours of an ICU stay is recommended for critically ill patients to deliver 80% to 100% of their estimated calorie and protein needs (20, 26). Achieving these estimated calorie and protein goals has been demonstrated to be associated with significantly decreased mortality and hospital stays in critical care patients (27). Our results in terms of calorie and protein delivery are in accordance with those recommended in the guidelines; this suggested favorable outcomes in our study population.

In conclusion, the present study determined the current status of nutritional support in ICUs in Turkey. Our findings confirm the importance of NSTs in providing adequate nutritional support via the optimal route and confirm the favorable outcomes that have been associated with enteral nutrition over parenteral nutrition.

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Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K.; Design - S.K., K.Demirağ., D.H.B.; Supervision - O.A.; Data Collection and/or Processing - H.S., M.G., Ö.C., Z.Ü.; Analysis and/or Interpretation - K.Demirağ., D.H.B.; Literature Search - T.E., K.D.; Writing Manuscript - K. Demirağ.; Critical Review - S.K.

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Malnutrition and associated risk factors in nursing home residents in Turkey

Cafer Balcı[1], Zekeriya Ülger[2], Meltem Gülhan Halil[1], Derya Hopancı Bıçaklı[3], Gülistan Bahat Öztürk[4], Zeynel Abidin Öztürk[5], Fatih Sümer[1], Özlem Yılmaz[4], Sevilay Muratlı[4], Hülya Sungurtekin[6], Kubilay Demirağ[7], Osman Abbasoğlu[8], Sadık Kılıçturgay[9]

[1]Department of Geriatric Medicine, Hacettepe University School of Medicine, Ankara, Turkey
[2]Department of Geriatric Medicine, Çankaya Hospital, Ankara, Turkey
[3]Department of Oncology, Ege University School of Medicine, İzmir, Turkey
[4]Department of Geriatric Medicine, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
[5]Deparment of Geriatric Medicine, Gaziantep University School of Medicine, Gaziantep, Turkey
[6]Department of Anesthesiology and Reanimation, Pamukkale University School of Medicine, Denizli, Turkey
[7]Department of Anesthesiology and Reanimation, Ege University School of Medicine, İzmir, Turkey
[8]Department of General Surgery, Hacettepe University School of Medicine, Ankara, Turkey
[9]Department of General Surgery, Uludağ University School of Medicine, Bursa, Turkey

ORCID IDs of the authors: C.B. 0000-0002-1478-1106; Z.Ü. 0000-0002-6325-496X; M.G.H. 0000-0001-7597-8140; D.H.B. 0000-0003-1594-3266 ; G.B.Ö. 0000-0001-5343-9795; Z.A.Ö. 0000-0002-1717-2824 ; F.S. 0000-0003-3980-5036; Ö.Y. 0000-0001-9868-2828; S.M. 0000-0002-0237-1433; H.S. 0000-0002-9453-5625; K.D. 0000-0003-1311-7972; O.A. 0000-0001-7069-929X; S.K. 0000-0002-2427-8344

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ABSTRACT

Objective: Malnutrition is a common problem in nursing home residents. The aim of this study was to evaluate the prevalence of malnutrition and to determine the factors independently associated with malnutrition in this setting.

Methods: A cross-sectional, multi-center study was conducted in 21 nursing homes in Turkey. Nutritional status was assessed using the Mini Nutritional Assessment (MNA). Data on possible associated factors were collected using validated scales.

Results: The study included 1224 residents; 45.7% of the residents were at risk for malnutrition and 23.4% were malnourished. Cognitive impairment, dependence in activities of daily living, and dysphagia were significantly associated with malnutrition.

Conclusion: Malnutrition is a prevalent problem in nursing homes in Turkey. Systematic screening and well-defined tailored interventions should be further developed and evaluated in nursing home residents.

Keywords: Malnutrition, nursing home, residents

Introduction

With increased life expectancy among older adults, increased health-care spending, in particular for institutional care, has become an issue of concern in many countries (1). Malnutrition appears to occur frequently in older adults and has been associated with adverse health outcomes. The prevalence of malnutrition among older adults varies between 0% and 78%, and this variety is mainly due to the inclusion of different settings, age categories, underlying diseases, and screening instruments (2). The outcome of chronically poor nutritional status and unrecognized or untreated malnutrition is frequently associated with considerable dysfunction and disability, reduced quality of life, increased institutionalization, premature or increased morbidity and mortality, and increased health-care costs (3).

Screening for malnutrition among nursing home residents is a crucial first step for early affected older adults, and those at risk should be followed by comprehensive geriatric assessment and initiation of appropriate nutritional treatment (4, 5). Factors associated with malnutrition, such as immobility, frailty, dementia, depression, and difficulties in eating and swallowing, are also considered as risk factors for institutionalization. Thus, an institutionalized older adult is more predisposed to malnutrition compared to community-dwellers. Recovering nutritional status is difficult for the already malnourished older adults; therefore, it is important to evaluate the nutritional risk of nursing

Corresponding Author: Cafer Balcı; caferbalci@gmail.com

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home residents early to prevent malnutrition and improve their nutritional status.

There are numerous studies that have evaluated the prevalence of malnutrition among nursing home residents in Turkey (6, 7), but to the authors' knowledge extensive studies identifying the factors associated with malnutrition in Turkish nursing homes are missing. Thus, this study aimed to report on (i) the prevalence of malnutrition and (ii) the associated factors of malnutrition in older adults living in Turkish nursing homes.

Methods

Study design and setting

This cross-sectional, multi-center study was conducted in 21 nursing homes in 12 different cities. A stratified random sampling was performed based on geographical region, number of beds, and funding characteristics (government or privately funded) among 362 nursing homes in Turkey. In each participating nursing home, volunteer residents 65 years and older who were residing at that center for at least 6 months were included in the study. Residents with the following conditions were excluded: (1) unable to communicate with others, (2) hospitalization in the previous 6 months, (3) residents who were not suitable for bioelectrical impedance analysis, and (4) bedridden. All participants (or legal proxies for those who were unable to sign) signed the informed consent. The study protocol was approved by the Gazi University Ethics Committee.

Data collection

Data on residents' demographic characteristics, anthropometric measurements, nutritional status, dysphagia, cognitive state, and functional state were collected by the dietitians in March 2017. Dietitians were educated by the researchers before the study to optimize and standardize the data collection. During this course, information about the study, procedure, and methods for data collection was provided. Sample patient cases were used to support the training and increase the accuracy and reliability of data collection.

Demographic characteristics

Dietitians completed the questionnaire with the residents and/or the professional nursing home caregivers most familiar with the characteristics of the residents. The questionnaire included (1) demographic characteristics (age and sex), (2) medical records, and (3) nutritional status (eating habits, food intake status, and body weight changes).

Anthropometric measurements

Anthropometric measurements, including weight, height, calf circumference, and hand grip strength, were performed by the dietitians according to the standardized and recommended procedures and techniques. The residents weighed in light clothing and without shoes using a calibrated floor scale. Height was measured while the resident was barefoot and standing in an upright position, standing against a wall, and looking forward using a tape measure and was recorded in centimeters. Body mass index (BMI) was calculated according to the equation: BMI = weight (kg)/height^2 (m). Calf circumference was measured twice while the patient was sitting, pressing the foot completely on the floor, and flexing the knee 90° using a measuring cylinder from the largest portion of the calf. Care was taken not to compress subcutaneous tissue. The arithmetic mean was recorded in centimeters with a sensitivity of 0.1 cm. Hand grip strength was measured using a digital dynamometer (TKK 5401 Grip-D; Takei, Niigata, Japan), and each device was calibrated before the initiation of data collection. Residents took the test while sitting on a bed or chair and their shoulder adducted and neutrally rotated, elbow flexed at 90°, and wrist neutrally positioned. The resident's dominant hand was used for the assessment. Each resident was given a demonstration before the measurement and then asked to complete a total of three maximal isometric contractions. The average readings showing on the display of the dynamometer were recorded, and the mean hand grip strength was calculated.

Nutritional status

The nutritional status of the residents was evaluated using the full Mini Nutritional Assessment (MNAÒ) tool. Full MNAÒ is an extensively validated instrument for grading the nutritional status of older persons and provides a multidimensional assessment of the patient (8). Its structure consists of 18 questions grouped into four categories (dietary habits, general status, anthropometry, and self-perceived health and nutrition states). Residents with a total score of <17 were considered as "malnourished". Residents with a score between 17 and 23.5 were considered as "at risk for malnutrition", whereas those with a score of 24 and above were considered as "well nourished" (8).

Dysphagia

For dysphagia screening, Eating Assessment Tool-10 (EAT-10) was used. EAT-10 is a functional health status questionnaire that measures the symptomatic severity of dysphagia from the patient's perspective (9) and requires the patient to rate several swallowing issues (e.g., coughing during meals, losing weight because of swallowing problems, and loss of pleasure during meals) on a five-point scale (0=no problem, 4=severe problem). Overall scores range from 0 to 40 points, and patients with a total score of 3 or more points were classified as "at risk for dysphagia".

Cognitive state

The Mini-Mental State Examination (MMSE) was used for cognitive evaluation. MMSE is a test that assesses cognitive ability by examining orientation, attention and calculation, registration, recall, language, and ability to follow simple commands (10). It has 11 items with a total score 0 to 30, and a low score is indicative of cognitive impairment.

Table 1. Characteristics of the elderly according to their nutritional status (MNA)				
	Well nourished (n=379)	At risk for malnutrition (n=559)	Malnourished (n=286)	p
Age	77.3±7.7	78.9±8.2	80.8±9	<0.001
Gender, female	163 (43%)	297 (53.1%)	186 (65%)	<0.001
Weight, kg	74.1±15	68.2±16	55.6±12.9	<0.001
Height, cm	158±10.1	156±10	155±8.8	0.054
BMI, kg/m^2	28.7±5.5	24.9±6.4	21.3±5.3	<0.001
Calf circumference, cm	36 (25–52)	34 (19–54)	28 (12–47)	<0.001
Hand grip strength, kg	20.8±9.6	15.3±9.5	8.4±8.1	<0.001
MNA score	26±1.9	20.2±1.8	13.2±2.7	<0.001
MMSE score	23.4±7.8	18.9±10.4	7.3±8.9	<0.001
Katz ADL score	5.2±1.4	4.6±2.4	2.8±1.6	<0.001
EAT-10 score	1.3±4.1	3.5±8.2	5.1±10.7	<0.001

BMI: body mass index; MNA: mini nutritional assessment; MMSE: mini mental state examination; EAT: eating assessment tool; ADL: activities of daily living

Functional state

The functional state of the residents was assessed by Katz Index of Independence in Activities of Daily Living (ADL). The index ranks the adequacy of performance in six functions of bathing, dressing, toileting, transferring, continence, and feeding (11). Clients are scored yes/no for independence in each of the six functions, and a score of 6 indicates full function.

Statistical analyses

IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) 21.0 for Windows® was used for statistical analysis. Variables were examined using visual (histograms and probability plots) and analytical methods to determine whether or not they were normally distributed. Mean±standard deviation and median, minimum–maximum (min–max) values were defined for normally distributed variables and other quantitative variables, respectively. Number (percentage) was defined for qualitative variables. For the comparison of groups, Kruskal–Wallis test or one-way analysis of variance were used where appropriate. Correlation analyses between continuous variables were performed by Pearson or Spearman correlation analyses, where appropriate. Multivariate logistic regression model was created to identify the independent predictors of malnutrition. Hosmer–+Lemeshow goodness-of-fit statistics were used to assess model fit. A 5% type I error level was used to infer statistical significance.

Results

A total of 1224 nursing home residents who fulfilled the inclusion criteria were enrolled in the study. The mean age of the study population was 79.05±8.3 years, and 646 (52.8%) were female. The median (range) duration of stay in the current nursing home was 36 (9–74) months. In total, 1 in 4 of the residents (23.4%) were found to be malnourished, 45.7% were at risk for malnutrition, and 31% were well nourished. An overview of the general characteristics and the nutritional status of the residents according to the MNA are presented in Table 1. Malnourished older adults had lower weight, BMI, calf circumference, and hand grip strength than older adults at risk for malnutrition and those with normal nutritional status (p<0.001). Well-nourished nursing home residents had less cognitive deficits compared to residents at risk for malnutrition and those who are malnourished (p<0.001).

According to correlation analyses, the MNA score was positively correlated with the MMSE score (r=0.595, p<0.001), calf circumference (r=0.550, p<0.001), hand grip strength (r=0.477, p<0.001), and BMI (r=0.226, p<0.001) but negatively correlated with the EAT-10 score (r =−0.139, p<0.001) (Table 2).

The multivariate model (Table 3) showed that residents who had a lower cognitive status, dependence in ADL, and dysphagia were associated with a significantly higher prevalence of malnutrition.

Discussion

This is the first study in Turkey that evaluated a great number of institutionalized older adults from every region of the country. The study revealed that approximately 1 in 4 residents (23.4%) was malnourished and 1 in 2 residents (45.7%) were at risk for malnutrition. The participants of the present

Table 2. Correlations between MNA score and factors related to malnutrition

	MNA score	
	r	p
Katz ADL score	0.683	<0.001
MMSE score	0.595	<0.001
Calf circumference	0.550	<0.001
Hand grip strength	0.477	<0.001
BMI	0.226	<0.001
EAT-10 score	–0.139	<0.001

MNA: mini nutritional assessment; ADL: activities of daily living; MMSE: mini mental state examination; BMI: body mass index; EAT: eating assessment tool

Table 3. Independent factors affecting malnutrition according to logistic regression analysis

	Adjusted odds ratio (95% confidence interval)	p
Age, per year increase	0.99 (0.97–1.01)	0.7
Gender, female	0.75 (0.54–1.02)	0.07
Katz ADL score, per point increase	0.62 (0.56–0.68)	<0.001
MMSE score, per point increase	0.94 (0.92–0.96)	<0.001
EAT-10 score, per point increase	1.06 (1.03–1.1)	<0.001

ADL: activities of daily living; MMSE: mini mental state examination; EAT: eating assessment tool

study were older, mostly female, and with high care needs and thereby representative of nursing home populations.

In 2013, a cross-sectional study was used to report the prevalence of malnutrition among nursing home residents in the capital city of Turkey. This study included 534 nursing home residents. The MNA-Short Form (SF) was used to assess the nutritional status of the residents, and the authors reported that 15.9% of the residents were malnourished, and 53.6% of those were considered at risk for malnutrition (7).

Cankurtaran et al. (6) conducted a cross-sectional study in 1797 residents in 14 nursing homes from three different cities of Turkey to (i) gain insight into the prevalence of malnutrition and (ii) identify the factors associated with malnutrition. The MNA-SF was used to assess the presence of malnutrition. The authors concluded that 11.9% of the residents were malnourished and 38.3% of those were at risk for malnutrition. According to the regression analyses of the study, Get Up and Go Test, depression, hypertension, and functional impairment were found to be independently related to malnutrition.

These repeated cross-sectional studies allowed us to explore the change in the prevalence of malnutrition among institutionalized older people. The results of this study highlight that malnutrition and its risk are still widely present and that these problems are yet unsolved in Turkish nursing homes. Also, the alarming proportion of residents (45.7%) identified at nutritional risk during screening in this study indicates that the efforts undertaken in practice to reduce prevalence seem insufficient or are without success.

According to the above-mentioned multivariate logistic regression analysis, three major factors were found to be independently associated with malnutrition in nursing homes: a lower cognitive status of the resident, the level of dependence in ADL, and the presence of dysphagia.

The association between malnutrition and a lower cognitive status was also found in several other studies (12, 13). The relationship between cognitive impairment and nutritional risk is a complex and reciprocal problem. Anorexia, polypharmacy, and accompanying depression seen in dementia are some of the major risk factors for malnutrition in people with dementia (14). Cognitive impairment has several negative consequences on the health of older adults; it can influence the prognosis of various conditions, reduce the quality of life, and increase morbidity/mortality and hospital admissions. Good nutritional status is important in maintaining cognitive performance, and an altered nutritional status appears to predict the severity and progression of cognitive impairment. Given the high prevalence of dementia among nursing home residents and the vicious cycle of malnutrition and cognitive impairment, the nutritional status of the residents should be evaluated regularly from the beginning of their institutionalization.

An interdependence relationship between nutritional status and functional status was observed in a study that evaluated 240 patients older than 60 years who were recently hospitalized (15). Of those patients, 37.1% were classified as at risk for malnutrition, whereas 29.1% of the patients were classified as malnourished using the MNA. Similar to the present results, malnourished patients were more dependent in ADL than those with well-nourished patients.

Several previous studies have shown that dysphagia is an important risk factor of malnutrition in nursing homes (16-19). This was also the case in the present study. Underweight, previous weight loss, and malnutrition according to the subjective judgement of the nursing home staff were significantly related to dysphagia. Most likely, malnutrition was the consequence of dysphagia; thus, to prevent malnutrition,

dysphagia should be recognized at an early stage. Swallowing problems also increase the risk of inadequate fluid intake and can contribute to the development of malnutrition.

In this study, the nutritional status of the nursing home residents was captured by the MNA instrument, which is easy to perform and specifically developed for use in older adults and has been validated in different settings (8). The MNA items reflect the specific conditions relevant to older adults and are based on age-adapted thresholds for anthropometric measurements. The key benefit of the MNA is its capacity to detect the risk of malnutrition (8). This is important to assure tailored nutritional care to protect a resident's functional capacity and quality of life.

There are some limitations of this study that need to be addressed. The first limitation is the use of a cross-sectional design. This design did not allow to report on a causal relationship between malnutrition and causative factors for malnutrition. A longitudinal design is recommended to address this limitation. The second limitation is the voluntary participation in this study.

In conclusion, this study provides important information on the prevalence of malnutrition and its associated factors in a large multi-centered setting of nursing homes in Turkey. Considering the results of previous studies that evaluated malnutrition among nursing home residents in Turkey, this study demonstrates the "still" high prevalence of malnutrition and malnutrition risk in nursing homes. The authors believe that the data achieved by the study will be directive in planning screening and managing malnutrition in nursing homes and also be instructive for the policymakers in the cost-effectivity of screening and planning future directives.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi University.

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

Peer-review: Externally peer-reviewed.

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Effects of intradialytic parenteral nutrition on antioxidant capacity in hemodialysis patients aged over 60 years

İrem Olcay Eminsoy[1], Gökhan Eminsoy[2]

[1]Department of Nutrition and Dietetics, Başkent University Faculty of Health Sciences, Ankara, Turkey
[2]Department of Family Medicine, Başkent University School of Medicine, Ankara, Turkey

ORCID IDs of the authors: İ.O.E. 0000-0002-3621-0662; G.E. 0000-0002-6070-7329.

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ABSTRACT

Objective: The aim of the present study was to investigate whether intradialytic parenteral nutrition can affect the antioxidant capacity of hemodialysis patients aged over 60 years.

Methods: The study comprised 20 participants from the Baskent University Umitkoy Dialysis Center; 10 who had intradialytic parenteral nutrition [IDPN, study group (SG)] that included 500 cc of amino acid solution and 500 cc of dextrose were compared with the group that did not have IDPN for 1 month. The randomly selected group had IDPN. Serum albumin, prealbumin, cholesterol, blood urea nitrogen (BUN), creatinine, potassium, and phosphorus; weight; body mass index (BMI); hand muscle strength (HMS); and middle upper arm circumference (MUAC) were measured and compared at baseline and at the end of the study between two groups. After 4 weeks of treatment, thiobarbituric acid reactive substances (TBARS), glutathione peroxidase (GSH-Px), total antioxidant capacity (TAC), and tumor necrosis factor-alpha (TNF-α) values of two groups were compared.

Results: There was no statistically significant difference between the baseline and outcome values of both groups in weight, BMI, HMS, MUAC, BUN, creatinine, potassium, albumin, and cholesterol values during the 1 month period. The SG had 19.97±7.18 kcal/kg/day energy and 0.77±0.21 g/kg/day protein intake. The control group (CG) had 18.66±3.22 kcal/kg/day energy and 0.64±0.11 g/kg/day protein intake. TBARS were 1.84±0.10 μM in the SG and 1.95±0.11 μM in the CG (p=0.031). The mean of TAC was 334.34±23.20 mmol/L in the SG and 290.23±17.72 mmol/L in the CG (p=0.002). The mean of GSH-Px was 305.63±35.31 U/L in the SG and 244.80±17.66 U/L in the CG (p=0.001). The mean of TNF-α was 171.24±25.37 pg/mL in the SG and 193.85±11.82 in the CG (p=0.017).

Conclusion: Results suggest that energy and protein intake were very low in both groups. TBARS and TNF-α were lower in the SG than in the CG. TAC and GSH-Px were higher in the SG than in the CG. IDPN can be used both to increase the protein and energy intake and antioxidant capacity for patients aged over 60 years.

Keywords: Antioxidant capacity, elderly, intradialytic parenteral nutrition, malnutrition

Introduction

Protein energy wasting (PEW), inflammation, impaired immune responsiveness, and oxidative stress (OS) are the strongest risk factors for mortality in chronic dialysis patients. 27.3% of hemodialysis patients (HDPs) have moderate to severe malnutrition (1, 2). Hemodialysis (HD) removes approximately 10–12 g of amino acids and 200–480 kcal of energy in each session. Energy and protein consumption of HDP may be lower than recommended (3). Protein and energy malnutrition is very common in HDP and end-stage renal disease (ESRD) that affects 50% of the patients (4). Inadequate nutrient intake is associated with age, dialysis age, acute or chronic comorbidities, fluid overload, anemia, and poor appetite (5). Intradialytic parenteral nutrition (IDPN) is a mixture of lipid, amino acid, and glucose solution (4). IDPN improves body weight and serum albumin level in malnourished HDP (6). Prealbumin and Subjective Global Assessment (SGA) are important markers for malnutrition. It is suggested that IDPN has to begin in a condition not worse than SGA-B to improve the survival and nutrition status of HDPs (7).

Hemodialysis patients have increased OS because of an increased pro-oxidative activity and a decreased antioxidant system. Glutathione peroxidase (GSH-Px) is one of the enzymes that protect membrane lipids and cellular

Corresponding Author: İrem Olcay Eminsoy, irolcay@yahoo.com

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and extracellular components from oxidative damage (8). During lipid peroxidation, thiobarbituric acid reactive substances (TBARS) are produced (9). HDPs have significantly higher level of TBARS than peritoneal dialysis patients (10). Total antioxidant capacity (TAC) is decreased when OS occurs (11). HDPs have increased OS that they have greater risk for cardiovascular disease. Antioxidative treatment can be beneficial for reducing OS (12). Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that increases during damages in HDPs (13).

There are many factors that affect muscle loss, but the most important ones are inadequate protein intake and inactivity for elderly individuals. Consuming the proper amounts of dietary protein can slow down sarcopenia in aging. A daily protein intake of 1.3–1.4 g/kg/day can be safe and useful for healthy older adults (14). Serigne et al. (15) found that elderly HDPs have an energy intake of 20–25 kcal/kg/day and a protein intake of 0.84–0.95 g/kg/day. Protein and energy malnutrition ranges from 50% to 60% in dialysis patients (16). According to the results of the European study in chronic kidney disease stage 4 patients (EQUAL study), PEW was higher among women, increasing with age (17). Hand muscle strength (HMS) is an important parameter that can show sarcopenia, malnutrition, and/or frailty. The method is inexpensive, rapid, and simple for elderly individuals, but it is less common in HDPs (18).

Intradialytic parenteral nutrition can be a useful tool for elderly HDPs' malnutrition. OS is an important factor for all chronic patients, and HD can increase the OS for all patients. We attempt to understand the effects of IDPN for both antioxidant capacity and malnutrition in elderly HDPs in which the number of these patient groups increases each day.

Methods

This was a randomized, clinical, two-group comparison trial of nutritional counseling plus IDPN versus nutritional counseling alone in HDPs aged over 60 years. The study protocol was approved by the ethics committee of Baskent University (no. KA09/201, 08.05.2009). The study included approximately 20 HDPs who were aged over 60 years, with a dialysis age over at least 6 months, with three times a week HD session for 4 h, not using any medication that affects protein metabolism, and with no diabetes mellitus and cancer. A total of 20 patients were randomly selected, with 10 who could tolerate IDPN as the study group (SG) and the other 10 as the control group (CG).

All patients received nutritional counseling and followed their diet programs that were prepared for each patient, containing 35 kcal/kg/day energy and 1.2 g/kg/day protein. The dry weight of all patients was used for calculations. Daily food consumption of all patients was collected twice a week in which 1 day was a dialysis day for both groups at 0, 1, 2, 3, and 4 weeks of the study. Food consumption of all patients was calculated by the BEBIS program after one portion of the food was determined.

The SG included five female and five male patients who were given 500 cc of amino acid solution and 10% dextrose for 1 month in every dialysis session. The CG comprised two female and eight male participants who did not use any additives. Serum albumin, prealbumin, cholesterol, creatinine, potassium, and phosphorus; weight; body mass index (BMI); HMS; and upper middle arm circumference were measured at baseline and at the end of the study. After 4 weeks of treatment, TBARS, GSH-Px, TAC, and TNF-α values were measured for two groups. Normal laboratory values were based on the BU laboratory normal values.

Statistical analysis

Anthropometric measurements, biochemical results, and food consumption were analyzed by Statistical Package for the Social Sciences 17 (SPSS Inc., Chicago, IL, USA). The significance of the intra-group variability of HD energy, protein, carbohydrate, fat, and other nutrients was tested using the Freidman test. HDPs' energy, protein, and other nutrients were tested by using the independent samples t-test. The inter-group Mann–Whitney U test and the in-group Wilcoxon test were used to test the significance of the energy, protein, and other nutrients received by the HDPs.

Results

The average ages of the SG were 69.40±5.49 years in women and 69.80±5.49 years in men. The average ages of the CG were 67.50±10.60 years in women and 70.00±5.70 years in men.

The results of anthropometric measurements are shown in Table 1. There were no any differences between the initial and week 4 measurements of weight, BMI, HMS, and MUAC. BMI was 23.99±2.38 kg/cm^2 in the CG and 23.41±3.34 kg/cm^2 in the SG (p=0.986).

The results of laboratory findings are shown in Table 2. Increases in prealbumin levels were statistically significant in the CG at baseline and the end of the study. Prealbumin levels were 23.94±10.95 mg/dL at baseline and 29.79±8.17 at the end of the study in the CG (p=0.037). Potassium levels were 5.42±0.58 mmol/dL at baseline

Table 1. Anthropometric measurement of the control group and study group

	Control group		Study group		
Measurements	$\bar{\chi}$	**SD**	$\bar{\chi}$	**SD**	**p**
Initial weight (kg)	67.16	11.95	59.77	12.36	0.288
Weight week 4 (kg)	67.13	12.23	60.91	12.64	0.540
BMI initial (kg/cm^2)	24.00	2.25	23.34	3.23	1.000
BMI week 4 (kg/cm^2)	23.99	2.38	23.41	3.34	0.986
HMS initial	16.00	10.02	11.99	7.41	0.342
HMS week 4	16.84	10.65	12.21	6.70	0.210
MUAC initial (cm)	16.00	10.02	23.70	6.16	0.209
MUAC week 4 (cm)	16.84	10.65	24.70	4.87	0.379
Height (cm)	166.50	10.53	160.60	10.03	0.036

p: Mann–Whitney U test, $p<0.05$. BMI: body mass index; HMS: hand muscle strenght; MUAC: middle upper arm circumference; SD: standard deviation

and 5.28±0.88 mmol/dL at the end of the study in the CG (p=0.838), which was slightly lower, but was not statistically significant. There were no changes in blood cholesterol level of the patients.

Table 3 shows the average nutrient intake level of both the control and study groups. The average energy intake of both groups was very low. Energy intake was 18.66±3.22 kcal/kg/day in the CG and 19.97±7.18 kcal/kg/day in the SG (p=0.597). Protein intake was 0.64±0.11 g/kg/day in the CG and 0.77±0.21 g/kg/day in the SG (p=0.131). The average potasium consumption was 1094.06±230.14 mg in the CG and 889.63±339.39 in the SG (p=0.174). The average phosphorus consumption was 639.63±99.25 mg in the CG and 533.94±164.04 in the SG (p=0.151). The average zinc intake was 5.90±0.72 mg/day in the CG and 4.74±1.23 in the SG (p=0.028), and it is statistically important.

TBARS (μM), TAC (mmol/L), GSH-Px (U/L), and TNF-α (pg/mL) evaluation in the CG and SG are shown in Table 4. The blood levels of TBARS, TAC, GSH-Px, and TNF-α were evaluated for both the CG and SG. TBARS levels were 1.95±0.11 μM in the CG and 1.84±0.10 μM in the SG (p=0.031). TAC levels were 290.23±17.72 in the CG and 334.34±23.20 in the SG (p=0.002). GSH-Px levels were 244.80±17.66 U/L in the CG and 305.6±35.31 U/L in the SG (p=0.001). TNF-α levels were 193.85±11.82 pg/mL in the CG and 171.24±25.37 in the SG (p=0.017).

The rate of elderly individuals keeps growing. The elderly population rate was 7.7% in 2013, and it was 8.5% in 2017. According to the Turkey Institution of Statistics projections, it will be 16.3% in 2040 and 25.6% in 2080 in elderly individuals aged over 65 years (19). The percentage of HDPs aged 65 years and older followed up for >90 days in 2016 was 47.7% of all dialysis patients (20). By the time the elderly population rate increases, the HDP number will also increase in Turkey. The rate of elderly individuals in the general population keeps growing, and the dialysis population is increasing in Europe. Protein–energy malnutrition is common in HDPs (18, 21, 22). Malnutrition rates were 5%–10% for patients who were living at home, 30%–60% for patients who were living in some facilities, and 35%–60% for patients who were in the hospital (23).

OS in an important risk factor for cardiovascular disease in HDPs. Glutathione plays a key role for cellular resistance against oxidative damage. Studies about TAC in HDPs show controversial results. The use of multivitamin preparation, including vitamin E, can affect the level of TAC capacity (24, 25). In our study, the level of TAC was higher in the SG, and the amino acid solution can affect the level of TAC. Healthy dietary interventions, including low carbohydrates and Mediterranean diets, may have some beneficial effects on blood pressure, quality of life, and lipid profile, but the effects on OS is uncertain (26, 27). HD causes significant depletion of antioxidants. Vitamin C deficiency was associated with an increased level of several antioxidants and a decreased level of antioxidant GSH-Px (28). In our study, GSH-Px levels were higher in the SG than in the CG. On the other hand, vitamin C, fiber, and vitamin E were similar for the CG and SG. In one randomized, controlled study, the effects of the supplementation of soy or whey protein or placebo during dialysis treatment on the biomarker of inflammation (C-reactive pro-

Table 2. Laboratory findings according to groups and gender					
Laboratory	**Groups**	**Gender**	**Baseline X±SD**	**End X±SD**	**p**
BUN (mg/dL)	Control	Male	74.75±31.88	78.50±17.60	0.499
		Female	70.50±36.06	62.50±0.70	0.655
		Total	73.90±30.63	75.30±16.93	0.813
	Study	Male	69.60±14.89	78.20±15.58	0.345
		Female	55.80±18.74	76.00±14.83	0.138
		Total	62.70±17.53	77.10±15.38	0.059
Creatinine (mg/dL)	Control	Male	9.79±3.29	9.87±2.21	0.779
		Female	5.54±1.06	9.25±3.43	0.180
		Total	8.94±3.43	9.75±2.27	0.285
	Study	Male	9.25±1.76	10.09±1.74	0.345
		Female	7.01±1.67	7.90±1.66	0.138
		Total	8.13±2.00	9.00±1.97	0.139
Potassium (mmol/dL)	Control	Male	5.50±0.55	5.4±0.69	0.833
		Female	5.10±0.84	4.65±1.62	0.655
		Total	5.42±0.58	5.28±0.88	0.838
	Study	Male	5.44±0.52	5.66±0.99	0.345
		Female	5.20±1.39	5.36±1.01	0.684
		Total	5.32±1.00	5.51±0.92	0.306
Phosphorus (mg/dL)	Control	Male	4.55±1.50	5.46±1.60	0.161
		Female	3.88±0.21	7.04±0.92	0.180
		Total	4.42±1.35	5.77±1.59	0.047*
	Study	Male	4.62±1.02	5.88±0.87	0.080
		Female	4.33±1.49	5.05±2.05	0.225
		Total	4.47±1.21	5.46±1.55	0.028*
Albumin (mg/dL)	Control	Male	4.05±0.38	3.97±0.41	0.726
		Female	3.78±0.21	3.90±0.00	0.180
		Total	3.99±0.36	3.96±0.36	0.443
	Study	Male	4.04±0.49	3.95±0.24	0.686
		Female	3.77±0.52	3.94±0.39	0.225
		Total	3.90±0.50	3.95±0.30	0.575
Prealbumin (mg/dL)	Control	Male	26.20±9.51	30.65±7.35	0.123
		Female	14.90±15.55	26.35±13.93	0.180
		Total	23.94±10.95	29.79±8.17	0.037*
	Study	Male	25.92±7.86	25.30±8.46	0.588
		Female	27.16±6.48	33.98±5.69	0.080
		Total	26.54±6.87	29.64±8.19	0.153

Table 2. Laboratory findings according to groups and gender (continued)					
Laboratory	**Groups**	**Gender**	**Baseline X±SD**	**End X±SD**	**p**
Total cholesterol	Control	Male	162.87±34.44	178.75±45.57	0.141
		Female	183.50±6.36	199.50±62.93	0.655
		Total	167.00±31.64	182.90±46.17	0.153
	Study	Male	147.20±20.49	147.20±31.71	0.893
		Female	190.60±50.03	204.40±57.65	0.500
		Total	168.90±42.67	175.80±53.22	0.575
SD: standard deviation; BUN: blood urea nitrogen					

Table 3. Nutrient intake of the control group and study group			
Nutrients	**Control group X±SD**	**Study group X±SD**	**p**
Energy (kcal/day)	1239.86±166.12	1158.26±324.36	0.684
Energy (kcal/kg/day)	18.66±3.22	19.97±7.18	0.597
Carbohyrdate (g/day)	144.76±19.95	130.24±47.89	0.326
Fiber (g/day)	10.87±2.25	8.95±3.85	0.247
Protein (g/day)	42.59±8.05	45.63±9.05	0.143
Protein (g/kg/day)	0.64±0.11	0.77±0.21	0.131
Total fat (g/day)	53.60±10.03	43.79±12.24	0.165
Vitamin A (mg/day)	669.80±88.41	590.41±70.26	0.353
Vitamin E (mg/day)	5.65±1.41	5.08±1.95	0.257
Vitamin K (mg/day)	170.16±45.17	136.61±41.99	0.257
Vitamin B_1 (mg/day)	0.41±0.07	0.36±0.14	0.545
Vitamin B_2 (mg/day)	0.79±0.12	0.67±0.21	0.290
Niasin (mg/day)	6.13±2.10	4.87±2.33	0.112
Vitamin B_{12} (mg/day)	2.15±0.39	1.75±0.52	0.070
Vitamin B_6 (mg/day)	0.64±0.13	0.54±0.20	0.151
Vitamin C (mg/day)	47.93±19.97	41.02±25.72	0.406
Potassium (mg/day)	1094.06±230.14	889.62±339.36	0.174
Calcium (mg/gün)	421.66±69.69	346.80±109.76	0.082
Phosphorus (mg/day)	639.63±99.25	533.94±165.04	0.151
Iron (mg/day)	6.07±0.96	5.14±1.79	0.199
Zinc (mg/day)	5.90±0.72	4.74±1.23	0.028*
Sodium (mg/day)	2444.03±370.15	2225.89±772.50	0.326
p: Mann–Whitney U test, p<0.05. SD: standard deviation			

tein (CRP) and interleukin (IL)-6) were investigated. At the end of the study, it was found that intradialytic protein supplementation during a 6-month intervention reduced inflammation and improved the physical function of HDPs (29). The mean of TNF-α, which is one of the biomarkers of inflammation, was lower in the SG than in the CG.

Table 4. TBARS (μM), TAC (mmol/L), GSH-Px (U/L), and TNF-α (pg/mL) evaluation in the control group and study group

	Control group X±SD	Study group X±SD	p
TBARS (μM)	1.95±0.11	1.84±0.10	0.031
TAC (mmol/L)	290.23±17.72	334.34±23.20	0.002
GSH-Px (U/L)	244.80±17.66	305.63±35.31	0.001
TNF-α (pg/mL)	193.85±11.82	171.24±25.37	0.017

p: Mann–Whitney U test, p<0.05. TBARS: thiobarbituric acid reactive substances; TAC: total antioxidant capacity; GSH-Px: glutathione peroxidase; TNF-A: tumor necrosis factor-alpha; CG: control Group; SG: study group SD: standard deviation

Protein energy wasting is common in ESRD, and it is strongly associated with mortality and adverse outcomes. Intradialytic oral nutrition supplement was found to be beneficial. It reduced the mortality rate and improved some incidence of nutritional status for hypoalbuminemic HDPs (30). IDPN is especially effective with such low serum albumin values. While non-nutritional interventions should also be considered that lead to less inflammation or protein loss (31), it is important to help maintain good nutritional status. Inadequate food intake during HD days is a common practice, and in many countries, the meal is served during dialysis session (31).

A total of 20 HDPs with a serum albumin <39 g/L received 100 mL of 10% ω-3 polyunsaturated fatty acid (PUFA) emulsion during 11 consecutive HD sessions. BMI, serum albumin, transferrin, and lipids were measured before and after treatment. Serum IL-6 and high-sensitivity CRP levels were determined before and after the HD session at baseline and after 4 weeks of treatment. Short-term parenteral administration of ω-3 PUFA is safe and well-tolerated by HDPs. The intervention does not significantly influence markers of inflammation or change the nutritional status of chronic HDPs, but it may attenuate the inflammatory response to HD sessions (32). In our study, we only used amino acid and dextrose in the SG, so there was no effect of any lipid solution on the patients' inflammation parameters (1).

Elderly HDPs are increasing each day. Nutrition is one of the most important factors that affect the survival of the patients. IDPN can both affect the nutritional status and antioxidative capacity of the patients in our study. More longitudinal studies are needed to identify the effects of IDPN on antioxidant capacity in HDPs.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University (03.06.2009/181 KA09/201).

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

Peer-review: Externally peer-reviewed.

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Case Report
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Stability problems of pediatric parenteral nutrition solutions

Burcu Kelleci Çakır[1], Gülcan Paloğlu[2], Çiğdem Karababa[2], Kutay Demirkan[1], Şule Yiğit[3]

[1]Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara, Turkey
[2]Pediatric Nutrition Support Team, Hacettepe University Pediatric Hospital, Ankara, Turkey
[3]Department of Pediatrics Division of Neonatology, Hacettepe University School of Medicine, Ankara, Turkey

ORCID IDs of the authors: B.K.Ç. 0000-0003-2547-8919; G.P. 0000-0002-1799-3147; Ç.K. 0000-0001-8233-5354; K.D. 0000-0002-6427-5826; Ş.Y. 0000-0002-8755-0384.

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ABSTRACT

Parenteral nutrition (PN) must be considered an intravenous medication, containing over 50 ingredients and additives. Thus, the stability of the final product is always under risk. PN can be received in two ways: from a ready-to-use bag or from an individually tailored bag, both in adults and in pediatric patients. Pediatric PN admixtures are more susceptible than adult PN admixtures due to their nature. Patients who receive PN often need to receive parenteral medications concomitantly, and separate administration is challenging most of the time. Here we report two problems with stability encountered with pediatric PN bags. In the first case, the main focus is on the compatibility of heparin with PN. Compatibility of the medications via the Y-site or a three-way stopcock must be examined in such cases. If the medication is incompatible with PN, administration via the Y-site or addition into the PN mixture should be avoided. Emulsion disruption caused by heparin is a known example of incompatibility for pediatric PN. In the second case, the main focus is on the additives and their amount in the pediatric PN mixture. Compounding pediatric PN is mixing numerous additives in a small volume, which results in a highly concentrated solution that often causes calcium–phosphate precipitation. This may lead to serious consequences, including death. All the possible causes of instability, even the temperature of the environment, must be considered. In pediatric PN solutions, the cooperation between physicians and pharmacists is necessary for maintaining safe nutritional treatment.

Keywords: Clinical nutrition, clinical pharmacy, drug administration, incompatibility, parenteral nutrition

Introduction

Parenteral nutrition (PN) can be provided in two ways: from a ready-to-use bag or from an individually tailored bag, both in adults and pediatric patients. Using a standard, commercial, formulation has some advantages with regard to minimizing procedural incidents, and on the other hand, it does not always meet the nutritional needs of most patients. For pediatric patients, there are very limited bag options with a certain amount of energy and proteins provided. To secure individual patient requirements, tailored PN formulations are preferable in newborns, infants, and children (1, 2). Stability of the final product is always an obligatory consideration. PN is an intravenous medication, with more than 50 ingredients and additives (3). All these ingredients, additives, the order in which they are added, ways of delivery, and environmental characteristics influence the overall PN admixture stability. Stability means that the admixture maintains the same status throughout the preparation and infusion time. The clinically important and very susceptible components to instability are the lipid emulsions, the reaction of calcium–phosphate, vitamins, and trace elements. The instability reactions are influenced mostly by the addition of drugs and electrolytes, but also by the storage material and the environmental conditions such as the presence of oxygen, exposure to ultraviolet light, pH value, and high temperature (4).

Here, we report 4 cases in which two different types of stability problems occurred with PN solutions that were compounded for infants in our university pediatric hospital in a 1-week period (29 December 2016–02 January 2017).

Case Presentations

Stability problem 1

Event notification reports were sent to the Clinical Pharmacy Department by the Hospital Quality Assurance Unit on January 12, 2017, about dissociation observed on the

Corresponding Author: Burcu Kelleci Çakır, burcukey@yahoo.com
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upper side of the PN bags of 3 infant patients and detected by the nutrition support team nurses. After the evaluation by clinical pharmacists, it was observed that the contents and the concentrations in the label of PN bags were appropriate, except admixing 125–130 unit heparin to all three PN solutions. As an example, one of the patient's PN ingredients is provided in Table 1. The dissociation detected in these PN solutions was explained by the heparin-induced lipid instability.

Stability problem 2

An event notification report was sent to the Clinical Pharmacy Department by the Hospital Quality Assurance Unit on March 3, 2017, regarding the precipitation formation in the PN solution of 1 infant patient, which was detected by nutrition support team nurses. The contents and their concentrations in the label of PN bags were also evaluated by clinical pharmacists, and it was found that due to metabolic disorders, the PN solution was prepared without amino acids (Table 1). A lower final volume and higher pH value were expected in PN solutions without amino acids, which leads to a higher risk of calcium and phosphate interactions and precipitation in the solution. The precipitation detected in this PN solution was explained by the calcium–phosphate interaction due to increased pH and decreased volume of the final PN solution.

Table 1. Ingredients of parenteral nutrition solutions

	Stability problem 1 (mL)	Stability problem 2 (mL)
Amino acid (Primene®)	63	0
Dextrose 10%	91	0
Dextrose 20%	134	0
Dextrose 30%	0	150
Dextrose 50%	0	10
Lipid (Clinoleic®)	25	48
Sodium chloride 3%	15	26
Potassium chloride	5	0
Photassium phosphate	0	3
Calcium gluconate	12.5	8
Multivitamin (Slouvit®)	2.5	3
Multivitamin (Vitalipit®)	10	10
Heparin	125 unit	130 unit
Total volume	350	260

Discussion

Patients receiving PN often need to receive parenteral medications concomitantly; however, separate administration is not possible in practice for most of the patients. If another catheter is not available, some medications can be added to PN solutions, such as insulin or H2-receptor blockers according to the literature, and for other medications, compatibility via the Y-site or a three-way stopcock must be examined. If the medication is incompatible with the PN solution, this may result in various visual incompatibilities (e.g., emulsion disruption caused by heparin in the presence of calcium) (4, 5).

At many centers, mostly to maintain catheter patency and sometimes to decrease infections and hypertriglyceridemia, heparin is regularly added at a dose of 0.5–1 unit/mL to neonatal PN solutions (6, 7). Heparin causes solution destabilization through binding of divalent cations and influences the integrity of the emulsion (8, 9). When the irreversible destabilization (such as coalescence and oiling out) occurs, PN bags must be disposed immediately. The literature suggests that low doses of heparin are unlikely to destabilize PN solutions; however, more studies are needed to clarify this (10-13).

In the cases with Stability Problem 1, it was concluded that heparin was the only component that could be responsible for dissociation of these PN solutions. Although it was added within the limits indicated in publications (7), it was suggested that clinicians need to be more careful about adding heparin to PN bags due to stability problems, and if the patient needs higher doses of heparin, it should be administered via different catheter for patients receiving lipids in PN solutions.

Another concern about compounding pediatric PN is mixing numerous additives in a small volume that results in a highly concentrated solution often causing calcium–phosphate precipitation. This may have serious consequences, including death. The underlying physical and chemical factors responsible for an incompatibility between these ions can be the pH of the admixture, choice of salt type, amino acid concentration, mixing sequence, and infusion temperature (14).

In the cases with Stability Problem 2, it was concluded that calcium–phosphate precipitation was formed due to lack of amino acids in the PN solution, which leads to an increased pH of the solution. Besides, the lack of amino acids in the PN solution also leads to decreased final volume of the PN solution, resulting in calcium–phosphate precipitation because of higher concentrations of calcium

and phosphate. Therefore, it was suggested to apply either calcium or phosphate separately from PN solutions in patients who should not receive amino acids in PN solutions due to their clinical condition.

In addition, during the evaluation period, it was documented that the average room temperature in the newborn unit was between 25°C and 28°C degrees. Storage and environmental temperature may also have an effect on the stability of PN solutions, especially for calcium–phosphate precipitation. Therefore, to keep the room temperature under control in such a critical department was also suggested.

In conclusion, since PN solutions have a very sensitive stability due to over 50 ingredients, the preparation and application of PN solutions must be carried out carefully. If it is known that the drug is incompatible or under unknown compatibility condition, these drugs should never be added to the PN admixture or be infused via the Y-line. On the other hand, physical examination is important during the preparation, storage, and administration of PN solutions, and it should be kept in mind that precipitates may be masked due to lipid emulsions. The risk of calcium–phosphate precipitation formation should be especially considered in pediatric PN solutions, and the cooperation between physicians and pharmacists is necessary in such scenarios. While physicians demand a high electrolyte content with a small volume, pharmacist must ensure the stability of admixture. A multidisciplinary team approach may be required to maximize the impact of nutrition support service and to provide a safe and proper PN treatment to the patients.

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