Online ISSN 2667-6230

KEPAN
SOCIETY OF CLINICAL ENTERAL PARENTERAL NUTRITION-TURKEY

CLINICAL SCIENCE OF NUTRITION

VOLUME 6
ISSUE 2
AUGUST 2024

clinscinutr.org

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VOLUME 6 ▪ ISSUE 2 ▪ AUGUST 2024

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Clinical Science of Nutrition

Owner

On behalf of Turkish Society of Clinical Enteral and Parenteral Nutrition

Prof. Dr. Mutlu Doğanay, *President of the Society*

Publisher

Turkish Society of Clinical Enteral and Parenteral Nutrition

Official abbreviation: Clin Sci Nutr

ISSN (Online): 2667-6230

DOI Prefix: 10.62210

First Publication: 2019

Publication Type

International peer-reviewed journal

Publication Frequency and Language

Triannual (April, August, December), English

Editor in Chief

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Publishing Services

Akdema Informatics, Publishing, and Consultancy Trade LLC
Kızılay Mah. Gazi Mustafa Kemal Bulvarı No: 23/8 06420 Çankaya/Ankara, Türkiye
Tel: +90 533 166 8080
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Clinical Science of Nutrition is an international, peer-reviewed, open access journal. It publishes research articles, reviews, case reports, and letters to the editor on all aspects of nutrition and dietetics.

Clinical Science of Nutrition is a triannual journal that is published in English in April, August, and December.

Abstracting and indexing

Clinical Science of Nutrition is covered in the following abstracting and indexing databases;

- TR-Index
- EBSCO
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Aims and Scope

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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DOI: 10.62210/ClinSciNutr.2024.85

Is coffee effective on food intake in high fat diet-fed obese rats?

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This study was presented in the 19th World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease (online) 2021 as abstract.

Cite this article as: Macit Çelebi MS, Köksal E. Is coffee effective on food intake in high fat diet-fed obese rats?. *Clin Sci Nutr*. 2024;6(2):57-66.

ABSTRACT

Objective: Coffee might be effective in the treatment of obesity with its high polyphenol and caffeine content. In this regard, this study aimed to evaluate the effect of different coffee types on body weight, food intake, and biochemical parameters in obese rats.

Methods: Wistar Albino adult male rats were randomly divided into four groups (one control and three coffee groups) after obesity development (after six weeks), and three types of coffee (Turkish coffee, instant coffee, filter coffee) administration were performed for two weeks.

Results: Food consumption was statistically significantly lower in the Turkish coffee (15,6±1,06 g/d) and filter coffee group (16,9±0,8 g/d) compared to the control group (18,5±0,6) in the eighth-week ($p<0.001$). At the end of two weeks, there is no difference between the groups regarding weight in the rats ($p>0.05$). However, the body weight gain (g) change was lower in the Turkish coffee group ($p<0.001$). There was no significant difference between groups in biochemical parameters. However, negative correlations were obtained between NE (ng/L), Leptin (ng/ml), Adiponectin (mg/L), UCP-1 (ng/L), UCP-2 (ng/L), UCP-3 (ng/L) and average energy intake (kcal) in Turkish coffee administrated rats.

Conclusion: According to the study results, coffee consumption, especially Turkish coffee, has a reducing effect on food intake. This effect is likely due to the higher phenolic content of the given Turkish coffee than the same amount of filter and instant coffee. Further studies are needed to explain the effects of coffee consumption on body weight and other casual relationships, especially in the long term.

Keywords: Body weight, obesity, coffee,

INTRODUCTION

Obesity is a chronic disease with a dramatic increase and is defined by the accumulation of fat in adipose tissues.[1,2] Obesity is a multifactorial disease with complex pathophysiology still, in recent years, factors such as high energy density, easy access to delicious foods, difficulties in accessing healthy food, low physical activity levels have paved the way for the emergence of the disease.[3]

Achieving body weight loss is possible through a complex process involving psychosocial, biological, behavioral, and environmental factors.[4] However, sustainable changes in lifestyle and diet are effective in the treatment. Accordingly, studies have focused on some functional food ingredients that suppress the accumulation of body fat to support obesity treatment.[2,5] Polyphenols such as chlorogenic acid (5-cafeolinic acid), ferulic acid, gallic acid, curcumin, naringin, quercetin, capsaicin, cinamaldehyde, and caffeine have been reported to increase lipolysis and induces fatty acid ß-oxidation by gene modulation.[6]

Coffee is a widely consumed beverage with its caffeine, diterpenes; cafestol and kahweol, chlorogenic acid

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Received: October 16, 2023 Accepted: April 24, 2024
Published: May 17, 2024

esters; caffeic acid and kinic acid, trigonelline, N-methyl pyridinium, polysaccharides, peptides, melanoidins, potassium, niacin, magnesium.[2,7-9] Halvorsen et al.[7] stated that the beverage with the highest polyphenol content is coffee. Studies demonstrated possible health effects of coffee.[9-12] Although numerous studies have been evaluated the effects of coffee consumption on chronic diseases such as obesity, Type 2 diabetes, and atherosclerosis, and these are observational and epidemiological studies and can not prove causality.[9,10,13] In addition to the possible benefits of coffee, current data indicates that unfiltered, boiled coffee increases serum low-density lipoprotein-cholesterol (LDL-K) levels in individuals with mild and moderate hypercholesterolemia due to the high diterpenoid content of filter coffee.[14,15]In the literature, questioning the coffee consumption retrospectively, not specifying the type of coffee consumed clearly and evaluating the consumption of different coffee types under the same title makes it difficult to make a clear recommendation. Accordingly, models established in animal studies provide valuable contributions to increasing knowledge about mechanisms for the role of coffee in the treatment and prevention of obesity.[16,17] This study aimed to evaluate the effect of different coffee types on body weight and biochemical parameters in obese rats in this study.

METHODS

Animal model

Wistar Albino adult male rats (weighing 160-220 g, n = 24, 8-9 wk old) were purchased from and kept Gazi University Laboratory Animal Breeding and Experimental Research Center (Ankara). The reason for choosing the male Wistar albino rat breed is that they are more prone to the development of obesity.[18] Sample size was calculated with the Minitab Programme in line with food intake and body weight. During the study period, the room temperature was 24 ± 2 °C with 12-hour light-dark cycles; relative humidity was 35-40%. The luxury is kept in a plastic cage with wire lids so the noise level is below 85 dB. Approval for the ethics committee was obtained from Gazi University Experimental Animals Ethics Committee with E.125541 and E.35747 number. The animals were housed and handled per the ethical principles and guidelines.[19-21] Two animals were kept in each cage.

Main Points

- Obesity is a chronic disease with its increasing prevalence in the worldwide and rapid action should be taken to prevent it.
- In the treatment of obesity, the use of some nutrients such as caffeine and chlorogenic acid along with diet and lifestyle factors may be useful.
- Consumption of Turkish coffee and filter coffee may be beneficial for nutritional treatment in obesity through different mechanisms.

Analysis of coffee contents

Medium roasted instant, filter, and Turkish coffee samples obtained from a local coffee chain. Caffeine, chlorogenic acid, caffeic acid, p-coumaric acid analysis were conducted with Liquid Chromatography-Tandem Mass / Mass Spectrometry (LC-MS / MS) (Table 1).

Coffee treatment

In the studies, the amount of coffee to be given is determined by examining the dose-related changes between groups and, in some of them by dose conversion through amount (g).[2,22-33] European Food Safety Authority (EFSA) recommends 5,7 mg/kg/day (400 mg/day) caffeine intake in humans.[34] It is suggested that dose conversion in humans and animals should be done not with a simple conversion based on body weight but with conversion factors based on body surface area (Km factor).[35,36] In this study, caffeine intake for rats was determined as 35,4 mg/kg according to the following formula[36] based on EFSA recommendations.

- Animal equivalent dose (mg / kg) = Human dose (mg / kg) x Km ratio = 5.7 mg / kg x 6.2 (coefficient given for rats) = 35.4 mg / kg

No Observable Side Effect Dose (NOAEL) for caffeine intake in rats was determined as 1500 ppm (151-174 mg/kg/g).[37] Therefore, the amount of caffeine given in this study is predicted not to pose any danger to the rats. The chlorogenic acid, caffeic acid, and p-coumaric acid t (mg) contents of coffees containing the same amount

Table 1. Caffeine, chlorogenic acid, caffeic acid (mg / kg) content of coffee's

	Caffeine (mg/kg)	Chlorogenic acid (mg/kg)	Caffeic acid (mg/kg)	p-coumaric acid (mg/kg)
Instant coffee	30.478,36	9.909,0580	1.242,9994	1,7971
Filter coffee	14.230,18	5.493,2329	1.355,6425	3,4861
Turkish coffee	10.366,08	6.151,1607	1.616,8978	5,1207

mg: milligram, kg: kilogram

of caffeine (35,4 mg) were calculated according to the analysis results (Table 2).

Experiments

The rats were subjected to a one-week acclimation period for the transition from the standard feed. In this period the daily diet consisted of 25% high-fat diet (HFD), 75% standart diet (STD) for the first two days, 50% HFD, 50% STD for the next two days, and 100% HFD for the last three days. The high fat diet (C 1090 – 45 w/45%) was obtained from Altromin, Germany. At the end of six weeks, each group was randomly assigned to four coffee intervention (Control, Instant, Filter, Turkish coffee) groups. While following the HFD, the coffee administration was carried out for two weeks.

Intervention

Coffee administration of a fixed dosage of instant coffee, filter coffee and Turkish coffee was conducted per day for each rat. The daily water intake of the rats is 140 mL/kg.[21] In this line, rats are expected to consume 20-25 ml/day of water according to their weight at the beginning of the study. Coffee samples were prepared by the appropriate preparation method and solubility. Accordingly, preparation amounts of 10 g/100 ml for Turkish coffee, 6.3 g / 100 ml for filter coffee, and 8 g/100 ml for instant coffee were used.[38] After the caffeine doses required for the rats were prepared using the appropriate preparation method, the water consumption of the rats was monitored daily and diluted with water. Coffee samples were weighed with Precisa brand XB 220A model, sensitive to 0.0001 g. Sinbo brand Turkish coffee machine was used in preparing Turkish coffee, and Delongi filter coffee machine was used in preparing filter coffee. Instant coffee was prepared by dissolving the appropriate amount of coffee with boiled water. The prepared coffee samples were taken into Falcon PP tubes and then added to the water containers of the rats daily.

Rats were monitored daily for food, water intake, and leftovers. The rats were weighed before the start of the intervention and every week afterward with a Presica brand BJ 6100D model sensitive to 0.1 g. Body weight and height were measured at the end of the sixth week. The length of the area from the nose to the anus for the length was measured with an inelastic tape measure.[20] After the measurements, the Lee index [(body weight1 / 3 (g) / nose-anus length (cm)] × 1000) values were calculated, and the development of obesity was confirmed in rats with a value> 300.[39]

Dissection and Biochemical Analysis

At the end of the study, all rats were deeply anesthetized (45 mg/kg Ketamine (Alfamine 10%) + 5 mg/kg Xylazine (2% Alfazyne), and blood was collected intracardiacly. A slight pressure was applied to the injector; in the case of blood, the syringe plunger was slowly released when blood came. Blood samples taken into the tubes containing dry vacuum gel were centrifuged with Selecta centrifuge for 15 minutes at 3500 rpm, + 4°C. Serum and plasma were separated, and samples were stored at -80 °C until analysis.

After the liver, kidney, brain, and heart tissues were weighed quickly, they were stored in liquid nitrogen at -80 °C for further analysis.

The serum concentrations of ALT, AST, total cholesterol, LDL-C, HDL-C, and triglyceride levels were determined with Mindray brand BS300 model fully automatic biochemistry device. UV and UV enzymatic methods were used to conduct the analyses. Adiponectin, leptin, dopamine, epinephrine, norepinephrine, UCP-1, UCP-2, UCP-3 levels were determined with the commercial ELISA kit (BT LAB brand). The protocols included in the ELISA kit were applied in conducting the analyses.

Statistical analysis

All data are presented as mean (±) standard deviation (SD). Normality of data was checked using "Shapiro-Wilk Test", "Histogram", "Variance", and "Skewnes and Kurtosis", and variance homogeneity was tested by Levene's test. Independent Samples t-test for the analysis of the significance between the two groups and One Way Variance Analysis (ANOVA) for the f the significance between more than two groups. When significance was detected in multiple groups, subgroup test was performed to find out which group was significant, and "Tukey-HSD Test" was applied. "Pearson Moments Product Correlation Coefficient" was used in the relational analysis of two

Table 2. Chlorogenic acid, caffeic acid and p-coumaric acid contents (mg) of coffees containing the same amount of caffeine (mg)

Coffee	Caffeine (mg)	Chlorogenic acid (mg)	Caffeic acid (mg)	p-coumaric acid (mg)
Instant coffee	35,4	11,484	1,438	0,00207
Filter coffee	35,4	13,670	3,361	0,00866
Turkish coffee	35,4	20,910	5,474	0,02924

mg: milligram, kg: kilogram

numerical variables that were found to be suitable for normal distribution. The level of significance was p <0.05; p <0.001 and confidence interval was %95. The analysis of the data was carried out using the IBM SPSS Statistics v21 program.

RESULTS

Table 3 presents the body weight changes of the rats after the intervention were compared according to weeks. Accordingly, a statistically significant difference was detected between the body weight changes of the HFD Turkish coffee group in the 6th and 7th weeks and the 6th and 8th weeks (p<0.05), while the other groups' body weight changes revelaed no significant difference (p>0.05)

Table 4 shows a statistically significant difference in food consumption according to the coffee groups after the intervention (p<0.001). While there was no difference in food consumption in the sixth and seventh week, the Turkish coffee and filter coffee group's food consumption was statistically significantly (p<0.001) lower compared to the control group in the eighth week. The group with the lowest food consumption was determined as the Turkish coffee group (p<0.05).

As displayed in Table 5, no statistically significant was found between UCP-1 (ng/L), UCP-2 (ng/L), UCP-3 (ng/L), NE (ng/L), epinephrin (pg/ml), dopamine (ng/L), leptin (ng/ml), and adiponectin (mg/L) according to coffee groups.

As displayed in Table 6, a statistically significant positive correlation was found between body weight (kg) and LDL-C (mg/dl), dopamine (ng/L); the negative correlation between leptin (ng/ml), UCP-2 (ng/L), UCP-3 (ng/L) in Turkish coffee group. There is a positive correlation between AEI and HDL-C (mg/dl); a negative correlation between AST (U/L), NE (ng/L), leptin (ng/ml), adiponectin (mg/L), UCP-1 (ng/L), UCP-2 (ng/L), UCP-3(ng/L) in Turkish coffee group.

DISCUSSION

Obesity is a chronic disease with complex pathophysiology.[3] Due to its increasing prevalence in recent years, approaches to support existing treatments may be beneficial, and caffeine and some phenolic components may be effective in treatment.[6] This study aimed to evaluate the effects of the consumption of coffee, which is an important source of caffeine and phenolic components, as instant coffee, filter coffee, and Turkish coffee on food intake, body weight, and biochemical findings.

In this study, the effects of coffee were observed by comparing the post-intervention period (7th and 8th weeks) with the last week (6th week) before the intervention in the rats. According to the results, there was no difference in body weight between the groups after the intervention. The rats were kept continuing gain weight and coffee consumption did not suppress the increase. This was an expected result due to the short intervention period as 2 weeks. However, when this increase is evaluated according to weeks, body weight gain (g) in the Turkish

Table 3. Comparison of average body weight changes (g) of rats after the intervention according to weeks

Group		Weeks	$\bar{X}$±SD	p
HFD	Control	6-7th weeks	-16,83±32,92	0,266
		7-8th weeks	4,67±46,15	0,814
		6-8th weeks	-12,17±26,24	0,308
	Instant coffee	6-7th weeks	-21,83±27,58	0,110
		7-8th weeks	3,83±26,32	0,736
		6-8th weeks	-18,00±20,67	0,086
	Filter coffee	6-7th weeks	-19,50±17,18	0,096
		7-8th weeks	4,67±16,40	0,517
		6-8th weeks	-14,83±9,39	0,134
	Turkish coffee	6-7th weeks	-20,50±15,68	0,024*
		7-8th weeks	-1,67±10,67	0,718
		6-8th weeks	-22,16±12,93	0,009*

Difference between the weeks before and after the administration within the groups was evaluated with the Paired Samples T Test. *p<0.05, **p<0.001 HFD: High fat diet

Table 4. Comparison of food consumption (g/day) after intervention by diet groups

Group		Before coffee administration (6th week)	After coffee administration (7th week)	After coffee administration (8th week)
		X±SD	X±SD	X±SD
HFD	Control	15,5±0,53	16,1±0,35	18,5±0,68[a]
	Instant coffee	16,7±0,38	17,1±1,10	17,1±0,67[ab]
	Filter coffee	16,8±1,17	17,0±1,30	16,9±0,87[bc]
	Turkish coffee	17,0±1,33	16,6±1,94	15,7±1,06[d]
		p>0,05[¥]	p>0,05[¥]	p<0,001[¥]

[¥]Difference between groups in the same week was evaluated by ANOVA Test. [a.b.c.d] The difference between groups was evaluated with the Tukey-HSD Test in order to compare all groups with each other. Different letters indicate significant differences between groups for each column, while the same letters indicate non-significant differences. a There is no statistically difference between control and filter coffee group, b There is no statistically difference between instant coffee and filter coffee group, c There is no statistically difference between control, filter coffee and Turkish coffee group, d There is statistically significant difference between control, filter coffee, instant and Turkish coffee group. *p<0.05, **p<0.001 HFD: High fat diet.

Table 5. Biochemical findings of the rats

Biochemical parameters	HFD				p
	Control	Instant coffee	Filter coffee	Turkish coffee	
	X±SD	X±SD	X±SD	X±SD	
UCP-1 (ng/L)	1,5±0,31	1,6±0,24	1,5±0,26	1,6±0,37	0,842
UCP-2 (ng/L)	102,7±67,31	79,5±10,47	81,6±11,77	81,1±13,70	0,630
UCP-3 (ng/L)	1,7±0,93	1,3±0,13	1,4±0,15	1,3±0,18	0,611
Norepinephrine (ng/L)	50,8±9,39	50,8±4,66	56,4±10,86	50,7±7,62	0,582
Epinefrin (pg/ml)	231,7±27,55	225,9±37,13	214,6±25,18	178,4±54,64	0,099
Dopamin (ng/L)	63,6±6,21	69,6±10,17	66,8±5,29	85,1±41,24	0,347
Leptin (ng/ml)	1,0±0,67	0,8±0,10	0,8±0,12	0,8±0,14	0,630
Adiponektin (mg/L)	2,2±0,41	2,4±0,49	2,5±0,42	2,4±0,36	0,573
Difference between groups was evaluated by ANOVA Test. *p<0,05; **p<0,001. HFD: High fat diet.					

Table 6. Correlation of biochemical findings, body weight (g), and energy (kcal) intake in the in the HFD group (r)

Biochemical parameters	Control		Instant coffee		Filter coffee		Turkish coffee	
	BW	AEI	BW	AEI	BW	AEI	BW	AEI
	r	r	r	r	r	r	r	r
Dopamine (ng/L)	,647	-,497	-,057	-,568	-,410	-,373	-,487	-,504
Epinephrine (pg/ml)	-,730	-,046	,431	,492	,591	,774	-,401	,058
Norepinephrine (ng/L)	,202	**-,814***	,682	-,794	,013	,106	-,718	**-,856***
Leptin (ng/ml)	-,570	-,388	,156	-,236	,677	,704	**-,893***	**-,943****
Adiponectin (mg/L)	,272	-,739	**,828***	-,807	-,006	-,009	-,736	**-,983****
UCP-1 (ng/L)	,633	-,729	-,448	-,264	-,220	-,014	-,498	**-,910***
UCP-2 (ng/L)	-,570	-,388	,156	-,236	,677	,704	**-,893***	**-,943****
UCP-3 (ng/L)	-,576	-,379	,155	-,238	,680	,706	**-,892***	**-,945****

The relationship between biochemical parameters, body weight and average energy intake was evaluated with Pearson Correlation Coefficient (r). *p<0.05; **p<0.001. BW: Body weight (g), AEI: Average Energy Intake (kcal), ng: nanogram, L: litre, mg: miligram

coffee group is the rate of body weight gain had slowed down after the coffee administration (Table 3). These positive effects of Turkish coffee on body weight change might be due to its high phenolic component content. It is known that the bioactive components in coffee affects body weight through regulation of leptin and insulin levels, activation of PPAR-α, and reduction in fat absorption.[8,40,41] Chlorogenic acid esters from hydroxycinnamic acids (p-coumaric acid, caffeic acid, ferulic acid) and quinic acid conjugates are among the main phenolic components in coffee. Studies have shown that they have significant effects on body weight.[8,14,42] When the caffeine dose was fixed, the chlorogenic acid, caffeic acid, p-coumaric acid intakes of the groups were as instant (11,484 mg, 1.438 mg, 0.00207 mg, respectively), filter (13.670 mg, 361 mg, 0.00866 mg) and Turkish coffee (20,910 mg, 5.474 mg, 0.02924 mg respectively) group. Accordingly, the highest intake of chlorogenic acid, caffeic acid, and p-coumaric acid is in Turkish coffee, followed by filter coffee. These findings might support the positive effects of Turkish coffee.

In the literature, there are studies examining the effects of different coffee or active ingredients. However, no study has focused on the effects of Turkish coffee. According to the study results, coffee, green coffee, decaffeinated coffee[43]; green coffee and green coffee extract[8,41]; instant coffee[31]; decaffeinated coffee[44] reduce body weight or suppress its change. Contrary to these studies, some studies that did not detect any relationship between obesity and coffee[14,42], trigonelline (20 mg/day), and cafestol (1 mg/day) interventions did not detect any change in the body weight of Sprague Dawley rats similar to our study. They stated that this was due to the insufficient doses given by Panchal et al.[14] Despite high dose (Colombian coffee extract (50 g/100 ml water) coffee administration) in rats that provided chronic coffee consumption (16 weeks), there was no effect of coffee on body weight. Shimoda et al.[41] found body weight loss in mice given green coffee bean extract for 14 days. Although it is known that the effect of caffeine on body weight usually occurs due to chronic consumption, no long-term effect was found in the results of the given study. In contrast, the short-term impact draws attention to the importance of the content and dose of the coffee or active substance applied. It is predicted that the amount of coffee given in the current study is sufficient based on caffeine contrary to mentioned study.[14] Still, the high phenolic component content of Turkish coffee is effective in the emergence of the difference only in the Turkish coffee group. The reason why this study did not show significant effects on body weight was due to the short intervention period of the study. The reason for the positive effects of coffee of the same intervention period in Shimoda's study may be the difference in the animal species used.[41] In addition, extending the administration duration will help body weight loss more effectively.

In this study, there was a difference between the groups in the food consumption of rats after coffee administration. While the food consumption of the control groups increased by weeks, the food consumption decreased or did not change (the increase was suppressed) in the coffee-consuming groups. While food consumption tends to increase in the control group, it is predicted that the decrease or change in other groups is due to the effects of coffee on appetite. While food consumption increased, especially in the control group, there was no significant difference between weeks in the instant and filter groups ($p>0.05$). The most significant decrease in food and energy intake by weeks was observed in Turkish coffee group ($p<0.05$). Phenolic component content of coffee might involve in these results. Caffeine and phenolic compounds have suppressive effects on appetite. It is known that the intake of caffeine 0.5-4 hours before a meal reduces the acute energy intake, especially compared to the intake 3-4.5 hours before. The volume of coffee given is also crucial in observing this effect; it is stated that coffee provided in high volume may affect food intake by filling the stomach capacity.[45] However, Turkish coffee is prepared in lower volumes than compared to filter and instant coffee. Caffeine is the most widely used psychoactive component globally, and its use dates back to the Paleolithic Ages. Many supplements support that body weight loss contains caffeine and are described as "appetite suppressors" and have a "thermogenic effect". However, these products often contain different components, such as ephedrine. This makes it difficult to reveal the effects of caffeine alone.[45] Different mechanisms explain the relationship between caffeine and appetite. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 are among these mechanisms. However, studies show that coffee consumption does not acutely affect food intake in healthy individuals.[46] It has been reported that fasting levels in individuals who take coffee and decaffeinated coffee are the lowest in those who take decaffeinated coffee. Peptide YY levels also tend to increase in this group. In a randomized controlled study evaluating the effect of caffeine dose on appetite, coffee containing 3 and 6 mg/kg caffeine was given to obese and normal-weight individuals. At the end of the study, it was observed that energy intake decreased in obese individuals who took only 6 mg/kg of caffeine. These results revealed that the idea that possible appetite-suppressing effects may be different in obese and normal-weight individuals. It is known that obese individuals have other metabolic and hormonal profiles compared to normal-weight individuals. Therefore, these individuals may respond differently to the effect of coffee on appetite hormones, and the rate of caffeine metabolism

may differ between individuals.[46] Since the caffeine dose was fixed in all groups in this study, the dose-dependent caffeine effect could not be interpreted. However, despite the increase in food consumption in the control group, suppression or decrease in food consumption in coffee-consuming subgroups proves that caffeine shows appetite-suppressing effects. Another mechanism explaining the effects of caffeine on appetite comes from the dopamine/adenosine interaction in the nucleus accumbens. This interaction and adenosine are known to be effective in taste. Caffeine, on the other hand, acts on adenosine A1, A2A, A2B receptors. It is stated that caffeine reduces the rewarding behavior towards delicious foods by blocking adenosine receptors.[47] In addition; cholinergic mechanisms are effective with the satiety signal. Caffeine increases the amount of acetylcholine in the nucleus accumbens. It also suppresses appetite by increasing serotonin levels in the hypothalamus.[48]

In addition to caffeine, phenolic compounds in coffee have effects on appetite. The most significant decrease in food consumption is in Turkish coffee and filter coffee since that this group has the highest amount of phenolic compounds. While there are studies evaluating the effect of different coffees or coffee components on nutritional intake, this study is the first study on these topic-studies that do not detect any relationship between coffee components and food consumption. Shokouh et al.[42] reported no change in food consumption compared to the control group as a result of the intervention of caffeic acid (30 mg/day), trigonelline (20 mg/day), and cafestol (1 mg/day) administered simultaneously with a high fructose diet for 12 weeks. In another study, rats administered decaffeinated green coffee and 0.15% 5-caffeoylquinic acid together with no change in food intake.[49] Similarly, Jia et al.[43] did not report any change in food intake in groups receiving different doses of coffee (coffee, green, coffee, decaffeinated coffee-9 weeks) in their study on mice. Our study suggests that the bioactive components of coffee may exert their effects on appetite together with a synergistic effect.

Coffee and coffee ingredients might affect biochemical parameters according to study results.[14,42,49] In their study on Sprague-Dawley rats, Kobayashi-Hattori et al.[2] found an increase in epinephrine, norepinephrine, and dopamine levels 30 minutes after caffeine administration in rats given different doses of caffeine (0.025%, 0.05, 0.1-21 days) and reported that the decrease in body fat mass in rats might occur due to induction of lipolysis by catecholamines. These results show that caffeine affects the sympathetic nervous system. On the other hand, Kogure et al.[27] found a difference in epinephrine levels in mice administered subcutaneous caffeine (5 mg/kg). Still they did not detect any difference in noradrenaline and dopamine levels compared to the control group. It is known that catecholamine levels change in short-term administration.[2,27] In this study, it is thought that the application time was sufficient to change the catecholamine levels, but it was not reflected in the results because the short-term effect could not be observed. In addition, the negative correlation (r=-0.856) observed in norepinephrine levels and average energy intake in the Turkish coffee group supports the positive results related to the subject in the current literature.

This study found no significant difference between the groups for UCP-1, UCP-2, and UCP-3 levels ($p>0.05$) (data not shown in the table). However, in the Turkish coffee group, UCP-2, and UCP-3 levels were negatively correlated with body weight, and UCP-1, UCP-2 and UCP-3 levels were negatively correlated with mean energy intake (r=-0.910, r=-0.943, r=-0.945) (Table 5). The UCP family is in the mitochondria and effect on energy regulation. This group has subgroups as UCP-1, UCP-2, UCP-3. UCP-1 is found in white and brown adipose tissue, skeletal muscle, and pancreatic cells, UCP-2 is found in most tissues, and UCP-3 is found in skeletal muscle and brown adipose tissue.[50] It is known that the UCP-2 polymorphism is associated with obesity and that caffeine has effects on UCP-2. Muhammad et al.[51] reported that −866 G/A UCP2 gene variation affects the relationship between obesity and coffee consumption.[51] Kogure et al.[27] showed that subcutaneous administration of caffeine (5 mg/kg) in obese mice stimulated thermogenesis by increasing UCP-1 and UCP-2 mRNA expression in brown adipose tissue and UCP-2 and UCP-3 expression in skeletal muscles.[27] Daleprane et al.[52] also reported that thermogenesis and mitochondrial biogenesis in brown adipose tissue were higher with increased gene expression of UCP-1. It is thought that the negative correlations detected in the high-fat diet Turkish coffee group can be interpreted together with the increase in body weight, suppression in feed and energy intake in the same group. These results suggest that this group may have activated thermogenesis-mediated mechanisms reported by Kogure et al.[27]

In this study, adiponectin and leptin levels did not differ significantly between the groups ($p>0.05$) (Table 5). However, in the Turkish coffee group, leptin was negatively correlated with body weight, and adiponectin was negatively correlated with body weight and average energy intake (r=-0.893, r=-0.943, r=-0.983, respectively) (Table 5). While adiponectin levels decrease in obese and diabetic individuals, leptin levels are positively correlated with body fat mass and negatively correlated with adiponectin.[53] Studies present different results regarding the effect of coffee on adiponectin and leptin levels. Choi et al.[8] found a decrease in adiponectin and leptin levels

in mice given a high-fat diet and green coffee extract at different doses (50, 100, 200 mg/kg). Shokouh et al.[54] detected an increase in adiponectin levels as a result of the intervention of caffeic acid (30 mg/day), trigonelline (20 mg/day), and cafestol (1 mg/day) administered simultaneously with a high fructose diet for 12 weeks. Leptin and adiponectin reveal their effects on obesity by regulating lipolysis. Mature adipocytes produce adiponectin, which exerts an anti-inflammatory effect on insulin sensitivity, glucose uptake, increased fatty acid oxidation, and hormone-mediated lipolysis. Conversely, leptin prevents lipid accumulation in adipose tissue with its effect on food intake and fatty acid oxidation.[8] In addition, leptin levels affect energy intake by regulating food intake. The relationship between coffee consumption and adipokines may be related to the antioxidant content of coffee.[53] While there was no difference between the groups in terms of leptin and adiponectin levels in this study, the negative correlation between body weight and average energy intake in the Turkish coffee group suggests that the antioxidant content of Turkish coffee reveals this effect.

This study provides important data to show the effect of coffee consumption on obesity-related parameters. In addition, it is the first study related to obesity in which different coffee types including Turkish coffee types are evaluated together. According to the study results, coffee consumption, especially Turkish coffee, reduced food intake. This effect might be due to the higher amount of phenolic content of the given Turkish coffee than the same amount of filter and instant coffee (Table 2). Caffeine and phenolic components in coffee affect food intake by acting on the appetite center, gastric emptying, and taste receptors. In addition, the tendency of body weight change to increase in coffee-consuming groups is suppressed, and this situation is predicted to continue with chronic coffee consumption. In this study, significant effects of coffee consumption on biochemical results were not detected. This is likely because the short intervention period did not change the biochemical findings statistically.

Strenghths

The administration of different coffee types together is the most important strength of this study. In the literature studies using one type of coffee, using decaffeinated coffee as a control, the amount of caffeine, coffee, or other components as low/high dose without any calculation makes it challenging to develop recommendations based on the results. In this study, analysis of coffee samples and dose-controlled application facilitates the interpretation of the results. With the dose conversion calculated according to analysis results, the maximum recommended caffeine intake dose in humans (400 mg/day) was reached, and no adverse results were observed at this dose. Future studies are needed to make a more mechanistic explanation.

Limitations

The coffee administration duration is the most important limitation of this study. Based on the suppression of the increasing trend in body weight change, it is thought that if this period is extended, the body weight of the groups will reach a level closer to the control group. In addition, the effect of coffee on biochemical findings can be observed with the extension of this period. However, possible side effects should be considered in this recommendation.

Acknowledgements: Authors would like to thank Diagen for their contribution to the biochemical analyses and Gazi Univesity Laboratory Animals Breeding and Experimental Researches Center staff for their help during the experimental process. This study was presented in the 19th World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease (online) as abstract.

Ethical approval: The study was approved by the Ethics Committee of Gazi University (E.125541/20/09/2018; E.35747/18/03/2019).

Informed consent: Not applicable.

Author contributions: Concept – M.S.M.Ç.,E.K.; Design – M.S.M.Ç., E.K..; Supervision – E.K.; Resources – M.S.M.Ç., E.K.; Materials – M.S.M.Ç.; Data Collection and/ or Processing – M.S.M.Ç.; Analysis and/or Interpretation – M.S.M.Ç.,E.K.; Literature Search – M.S.M.Ç.; Writing Manuscript – M.S.M.Ç.; Critical Review – E.K.

Funding: This study was supported by Scientific and Technical Research Council of Türkiye (TUBITAK) 2211-A scholarship program and Gazi University Scientific Research Projects Unit with project code 47/2019-01.

Conflict of interest: The authors declare that there is no conflict of interest.

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CLINICAL SCIENCE OF NUTRITION
Original Article
DOI: 10.62210/ClinSciNutr.2024.82

Nutrition nurses' status, practices, and routines: an online cross-sectional survey

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Cite this article as: Gök Metin Z, Pars H, Boeykens K. Nutrition nurses' status, practices, and routines: An online cross-sectional survey. *Clin Sci Nutr*. 2024;6(2):67-79.

ABSTRACT

Objectives: Nutrition is an integral component of care in the intensive care unit. However, no international comparison has been published about the status and practices of nutrition nurses, their legal titles, gained certificates, and routine duties. To describe the working conditions, educational background, nutrition-related practices, challenges, and future development needs of nutrition nurses in Türkiye, the European countries, and the USA.

Methods: A cross-sectional design was used. A thirty-three-item online cross-sectional survey was sent to nutrition support nurses in collaboration with national nutrition societies. The data were collected between November 2020 and August 2021. One-way ANOVA and chi-squared test were used to compare the three countries.

Results: Eighty-one nurses completed the survey: 44 (54.4%) from Türkiye, 27 (33.3%) from the European countries, and 10 (12.3%) from the USA. All nurses in Türkiye reported having a clinical nutrition support team, while 88.8% in the European countries and 80% of nurses in the USA had this team (p=0.040). Significant differences were found in terms of nurses' age, length of service, estimated number of ambulant nutritional consultations per week, and time spent on nutritional practices during work (p<0.001). The type of first-line test for nasogastric tube placement was X-ray confirmation (70%) in the US, whereas it is auscultation (77.2%) in Türkiye and pH-testing of gastric aspirate (81.4%) in the European countries (p<0.001). The most frequently reported professional challenge among nurses in Türkiye (66%) and the European countries (22.5%) was having no legal job title.

Conclusion: These findings reflect the broader picture of nutrition nurses' status and point out the need to develop standardized strategies for education and evidence-based nutrition practices. This study has revealed important differences in the roles and responsibilities of nutrition nurses. The study guides the future development needs of nutrition nurses, highlighting the standardized guidelines and protocols for nutrition practices and calling for comprehensive training programs.

Keywords: Evidence-based practice, knowledge, nursing, nutrition, practices

INTRODUCTION

After an appropriate nutritional assessment, artificial nutritional support (ANS) in the form of enteral (EN) and/or parenteral nutrition (PN), is frequently used in intensive care units, hospitals, nursing homes, and home care settings.[1,2] Nutrition support is often offered to patients through a multidisciplinary nutrition support team (NST). In most cases, the core membership of an NST consists of the following NST members: a clinician, a nurse, a dietitian, and a pharmacist.[3,4] In this team, nurses, as "nutrition nurses (NN)", undertake important responsibilities and duties in providing effective and comprehensive services to patients in need of nutritional support, in accordance with established workplace policies, goals, rules, and regulations. The responsibilities of an NN vary

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Received: February 10, 2024 Accepted: March 14, 2024
Published: April 24, 2024

depending on the practitioner's educational background, position, and practice environment. The scope of practice encompasses but is not limited to direct patient care, including intravenous access, educating patients and caregivers, and participating in research activities.

NN focus on three major areas: clinical practice, academia/research, and entrepreneurship/industry, along with a special emphasis on geriatrics, obesity, surgical specialties, wound-ostomy care, pediatric or neonatal care, solid organ transplantation, oncology, palliative care, ICU, and infection control.[2,5,6] Since NN collaborate with other disciplines across the continuum of care, they play a pivotal role in providing formal and informal training to the interdisciplinary healthcare team.[2,7] The main responsibilities of nutrition support nurses include participating in the assessment of nutrition status and nutritional requirements, in the development and monitoring of a specialized nutrition care plan, assisting in the placement of enteral or parenteral feeding access, and in the prevention/management of enteral and/or parenteral access devices and complications. An important aspect of the role is serving as a patient advocate while also providing training and education to patients, caregivers, and various healthcare workers.[3-5]

In the absence of skilled and experienced healthcare staff during ANS, serious and sometimes life-threatening complications may occur, such as aspiration pneumonia, misplacement of nasogastric (NG) tubes, local gastrostomy problems, total parenteral nutrition (TPN)-related catheter sepsis, metabolic and mechanical complications.[3,8] Studies demonstrate that having an NST creates added value in patients on ANS.[4,5] Another important issue is having clear policies, communication, responsibilities, and agreements between each member of the NST. In this way, a specialized, coordinated, and successful nutrition support service may be provided to patients. However, in many countries, there is still a lack of regulation and formal high-quality education for advanced practice in the NN.[2,8]

In addition, in most countries, NN do not have a protected title, there are significant differences between the scope of practice and application of standards, and certification programs, and even many institutions around the world could not establish a well-organized NST.[7,9] At this point, some national and international nutrition societies are trying to develop standards of practice for NN to improve the quality of care and practice.[10-13] Looking at the literature, a few studies have investigated the knowledge level and competencies of NN and no studies or international comparisons have been published about their current status and practice, legal title, places of employment, certificates obtained, routine duties, e.g.[14-18] Therefore, the current survey aimed to describe the background, role, and scope of practice of NN in Türkiye, the European countries and the USA.

Main Points

- This cross-sectional survey is the first to demonstrate the different educational backgrounds, employment, and scope of practice among nutrition nurses in various countries including Türkiye, Belgium, England, the Netherlands, and the United States of America (USA).
- This study highlights that there is a wide range of differences in nutrition practices in different parts of the world.
- The present study calls for collaboration among international nutrition societies with nursing professionals, hospital managers, universities, and ministries of health to improve high-quality education and certification programs, credentialing boards, legal title protection, and enhance recognition of nutrition nurses.

MATERIAL AND METHODS

Study Design

The study utilized a cross-sectional design and collected data through a web-based questionnaire. Because it was not feasible to conduct a community-based national or international sample survey during the COVID-19 period, the research team decided to collect the data online.

Study Sample

Nurses from Türkiye, Belgium, England, the Netherlands, and the USA, who were working fully or partially in the field of (artificial) nutrition, were invited to complete the survey using a convenience sampling method. The study sample consisted of nurses (n=81) who were actively working in clinics and volunteered to participate in the study.

Data Collection

The data collection form was developed based on the literature searches[2,4-7] and consisted of five sections and a total of 33 questions:

- Section I: Socio-demographic characteristics (e.g. age, gender, country of residence)
- Section II: Educational and scientific activities (e.g. educational level, degrees, certificates, legal title, membership in national and international nutrition societies, participation in congresses, e.g.)
- Section III: Working conditions (current medical discipline, duration of professional experience, membership in an NST, e.g.)

- Section IV: Nutrition standards of clinical practice (e.g. nutrition screening, nutrition assessment, naso-intestinal tube insertion, preparation of necessary equipment for nutrition support, nutrition care plan, EN and PN access care, and education/training activities during patient visits with the NST, follow-up of patients' EN, and PN at home)
- Section V: Challenges related to working conditions and nutritional practices.

The data collection was set up with the assistance of two experienced NNs and two academics in the field of nutrition. An invitation letter containing a brief introduction of the background, objectives, procedures, voluntary nature of participation, declarations of anonymity and confidentiality, instructions for filling in the questionnaire and contact details of the researchers were provided to the participants to obtain informed consent. Two online survey links for nurses (https://docs.google.com/forms/d/e/1FAIpQLSfvRSsOpBWfoqrEaurMi3B-gpKV5VmJpkeBLQl-Gst1f0ns4g/viewform?usp=sf_link) and international nurses (https://docs.google.com/forms/d/e/1FAIpQLSeiljoUhTyZKvmoSGQq95suylrre1H7KajCob00pEqKNVlyaQ/viewform?usp=sf_link) were generated using Google Forms, and the invitation links were sent to nurses via e-mail and/or/ WhatsApp Messenger Groups. By clicking on the URL link, participants were directed to the cover letter, and the question "Do you agree to participate in this survey?" was asked at the bottom of the first page. Participants were directed to the next page of the survey only if they answered 'yes'. Question styles on the survey included single-choice, multiple-choice, and Likert scales. The survey could be completed on a computer, tablet, or cell phone. Nurses were requested to complete survey questions before clicking through to the next section. 'Go back' option was available on all pages, allowing participants to revisit and change a response if needed. The survey was available for 8 weeks, from November 2020 to August 2021, to allow nurses enough time to complete it. The authors did not use additional strategies to encourage survey completion, including financial incentives, alternating survey mailings, and postcard reminders. Multiple survey entries were prevented by unique web links. Nurses completed the survey at their convenience, and the survey took a minimum of 20 minutes to complete. The survey data were stored in a database on a password-protected computer as an encrypted file.

Ethical Considerations

The Ethics Committee of Hacettepe University Non-Interventional Clinical Research Ethics Board (Number: 2020/16-34) approved study protocol and informed consent procedures before the formal survey. Participants had to answer a yes-no question to confirm their willingness to participate voluntarily. After confirming the question, the participant was directed to complete the self-report questionnaire. Anonymous responses were enabled in the Google form for security reasons settings, ensuring that respondents' IP addresses, locations, and contact information were not recorded.

Data Analysis

The data analyses were conducted using SPSS version 25.0. The normal distribution of data was checked with the Shapiro-Wilk test. Descriptive statistics were reported as "mean ± standard deviation" for variables with normal distribution and as "median (min; max)" for variables with non-normal distribution. Frequencies and percentages were used to provide information about nutrition nurses and their practices by country. ANOVA was used to assess the significance of differences between groups based on mean values. The chi-square test or Fisher's exact test (when the chi-square test assumptions do not hold due to low expected cell counts) was used to compare the three study groups, where appropriate. Levene's test was used to assess the homogeneity of the variances. When an overall significance was observed, pairwise post-hoc tests were performed using Tukey's test. The statistical significance level was set at $p < 0.005$ (two-tailed).

RESULTS

Sample Characteristics

Data on the individual and working characteristics of the participants are given in Table 1. A total of 81 participants completed the survey. The mean age of the participants was 39.0(SD=6.38) in Türkiye, 46.61(SD=7.36) in the European countries, and 56.36 (SD=13.67) years in the USA. Nurses in Türkiye were younger than nurses in the European countries and the USA ($p<0.001$). Regarding the educational level, half of the nurses had a bachelor's degree in Türkiye (50%) compared to 48.1% in the European countries and 20% in the USA. Only two nurses in the USA had a Ph.D. degree. 44.1% of nurses in the European countries, and 80% in the USA reported having at least a certificate or diploma in nutrition. The mean length of service was 5.52(SD=7.38) years in Türkiye, while it was 9.48(SD=5.97) years in the European countries, and 19(SD=17.06) years in the USA ($p<0.001$). Almost half of the nurses in Türkiye (47.7%) reported having a protected nurse title (nutrition nurse) compared to those in the European countries (77.7%) and the USA (80%) ($p=0.003$). All nurses in Türkiye reported having a clinical nutrition support team, compared with 88.8% in the European countries, and 80% in the USA nurses had this team ($p=0.040$). Only two Turkish nurses mentioned having a speech therapist in their NST. In the USA, this was 87.5%. Regarding the presence of a steering committee, 90.9% of Turkish nurses reported having this team compared to

Table 1. Characteristics on nutrition nurses (n=81)				
	Türkiye n (%) n= 44 (54.3)	**European Countries n (%) n=27 (33.3)**	**USA n (%) n=10 (12.3)**	**P value**
Age (in years) Mean (SD)	39.00±(6.38) (25-54)	46.61±(7.36) (31-56)	56.36±(13.67) (33-71)	**<0.001**
20-30	4 (9.1)	0 (0.0)	0 (0.0)	**<0.000**
31-40	22 (50.0)	7(25.0)	2 (20.0)	
41-50	16 (36.3)	10 (35.7)	2 (20.0)	
>50	2 (4.6)	10 (35.7)	6 (60.0)	
Gender				
Female	43 (97.7)	26 (96.2)	9 (90.0)	0.466
Male	1 (2.3)	1 (3.8)	1 (10.0)	
Educational level				
Associate degree	5 (11.3)	5 (18.5)	0 (0.0)	-
Bachelor's degree	22 (50.0)	13 (48.1)	2 (20.0)	
Master degree	15 (34.1)	8 (29.6)	3 (30.0)	
Doctorate degree	2 (4.5)	0	0	
Master degree with nutritional certificate	0	1 (3.8)	3 (30.0)	
Doctoral degree with nutritional certificate	0	0	2 (20.0)	
Nutrition certificate and awarding institute (without master and doctoral degree)				
Yes	20 (45.5)	12 (44.4)	8 (80.0)	0.144
Source/organization/institution provided these certificate(s)*				
Health Ministry	6 (30.0)	-	-	-
Educational Institution	0 (0.0)	7 (58.3)	3 (37.5)	
Education and Training Hospital	3 (15.0)	-	-	
University Hospital	5 (25.0)	-	-	
National Nutrition Society	5 (25.0)	4 (33.3)	4 (50.0)	
International Nutrition Society	1 (5.0)	1 (8.33)	1 (12.5)	
Title within the specialist nutrition nursing field				
Nutrition Nurse	38 (86.5)	7 (25.0)	0 (0.0)	
Nutrition Nurse Specialist	6 (13.5)	7 (25.0)	2 (20.0)	
Clinical Nutrition Nurse Specialist	-	8(29.6)	3 (30.0)	
Consultant Nutrition Nurse	-	1 (3.8)	3 (30.0)	
Clinical nurse specialist (nutrition support focus)	-	4 (14.8)	2 (20.0)	
Duration of professional experience (mean; SD; min-max)	5.52 (7.38) (1-18)	9.48 (5.97) (1-21)	19.00 (17.06) (1-45)	**<0.001**
Is the title approved by a regulatory authority?				
Yes	32 (72.7)	13 (48.1)	7 (70.0)	0.051
Is Nutrition Nurse (NN) a protected title in your country?				
Yes	21 (47.7)	21 (77.7)	8 (80.0)	**0.003**

Abbreviation: ICU, Intensive Care Unit; NST, Nutrition Support Team
* Multiple choice.

Table 1. Continued				
	Türkiye n (%) n= 44 (54.3)	**European Countries n (%) n=27 (33.3)**	**USA n (%) n=10 (12.3)**	**P value**
Current medical discipline*				
ICU	22 (50.6)	10 (37.1)	6 (60.0)	-
Surgery	14 (32.2)	14(51.8)	2 (20.0)	
Internal Medicine	15 (34.5)	14 (51.8)	5 (50.0)	
Pediatrics	6 (13.8)	1(3.71)	5 (50.0)	
Reanimation Unite	6 (13.8)	5(18.5)	5 (50.0)	
Geriatrics	10 (23.0)	6 (22.2)	2 (20.0)	
Oncology	5 (11.5)	9 (33.3)	2 (20.0)	
All specialist	5 (11.5)	2 (7.40)	2 (20.0)	
Enrollment in the nutrition field *				
Job advertisement in the hospital	11 (25.3)	14 (51.8)	1 (10.0)	-
Job advertisement from another hospital	1 (2.3)	4 (14.8)	1 (10.0)	
On a proposal by a physician	7 (16.1)	4 (14.8)	2 (20.0)	
On a proposal by a hospital management	10 (23.0)	2 (7.40)	3 (30.0)	
On a proposal by another colleague	19 (43.7)	3 (11.1)	3 (30.0)	
Presence of a nutrition team				
Yes	44 (100.0)	24 (88.8)	8 (80.0)	**0.040**
NST members				
Physician	44 (100.0)	24 (100.0)	4 (50.0)	-
Nurse	44 (100.0)	24 (100.0)	8 (100)	
Dietician	43 (97.7)	24 (100.0)	7 (87.5)	
Pharmacist	42 (95.5)	24 (100.0)	8(100)	
Speech therapist	2 (4.5)	17 (70.8)	7 (87.5)	
Presence of a steering committee				
Yes	40 (90.9)	23 (85.1)	6(60.0)	**<0.005**
Steering committee members				
Physician	40 (90.9)	23 (100.0)	6 (100.0)	-
Nurse	39 (88.6)	23 (100.0)	6 (100.0)	
Dietician	39 (88.6)	23 (100.0)	6 (100.0)	
Pharmacist	35 (79.5)	18 (78.2)	6 (100.0)	
Nursing director	12 (27.3)	7 (30.5)	0 (0.0)	
Medical director	11 (25.0)	5 (21.7)	2 (33.3)	
Other person from the hospital management	17 (38.6)	15 (65.2)	1 (16.6)	
Head nurse(s)	10 (22.7)	12 (52.1)	0 (0.0)	
Kitchen staff member	5 (11.4)	14 (60.8)	0 (0.0)	
Speech therapist	2 (4.5)	13 (56.5)	0 (0.0)	

Abbreviation: ICU, Intensive Care Unit; NST, Nutrition Support Team
* Multiple choice.

the nurses in the European countries (60%) (p<0.005).

Educational and Scientific Activities

Educational and scientific activities related to nutrition are presented in Table 2. Membership in an international nutrition society was higher in the European countries (22.2%) than in Türkiye (4.5%). On the other hand, Turkish nurses had higher participation in intramural training/courses compared to the European countries and the USA, 81.8%, 59.2%, and 40%, respectively. Nurses in Türkiye (58.3%), the European countries (25%), and the USA (40%) acknowledged that in-service education programs/courses were not conducted on an occasional basis. All nurses in the US reported conducting clinical research compared to nurses in Türkiye and the European countries (60%, and 70.3%, respectively) (p=0.031). Although not shown in the table, several resources were mentioned to gain nutrition knowledge. Nurses in Türkiye used the internet, scientific databases, protocols, etc. (61.4%), while nurses in the USA and the European countries relied more on national nutrition guidelines (75.7%) and their colleagues (75.7%). Overall, most nurses rated their knowledge as good, while 30% of nurses in the USA rated their practice skills as excellent.

Nutritional Practices

Table 3 summarizes the nutritional practices of NN. Turkish nurses were more involved in nutritional assessment than their counterparts in the European countries, and the USA (81.8%, 74%, and 60%), respectively. Peripheral venous catheters for peripheral TPN were less used in Türkiye (65.9%) compared to the European countries (88.8%) and the USA (90%) (p<0.001). Nurses in Türkiye (59.1%) were less involved in placing NG tubes compared to nurses in the European countries (88.8%), and the USA (100%) (p<0.001). Most nurses in the USA (90%) and the European countries (88.8%) were involved in the follow-up of patients on HEN or HPN, whereas only 45.5% of nurses in Türkiye were involved (p<0.001).

Table 2. Education and scientific activities of nutrition nurses (n=81)

	Türkiye (n=44) n (%)	European Countries (n=27) n (%)	USA (n=10) n (%)	P value
Membership of an international nutrition society?				
Yes	2 (4.5)	6 (22.2)	1 (10.0)	0.235
Participation in any in-service education programs/courses				
Yes	36 (81.8)	16 (59.2)	4 (40.0)	**0.020**
Frequency of education programs/courses				
At least once a year	7 (19.4)	4 (25.0)	0 (0.0)	-
More than once a year	8 (22.3)	8 (50.0)	0 (0.0)	
Not specified (on an occasional basis)	21 (58.3)	4 (25.0)	4 (40.0)	
Participation in any extramural scientific or educational nutritional program?				
Yes	35 (79.5)	20 (74.1)	6 (60.0)	0.727
Conducting clinical study				
Yes	24 (60.0)	19 (70.3)	10 (100.0)	**0.030**
Perceived nutritional knowledge				
Excellent	4 (9.1)	3 (11.1)	3 (30.0)	0.197
Good	26 (59.1)	19 (70.3)	6 (60.0)	
Moderate	10 (22.7)	5 (18.6)	1 (10.0)	
Low	4 (9.1)	0 (0.0)	0 (0.0)	
Perceived nutritional practice skills				
Excellent	6 (13.6)	7 25.9)	3 (30.0)	0.396
Good	31 (70.5)	18(66.6)	7 (70.0)	
Moderate	3 (6.8)	2 (7.5)	0 (0.0)	
Low	4 (9.1)	0 (0.0)	0 (0.0)	

Table 3. Nutritional practices of nutrition nurses (n=81)				
Participate or train (in) following nutritional standards of clinical practice	**Türkiye (n=44) n (%)**	**European Countries (n=27) n (%)**	**USA (n=10) n (%)**	**P value Difference**
	Yes	**Yes**	**Yes**	
Nutrition screening	36 (81.8)	20 (74.0)	6 (60.0)	0.603
Nutrition assessment	39 (88.6)	18 (66.6)	7 (70.0)	**0.040**
Nasogastric tube insertion	26 (59.1)	24 (88.8)	10 (100.0)	**0.007**
Naso-intestinal tube insertion	7 (15.9)	18 (66.6)	5 (50.0)	**<0.001**
Peripheric venous catheter insertion	29 (65.9)	24 (88.8)	9 (90.0)	**<0.001**
Preparation of necessary equipment for nutrition support	36 (81.8)	25 (92.5)	10 (100.0)	0.187
Nutrition care plan and follow-up (artificial nutrition)	36 (81.8)	22 (81.5)	10 (100.0)	0.277
Enteral access care or teaching (patients, caregivers, other health-care professionals)	39 (88.6)	26 (96.2)	10 (100.0)	0.313
Parenteral access care or educational activities (patients, caregivers, other health-care professionals during patient visits with the NST	38 (86.4)	20 (74.0)	10 (100.0)	0.167
Participating in patient visits with the NST	39 (88.6)	27 (100.0)	10 (100.0)	0.106
Follow-up of patients with HEN or HPN	20 (45.5)	24 (88.8)	9 (90.0)	**<0.001**
Data collection and recording related to nutrition	37 (84.1)	25 (92.5)	9 (90.0)	0.396
Conducting clinical research	24 (54.5)	19 (70.3)	10 (100.0)	**0.031**
Method of external NGT length insertion*				
NEX (for adults)	36 (81.8)	18 (66.6)	4 (40.0)	**<0.001**
NEX + 10 (for adults)	10 (22.7)	18 (66.6)	3 (30.0)	
NEMU (for children)	6 (13.6)	1 (3.7)	5 (50.0)	
First line method for confirming correct nasogastric tube position				
X-ray	3 (6.8)	3 (11.1)	7 (70.0)	**<0.001**
pH testing of gastric secretion	2 (4.5)	22 (81.4)	3 (30.0)	
Auscultation	34 (77.2)	0 (0.0)	0 (0.0)	
Aspiration and visual inspection of gastric fluid	5 (11.3)	2 (7.4)	0 (0.0)	
Alternative methods for confirming nasogastric tube position*				
X-ray	15 (34.1)	27 (100.0)	5 (70.0)	**<0.001**
pH testing of gastric secretion	2 (4.5)	11 (40.7)	3 (30.0)	
Auscultation	23 (52.2)	1 (3.7)	5 (50.0)	
Aspiration and visual inspection of gastric fluid	25 (56.8)	4 (14.8)	3 (30.0)	

Abbreviation: ANS, Artificial Nutrition Support; HEN, Home Enteral Nutrition; HPN, Home Parenteral Nutrition; NEMU; Nose-ear-mid-umbilicus; NEX, Nose-ear-xiphoid; NGT, Nasogastric tube; NST: Nutrition Support Team
* Multiple choice.

Table 3. Continued				
Participate or train (in) following nutritional standards of clinical practice	**Türkiye (n=44) n (%)**	**European Countries (n=27) n (%)**	**USA (n=10) n (%)**	**P value Difference**
	Yes	**Yes**	**Yes**	
Number of inpatients with ANS per week				
No	3 (6.8)	3 (11.1)	0 (0.0)	0.224
1-10	5 (11.4)	3 (11.1)	3 (30.0)	
11-20	10 (22.7)	9 (33.3)	3 (30.0)	
21-30	12 (27.3)	5 (18.5)	1 (10.0)	
31-40	5 (11.4)	1 (3.8)	1 (10.0)	
>41	3 (6.8)	0 (0.0)	2 (20.0)	
Number of outpatients with HEN in the previous year				
No	22 (50.0)	4 (14.8)	2 (20.0)	0.230
1-25	8 (18.2)	8 (29.6)	1 (10.0)	
26-50	2 (4.5)	5 (18.5)	1 (10.0)	
51-100	5 (11.4)	4 (14.8)	3 (30.0)	
>101	7 (15.9)	5 (18.5)	3 (30.0)	
Number of outpatients with HPN in the previous year				
No	29 (65.9)	7 (25.9)	2 (20.0)	0.288
1-25	10 (22.7)	8 (29.6)	3 (30.0)	
26-50	1 (2.3)	3 (11.1)	3 (30.0)	
51-100	2 (4.5)	4 (14.8)	1(10.0)	
>101	2 (4.5)	5 (18.5)	1 (10.0)	
Number of ambulant nutritional consultations (per week)				
No	25 (56.8)	4 (14.8)	3 (30.0)	**<0.001**
1-5	12 (27.3)	11 (40.7)	2 (20.0)	
6-10	5 (11.4)	10 (37.0)	2 (20.0)	
>11	1 (2.3)	2 (7.5)	3 (30.0)	
Type of patients receiving nutrition support				
Adults	31 (70.5)	21 (77.7)	5 (50.0)	0.160
Pediatrics	5 (11.4)	0 (0.0)	2 (20.0)	
Both adults and pediatrics	8 (18.2)	6 (22.2)	3 (30.0)	
Specific time for nutrition activities				
≤ 25%	10 (22.7)	0 (0.0)	0 (0.0)	**0.002**
> 25% ≤ 50%	11 (25.0)	2 (7.5)	2 (20.0)	
> 50% ≤ 75%	4 (9.1)	2 (7.5)	3 (60.0)	
> 75%	19 (43.2)	23 (85.2)	5 (50.0)	

Abbreviation: ANS, Artificial Nutrition Support; HEN, Home Enteral Nutrition; HPN, Home Parenteral Nutrition; NEMU; Nose-ear-mid-umbilicus; NEX, Nose-ear-xiphoid; NGT, Nasogastric tube; NST: Nutrition Support Team
* Multiple choice.

As for the control of the NG tube location, the NEX (nose-ear-xiphoid) method was the most preferred technique in Türkiye (81.8%) for adults compared to EC and the USA (66.6%, 40%, respectively) (p<0.001). As for the NEX+10 method, just 22.7% of Turkish nurses utilized compared to the European Countries and the USA (66.6%, and 30%, respectively) (p<0.001). NEMU (nose-ear-mid-umbilicus) method used for children was practiced in 13.6% in Türkiye, 3.7% in the European Countries, and 50% in the USA (p<0.001).

As for the USA external measurement of internal NG tube length, nurses in the US primarily used radiographic confirmation (70%) as a first-line test to confirm the correct tip position of nasogastric (NG) tubes, whereas in Türkiye, auscultation (77.2%) and pH testing of gastric aspirate (81.4%) were more common (p<0.001). When considering alternative methods to confirm tube position, 100% of nurses in the European countries utilized radiography, whereas only 70% of nurses in the USA and 34.1% in Türkiye used this method (p<0.001). Regarding the number of outpatients per week, nurses in Türkiye (56.8%) reported never seeing outpatients (p<0.001). 85.2% of nurses in the European countries, the USA nurses (50%), and 43.2% of those in Türkiye have specified that spend more than 75% of their time at work on nutrition (p=0.002).

Figure 1. Challenges of nutrition nurses

Nutrition-related Challenges

Nutrition nurses deal with several challenges concerning their general practice or job. Relevant items are presented in Table 4 and Figure 1. There is no legal title and/or job protection for nurses in Türkiye (66%) and a quarter of nurses in the European countries.

DISCUSSION

This online cross-sectional survey is the first to demonstrate the different educational backgrounds, employment, and scope of practice among NN. The mean age and seniority of nurses in the European countries and the USA were higher than in Türkiye. Only a few nurses in the USA graduated from a nutrition-related master's program and had a Ph.D. degree. The ASPEN membership database showed that 28% of the members were nurse practitioners and 38% of those had a master's degree. The same report stated that the number of nurses with a doctoral degree has increased over the years.[19] Considering the educational activities of NN, intramural activities were irregular, and the participation rate was similar in all the countries. Turkish nurses reported frequent use of the Internet to gather information related to nutrition, while nurses in other countries mostly rely on national nutritional guidelines and their colleagues. Additionally, membership in (inter)national nutrition societies was higher in both the USA and the European countries. In Türkiye, almost all nurses were entitled to "NN", while "NN specialists" only

Table 4. Nutrition-related challenges of nutrition nurses (n = 81)

Notification of local, legal, practical and/or organizational challenges as a nutrition nurse	Türkiye (n=44) n (%)	European Countries (n=27) n (%)	USA (n=10) n (%)
Have no legal title or legal job protection	29 (65.9)	6 (22.5)	1 (10.0)
Have no other direct colleague who does the same job	4 (9.1)	2 (7.5)	2 (20.0)
Lack of support from other health-care workers in the hospital or in my organization	2 (4.5)	0 (0.0)	0 (0.0)
Inability to advance in career (from novice to expert)	2 (4.5)	0 (0.0)	0 (0.0)
The possibility of losing job	0 (0.0)	5 (13.5)	1 (10.0)
Have no formal job description as a nutrition nurse	1 (2.3)	1 (3.8)	0 (0.0)
Being a nutrition nurse is not interesting and challenging enough	0 (0.0)	2 (7.5)	0 (0.0)
The job time is not enough to do the job properly	0 (0.0)	5 (13.5)	1 (10.0)
Lack of support from the hospital management	1 (2.3)	3 (11.1)	0 (0.0)

seemed to exist outside Türkiye. The ASPEN's nutrition support nurses section published core competencies for NN in 2008. However, the present study revealed that education and recognized titles included a variety of titles reported by nurses as practitioners and nutrition support clinicians. Previous reports also confirmed our findings that there is a variety of job titles reported by the nurses, such as nurse practitioner, and nutrition support clinician.[19]

This study revealed that there were important differences between NN practices, including the measurement of external NGT length insertion and confirming the correct position of the NGT. In the European countries and the USA, nurses frequently assist in the insertion of NG, naso-intestinal, PEG, and PEJ tubes, while nurses in Türkiye rarely perform these activities. The gastric route is accepted as the most appropriate choice for enteral nutrition support when there is no contraindication.[20]

The placement of NG tubes by nurses or physicians to administer fluids, tube feedings, or drugs is common in daily clinical practice.[21-24] Correct placement and positioning are essential to prevent associated morbidity and mortality (e.g., aspiration pneumonia) within the proper placement. NG tube placement starts with a measurement of the expected internal length. The NEX approach (distance from the tip of the nose-earlobe-xiphoid process) remains the method most widely taught in nursing programs and used by practicing nurses for tube insertion in adults, but it may not be the safest approach as demonstrated in an integrative review.[25-27]

Incorrect NG tube placement in pediatric and adult patients has been integrated into reporting systems.[25-29] The Pennsylvania Patient Safety Agency reported 166 NG tube misplacements between 2011 and 2016, including 10.2% in children.[29] The United Kingdom National Health Services and the U.S. Food and Drug Administration reported significant cases of incorrect placement of NG tubes. Most of these cases had a history of immediate treatment such as decompression and chest tube placement, with some cases resulting in cardiopulmonary arrest and death.[30-34] Similar findings have been reported in the UK, which would equate to 5149 misplacements, 963 pneumothoraxes, and 218 deaths per year due to misplacement of NG tubes.[35-37] To prevent these complications safe testing methods should be applied to confirm the correct tip position.

In line with this, nurses may consider checking the position of NG tubes after insertion, and during the nutrition support based on data-driven knowledge. An abdominal X-ray remains the gold standard, but X-ray interpretation must be performed by a competent person, and if there is any doubt about misinterpretation, the advice of a radiologist should be sought.[25,36,38-45] The NPSA reported 45 incidents of X-ray misinterpretation, 12 of which resulted in patient death. In their patient safety alert, they recommend that an X-ray should be used as a second-line test when no aspirate could be obtained, or pH indicator paper has failed to confirm the position of the nasogastric tube.[36] Looking at bedside methods for confirmation, pH-testing (pH ≤ 5) on gastric aspirate excludes pulmonary placement and reduces the risk of esophageal placement to a minimum.[36,46-50] Other methods, such as auscultation and visual evaluation of gastric aspirates, are considered unsafe.[34,39,47,51-57] This survey demonstrated that nurses in Türkiye still rely on unsafe methods to check the position of an NG tube, such as auscultation and visual inspection of sucked aspirates without checking the pH. This highlights the need for re-education in nursing schools, care facilities, and home care. In general, it is clear that there is still some educational work to do to increase awareness about the safest methods of nasogastric tube insertion and/or tip confirmation.

Regarding the correct nasogastric tip location, most nurses in Türkiye (77.2%) still rely on auscultation, which has been proven to be unsafe.[58] For both adults and children, there is scientific evidence that the NEX is incorrect.[59] In children, the NEMU (distance from the nose to the ear to the mid-umbilicus) or an age-related height-based method should be used. Only nurses outside Türkiye use this method.

One of the most striking findings of our study is that NN in Türkiye, the European countries, and the USA reported important nutritional challenges. NN stated that they struggle with the same issues including the amount of time spent on nutrition and the lack of other colleagues doing the same job. On the other hand, nurses in the European countries and the USA mainly emphasized the absence of a legal regulation to protect their title or profession. These findings reveal the need for new legal initiatives for professional recognition and improved local policies to improve working conditions and time management. In summary, it is evident that there are still many hurdles that need to be overcome.

Limitations

Our study had several limitations that need to be addressed. The response rate and reasons for not participating in the study are not included in this study. The volunteered nurses may have internet access or be more motivated to respond to the survey. This may be a source of bias. It is important to note that relatively few nurses from the USA participated in the study. Another limitation is that only nurses from a few European countries responded. The timing of the survey also needs to be considered; it was conducted during the COVID-19 pandemic, and this

may have influenced both the participation rate and the generalizability of the findings.

CONCLUSIONS

Eighty-one nurses responded to this online survey. Only a minority had a postgraduate degree, which is an apparent contradiction given the fact that a master's degree is a prerequisite for advanced practice nurses. International nutrition societies with a nursing section, hospital managers, universities, and ministries of health need to collaborate to improve quality education and certification programs, credentialing boards, legal title protection, and recognition of NN. Moreover, this study underlines that a wide range of differences exists among nurses in different parts of the world.

To minimize these differences, NN should be encouraged to share knowledge, discuss uniform job profiles, be an active part of an (inter)national nutrition society, and integrate more evidence-based research into their clinical practice. Standardized guidelines and protocols should be established, and nutrition nurses should be encouraged to participate in comprehensive training programs and research activities to integrate evidence-based information into clinical practice.

Acknowledgments: The authors would like to thank all those nurses, and NNNG members who participated in the study.

Ethical approval: This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Board (Number: 2020/16-34).

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

Author contributions: Concept – Z.G.M.,H.P.,K.B.; Design – Z.G.M.,H.P.,K.B.; Supervision – K.B.; Resources – Z.G.M.,H.P.,K.B.; Data Collection and/or Processing – Z.G.M.,H.P.; Analysis and/or Interpretation – H.P.,Z.G.M.; Literature Search – Z.G.M.,H.P.,K.B.; Writing Manuscript – Z.G.M.,H.P.,K.B.; Critical Review – K.B.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

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CLINICAL SCIENCE OF NUTRITION
Original Article
DOI: 10.62210/ClinSciNutr.2024.88

Development and validation of the attitude scale for the clinical nutrition care process of hospitalized patients for physicians

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Cite this article as: Ulusoy H, Delibalta B, Kangalgil M, Kumlu G, Kaynar K, Nuhoğlu İ. Development and validation of the attitude scale for the clinical nutrition care process of hospitalized patients for physicians. *Clin Sci Nutr*. 2024;6(2):80-87.

ABSTRACT

Objective: Evaluating physicians' attitudes towards malnutrition and clinical nutrition in hospitalized patients are crucial for the implementation of optimal nutritional care process and the prevent of hospital malnutrition. The aim of this study is to develop a scale that evaluates physicians' attitudes towards malnutrition in hospitalized patients.

Methods: Based on the existing literature on clinical nutrition and the clinical experience of experts in this field, a 5-point Likert-type attitude scale consisting of 12 items was developed. Analysis was carried out using Parallel Analysis to determine the number of factors in the Exploratory factor analysis based on the Polychoric correlation matrix and Unweighted Least Squares as the factor extraction method.

Results: There are 8 items in the 1st factor (Physician duties) and 4 items in the 2nd factor (Non-Physician duties). The Cronbach Alpha and McDonald's Omega coefficients of the scale were found to be 0.72 and 0.81 respectively, from the sub-dimensions 0.78 and 0.85 for the 1st Factor, and 0.66 and 0.75 for the 2nd Factor.

Conclusion: Attitude scale for the clinical nutrition care process of hospitalized patients for physicians is an instrument with good psychometric properties that measures examination of physicians' attitudes related to clinical nutrition care process.

Keywords: attitude scale, clinical nutrition care, physicians

INTRODUCTION

Malnutrition continues to be a serious problem that can increase morbidity and mortality in hospitalized patients.[1] The prevalence of malnutrition in the hospital setting has been reported between 28% and 73%, depending on the patient population and diagnostic criteria.[2-4] The prevalence of malnutrition in hospitalized patients is significantly high not only at admission but also before discharge.[5]

In hospitalized patients, providing adequate nutritional support reduces morbidity, mortality, and health care costs.[6,7] Despite the awareness of the importance and consequences of malnutrition, progress towards providing nutritional intervention in hospitalized patients remains insufficient.[8] The multidisciplinary team approach comes to the fore in the prevention of malnutrition and optimal management of nutritional care process in hospitalized patients. Nutritional support team consisting of physicians, dietitians, nurses and pharmacists specialized

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Received: January 11, 2024 Accepted: August 18, 2024
Published: August 27, 2024

in clinical nutrition primarily provide nutritional care.[9] In cases where physicians lack adequate training on nutrition, management of nutrition-related problems of hospitalized patients becomes more difficult.[10,11] Studies have found that physicians' knowledge on clinical nutrition is insufficient, and they are not aware of this situation and think that their knowledge is sufficient.[12,13] In contrast to these studies, even though the clinical nutrition knowledge level of medical oncology physicians is sufficient, it has been reported that there is a mismatch between physicians' knowledge, awareness and clinical practice.[14] Determining the attitudes of physicians towards malnutrition and clinical nutrition in hospitalized patients, the factors associated with this attitude and improving these attitudes as desired play an important role in the management and prevention of adult malnutrition in the hospital environment. The scales in the literature have been examined and a scale that includes the attitudes of physicians towards hospitalized patients and their own medical responsibilities has not been found. The aim of this study is to develop a scale that evaluates physicians' attitudes towards malnutrition and medical nutrition therapy in hospitalized patients.

MATERIAL AND METHODS

Sampling of the study

The study was conducted with 194 physicians selected through convenience sampling among those involved in the diagnosis and treatment processes of nutritional disorders between February 2020 and 2021. The study protocol was approved by the hospital ethic committee and was conducted in accordance with the Helsinki Declaration. Each participant was informed about the contents of the study prior to the survey and signed an informed con sent form which indicated voluntary participation in the research.

Scale Development Process

While developing the scale in the first stage, the literature on the subject was reviewed by the researchers (two physicians, one dietitian and one specialist in the field of measurement and evaluation) and previously developed scales were used during the writing process of attitude items.[15,16] Items related to the characteristics to be measured were written by taking into account the issues stated in the literature (expression, content, etc.) of the attitude level, as well as expert opinions. As a result of the examinations, the first draft form with 12 items was created in order to measure the attitude towards the clinical nutrition care process. The draft form prepared was applied to 106 assistant physicians working in inpatient services. The draft form was revised in accordance with the necessary statistical analyzes and the opinion of the measurement and evaluation specialist. Following the revision, a second draft form with 20 items was generated. The second draft form was evaluated by the same expert team and corrections were made in line with the feedback received. Afterwards, each item was examined one by one with a group of 7 physicians and the scale was finalized in terms of medical language and intelligibility. As a result of all the procedures, 12 items were included in the item pool. 7 of these items are positive and 5 of them are negative (1st,6th,7th,8th, and 12th items). A five-point Likert type scale was prepared to express the level of agreement with the items in the scale. The scale is rated in 5 categories ranging from (1) "strongly disagree" to (5) "strongly agree". After the measurement tool was applied to the study group, the score was graded by considering whether the items were positive or negative in scoring the answers. The answers given to the negative statements in the scale were recorded in the opposite direction.

Main Points

- Determining physicians' attitudes towards malnutrition and the factors associated with these attitudes is important in the prevention of hospital malnutrition.
- The developed attitude scale is a valid and reliable instrument to measure physicians' attitudes related to clinical nutrition care process.
- Future studies may help to improve optimal nutritional care by determining the factors affecting physicians' attitudes.

Statistical Analysis

In order to examine the dimensions of the theoretical structure by using the observed variables and to reveal the factor structures, Exploratory factor analysis (EFA) was performed on the data obtained as a result of the application of the 5-point Likert-type attitude scale. Since the answers to the scale consisted of scores ranging from 1 to 5, the data obtained for each item were multiple categorical data at the ranking level, factor analysis based on the polychoric correlation matrix was performed.[17] Analysis was performed using Parallel Analysis (PA) to determine the number of factors in EFA analysis and Unweighted Least Squares (ULS)[18] as factor extraction method. The ULS method was preferred[19], since the aim of EFA is to determine the latent variables that explain the relationships between the observed variables, and it is a method frequently used in small samples.[20] Varimax rotation method, one of the factor rotation methods, was used in order to facilitate the understanding and interpretation of the factor loads obtained as a result of factor analysis. Variance inflation factor (VIF), tolerance value (TV) and conditional index (CI) values were calculated to determine whether there is a multicollinearity problem

in the data set. Tolerance value above 0.01, VIF values below 10 and CI values below 30 indicate that there is no multicollinearity problem.[21] Mahalanobis distance values were calculated to examine the multivariate extreme values. By using the chi-square test for the presence of multivariate extreme values, the significance of the Mahalanobis distance values obtained at the 0.001 level was examined.[22] In this study, since the data obtained from the observed variables of the Likert-type scale were evaluated at the ordinal scale level, there was no need to examine the multivariate normality assumption.[23,24]

After checking the assumptions for EFA, the Kaiser-Meyer-Olkin (KMO) test and Bartlett's test were performed to ensure that the data set was suitable for factor analysis.[25-28] There is a common view in the literature that the minimum size for the factor load value of an item should be 0.30, but there are also theorists who argue that this size should be 0.40.[29] In this study, the minimum magnitude for the factor load value was taken as 0.30.

The FACTOR (ver. 12.01.02) program was used for analysis of the factor structure of the NT scale. SPSS (ver. 25) was used for analyzes of Cronbach's alpha reliability and factor analysis assumptions. The analyzes of the good fit values of the factor model and McDonald's Omega reliability were performed in RStudio (Ver. 1.1.463) software with the psych (Ver. 2.1.9) package.[30]

RESULTS

A total of 194 physicians, 52.6% were women and half of the participants were working in internal clinic. The experience of physicians varies between new initiation and 36 years, with a mean of 4.5 years. Table 1 indicates maximum and minimum values between 1 and 5 for the data set with 12 variables.

Exploratory factor analysis

Evaluation of suitability of data for factor analysis

There are no missing values in the data set when the assumptions required for the EFA are examined. Since there are no significant Mahalanobis distance values at the a=0.001 level, there are no multivariate extreme values in the data set. According to the minimum and maximum values of VIF, TV and CI, the data set does not have a multicollinearity problem (Table 2).

KMO and Bartlett test are given in Table 3. The KMO coefficient was found to be 0.76. This value shows that the sample size is sufficient for factor analysis. The fact that the p value is statistically significant as a result of the Bartlett test indicates that significant factors can be obtained from the correlation matrix. EFA was continued as the data were suitable for factor analysis by providing the assumptions regarding factor analysis. The correlation values between the variables in the scale are given in Figure 1. Correlations range from 0.80 to -0.13.

Table 1. Descriptive statistics for the data set

Variables	Number of Observations	Number of missing values	Min value	Max value	Mode value	Median value	Skewness	Kurtosis
V1	194	0	1	5	5	4	-0.560	-0.815
V2	194	0	1	5	5	4	-1.000	0.356
V3	194	0	1	5	4	4	-0.811	0.006
V4	194	0	1	5	5	4	-1.113	0.540
V5	194	0	1	5	3	4	-0.381	-0.634
V6	194	0	1	5	5	4	-0.737	-0.616
V7	194	0	1	5	3	3	-0.037	-1.183
V8	194	0	1	5	5	4	-0.662	-0.736
V9	194	0	1	5	3	3	0.097	-1.000
V10	194	0	1	5	4	4	-0.747	-0.122
V11	194	0	1	5	3	3	-0.145	-0.755
V12	194	0	1	5	4	4	-0.566	-0.761

Table 2. Results on multicollinearity

VIF min	VIF max	TV min	TV max	CI min	CI max
1.13	2.27	0.44	0.88	1	24.28

Table 3. Data suitability for factor analysis		
Kaiser-Mayer-Olkin (KMO)		0.763
Bartlett's Test	Chi-square value	957.216
	df	66
	p	0.000010 <0.05

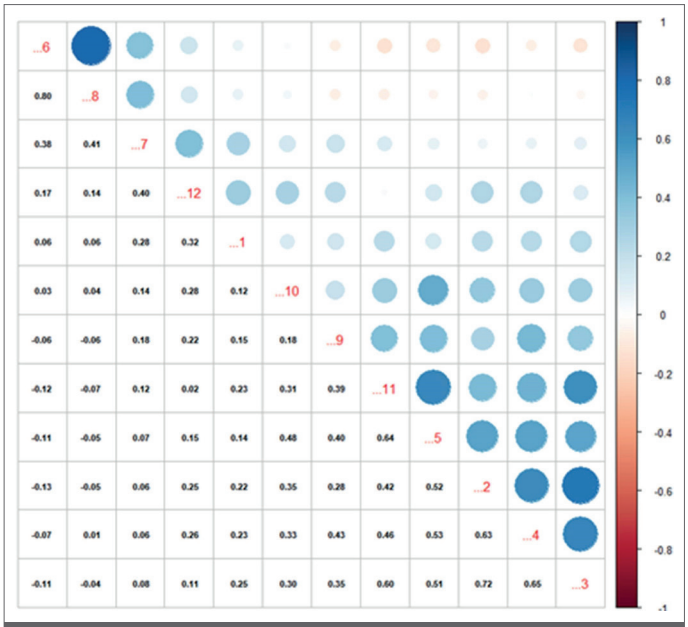

Figure 1. Correlation matrix between variables

Examination of the construct validity of the scale

Determining the number of factors

As a result of the factor analysis, it was decided to use the Varimax orthogonal rotation technique because the factor loadings of the items that loaded more than one factor were close and the items could not be separated into factors exactly. According to Parallel Analysis Based on Minimum Rank Factor Analysis recommended number of factors was obtained as 2 (Table 4). There are 3 variables with an eigenvalue above 1 for the 12-item scale. Eigenvalues and variance explanation rates for the scale are given in Table 5. The first variable (eigenvalue 4.018) explained 33.5% of the variance, the second variable (eigenvalue 2.285) explained 19% of the variance, while the third variable (eigenvalue 1.122) explained 9% of the variance. The first and second variables explain 52.5% of the variance in the attitude scale. The contribution of the third variable to the explained variance is less important than the first and second factors. After the factor analysis, the Scree Plot of the 12-item scale is shown in Figure 2. When Figure 2 is examined, it is understood that the components with high acceleration and rapid declines are the factors numbered 1 and 2, and the graph takes a horizontal appearance from factor number 3. As a result of the analyzes carried out to determine the number of factors, it was decided that the number of significant factors included in the scale should be two.

Determination of factor variables

The distribution of the 12 items in the attitude scale according to the factors and their factor loads are given in Table 6. The factor loads of the items that make up the scale vary between 0.306 and 0.853. First factor consists of 8 items (3, 4, 2, 5, 11, 9, 10, 1) while second factor

Table 4. Parallel analysis results			
Variable	**Real-data % of variance**	**Mean of random % of variance**	**95 percentile of random % of variance**
1	38.436*	17.092	19.557
2	20.373*	15.095	16.846
3	10.413	13.426	14.774
4	7.809	11.939	13.082
5	7.285	10.451	11.684
6	4.719	8.925	9.990
7	3.565	7.497	8.629
8	2.632	6.072	7.327
9	2.048	4.619	5.925
10	1.840	3.172	4.525
11	0.882	1.713	3.156
*Advised number of dimensions: 2			

Table 5. Explained eigenvalues and variance distributions			
Variable	**Eigenvalue**	**Proportion of Variance**	**Cumulative Proportion of Variance**
1	4.018	0.335	0.335
2	2.285	0.190	0.525
3	1.122	0.093	
4	0.900	0.075	
5	0.860	0.072	
6	0.763	0.064	
7	0.562	0.047	
8	0.429	0.036	
9	0.343	0.029	
10	0.333	0.028	
11	0.199	0.017	
12	0.185	0.015	

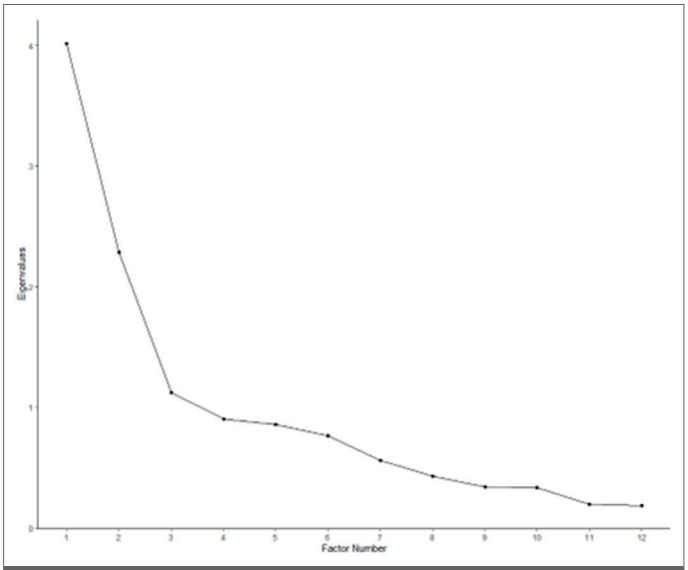

Figure 2. Scree plot graph

consist of 4 items (6, 8, 7, 12). Classifications of the items contained in the factors were deemed appropriate as "Physician Duties" for the items in Factor 1, and "Non-physician Duties" for the items in Factor 2.

Examining the reliability level of the scale

The internal consistency coefficient for the attitude scale and its sub-dimensions is given in Table 7. The Cronbach Alpha coefficient for the 1st and 2nd Factors was obtained as 0.78 and 0.66, and the Omega coefficient as 0.85 and 0.75. While the Cronbach Alpha coefficient for the attitude scale was 0.72, the McDonald's Omega coefficient was found to be 0.81.

Table 6. Factor loads and distribution of the Attitude Scale		
Item No	**Factor Load**	
	Factor 1	**Factor 2**
M3	0.801	
M4	0.761	
M2	0.750	
M5	0.741	
M11	0.688	
M9	0.497	
M10	0.468	
M1	0.306	
M6		0.853
M8		0.823
M7		0.550
M12		0.335

Goodness of fit statistics

In order to determine the level of fit of the model obtained as a result of exploratory factor analysis, the fit values of the model are given in Table 8. Root Mean Square Error of Approximation (RMSEA) 0.071; Goodness of Fit Index (GFI) 0.975; Non-Normed Fit Index (NNFI) 0.948; Comparative Fit Index (CFI) 0.966; Adjusted Goodness of Fit Index (AGFI) 0.962; Root Mean Square of Residuals (RMSR) 0.069; Weighted Root Mean Square Residual (WRMR) was found to be 0.066.

Table 7. Internal consistency coefficients of the Attitude Scale			
	Cronbach Alpha	**Omega**	**No. of items**
Factor 1 (Physician Duties)	0.78	0.85	8
Factor 2 (Non-physician Duties)	0.66	0.75	4
Attitude Scale	0.72	0.81	12

Table 8. Attitude Scale model fit values			
Fit Measures	**Acceptable fit values**	**Good fit values**	**Fit values of the model**
RMSEA	0.05≤RMSEA ≤0.08	0.00≤RMSEA≤0.05	0.071
GFI	0.90 ≤ GFI ≤ 0.95	0.95 ≤ GFI ≤ 1.00	0.975
NNFI	0.90 ≤ NNFI ≤ 0.95	0.95 ≤ NNFI ≤ 1.00	0.948
CFI	0.90 ≤ CFI ≤ 0.95	0.95 ≤ CFI ≤ 1.00	0.966
AGFI	0.85 ≤ AGFI ≤ 0.90	0.95 ≤ AGFI ≤ 1.00	0.962
RMSR	-	RMSR ≤ 0.072 (Kelley's criterion)	0.069
WRMR	-	WRMR ≤ 1.00	0.066

DISCUSSION

With this research, a valid and reliable scale was developed based on scientific studies and in consultation with medical professionals, dietitians and specialists to evaluate physician attitudes towards the clinical nutrition care process of hospitalized patients.

The factor analysis applied to the attitude scale was carried out based on the polychoric correlation matrix, since it is an ordinal scale with 5 categories. The Unweighted Least Squares method, which is preferred in small samples, was used to determine the latent variables that explain the relationships between the observed variables as a factor extraction method in factor analysis.[19] The two-factor model obtained for the attitude scale as a result of factor analysis explains 52.5% of the total variance. While 8 items of the 12-item scale with factor loads ranging from 0.80 to 0.31 constitute Factor 1 (Physician Duties), 4 items with factor loads ranging from 0.85 to 0.33 constitute Factor 2 (Non-Physician Duties). Providing clinical nutrition is a multidisciplinary team effort where each health professional has different duties, authorities and responsibilities.[9] For this reason, the two-factor model in the attitude scale was named as "Physician Duties" and "Non-Physician Duties". Regarding the reliability of the scale, The Cronbach Alpha and Omega coefficients were obtained as 0.72 and 0.81 respectively, 0.78 and 0.85 for the 1st factor, and 0.66 and 0.75 for the 2nd factor, indicating that the reliability level of the scale was sufficient. Good fit index values (RMSEA-0.07, GFI-0.97, NNFI-0.95, CFI-0.97, AGFI-0.96, RMSR-0.07, WRMR-0.07) for the model-data fit of the scale were obtained in the reference range. These values of model fit indicate acceptable and good fit values are within the reference range.[31-33] Our exploratory and confirmatory analyses show the strength of the scale items and the usability of the scale in assessing physicians' attitudes towards the clinical nutrition care process.

In conclusion, the validity and reliability of the 12-item attitude scale, which was developed to evaluate the attitudes of physicians towards the clinical nutrition care process in hospitalized patients, was provided at a sufficient level in line with the findings obtained. Future studies are recommended to examine attitudes of physicians towards clinic nutrition by making adaptations of the attitude scale to different languages and cultures. Also, determining the factors affecting the attitudes of physicians and the barriers to medical nutrition therapy can help develop optimal nutritional care.

Ethical approval: The study was approved by the Karadeniz Technical University Scientific Research Ethics Committee (2019/229 / November, 2019).

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

Author contributions: Concept and Design – HU, BD; Supervision – HU; Data Collection and/or Processing – HU, KK, IN; Analysis and/or Interpretation – GK, BD; Literature Search – MK; Writing Manuscript – HU, GK, MK; Critical Review – HU.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

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Supplementary Table 1

Klinik beslenme bakım sürecine yönelik tutum ölçeği	**Kesinlikle Katılmıyorum (1)**	**Katılmıyorum (2)**	**Kararsızım (3)**	**Katılıyorum (4)**	**Kesinlikle Katılıyorum (5)**
Hastaneye yatışı yapılan hastanın malnütrisyon değerlendirmesini yapmayı kendi görevim olarak görmem.					
Endikasyonu olan hastanın nütrisyon tedavisini düzenlemek benim görevimdir.					
Yatışı yapılan hastada nütrisyonel durum değerlendirmesi yapmayı kendi görevim olarak görürüm.					
Hastamda yetersiz nütrisyon destek tedavisi sonucu komplikasyon gelişirse sorumluluk hissederim.					
Hastanın yatışı süresince haftada bir nütrisyonel durum değerlendirmesini yapmak isterim.					
Hekim dışı sağlık personelinden, hastanın nütrisyonel durum değerlendirmesi için danışmanlık almak istemem.					
Hastanın malnütrisyon durumunu hasta kayıtlarına işlemeyi kendi görevim olarak görmem.					
Hekim dışı sağlık personelinden hastanın malnütrisyon tedavisi için danışmanlık almak istemem.					
Hastaneye yatış endikasyonu kalmamış malnütrisyonu olan hastayı taburcu etmek istemem.					
Malnütrisyonu olan hastayı taburculuk sonrası değerlendirmek üzere bir ay sonra kontrole çağırılması gerektiğini düşünürüm.					
Yeni yatan hastanın malnütrisyon durumunu değerlendirmek önceliklerim arasındadır.					
Hastanın taburculuk sonrası malnütrisyon durumu ile ilgili önerilerimi hasta-hasta yakınlarıyla paylaşmayı kendi görevim olarak görmem.					

CLINICAL SCIENCE OF NUTRITION
Original Article
DOI: 10.62210/ClinSciNutr.2024.87

Plate waste and malnutrition in intensive care patients

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Cite this article as: Karlı K, Sarıaslan M, Tümer G. Plate waste and malnutrition in intensive care patients. *Clin Sci Nutr*. 2024;6(2):88-96.

ABSTRACT

Objective: This study aimed to determine food waste rates in intensive care patients.

Methods: In this cross-sectional study, 45 patients in the intensive care unit were assessed for malnutrition risk using NRS 2002. Food waste rates were calculated by weighing the weight of the food served and left on the plate. Energy density of foods was calculated. The patients' energy and nutrient intakes were calculated. Evaluated according to the recommendations of the Türkiye Dietary Guidelines.

Results: 55.55% of the patients had severe malnutrition. Patients cannot consume 38.17% of the food served. The highest waste rate is in vegetables and salads (75.35%). The energy density of patients' food consumption is low. The patients' energy and protein intake was 828.56 kcal/day and 32.13 g/day. Energy and nutrient intake are below recommended, except for sodium and vitamin B12. A moderate positive correlation was found between hand grip strength and energy (r=413, p=0.001) and protein (r=453, p=0.001) intake.

Conclusion: Patients cannot consume approximately 40% of the food. Improved protein and energy intake increased muscle strength and performance. Since a decrease in food intake will cause malnutrition to worsen, there is a need to develop strategies to increase energy and protein intake in these patients.

Keywords: intensive care, malnutrition, plate waste, food intake

INTRODUCTION

Many Intensive care unit (ICU) patients struggle to maintain sufficient energy and nutrient intake. This insufficiency leads to increased catabolism, decreased fat tissue, and muscle mass loss, often resulting in severe malnutrition. The prevalence of malnutrition in ICU patients ranges between 38-78%[1], with a specific study in Turkey reporting a risk prevalence of 44.2%.[2]

Despite oral nutrition availability, ICU patients' nutritional needs are not fully met, making it challenging to reach target energy and protein levels promptly. Encouraging oral feeding and utilizing oral nutritional products can help improve daily intake, emphasizing the importance of considering food service quality in hospital settings.[3]

Several factors contribute to decreased food intake in ICU patients, including loss of appetite, the quality and appearance of hospital food differing from patients' usual diet, and delays in food service. Studies indicate that inpatients leave about half of the food served uneaten.[4,5] Simzari et al. highlighted the connection between plate waste and hospital malnutrition[6], underscoring the importance of addressing food waste in medical settings.

Although the optimal energy and protein intake for ICU patients remains uncertain, guidelines generally recommend an intake of 24-30 kcal/kg/day and 1.2-1.5 g/kg/day of protein.[7,8] Hospital diets designed for patients at risk of malnutrition typically provide approximately 30 kcal/kg of energy and 1.2-2.0 g/kg/day of protein.[9] Meals in hospitals in Türkiye are planned according to healthy

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Received: April 30, 2024 Accepted: June 26, 2024
Published: August 27, 2024

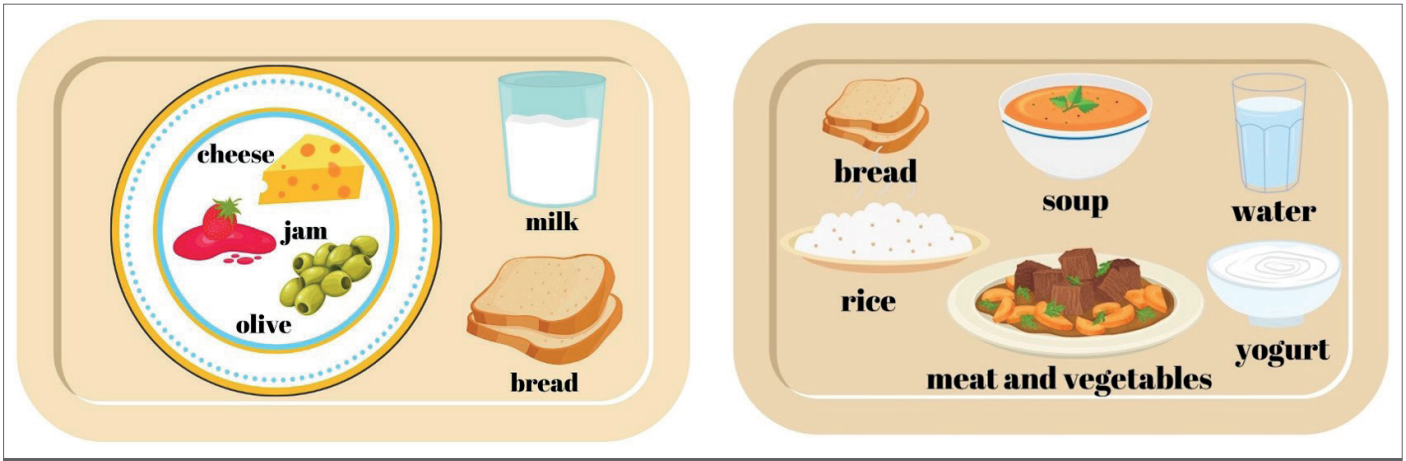

Figure 1. The typical structure of meals served in hospitals in Türkiye

nutrition principles, including foods from the dairy, meat, cereal, vegetable, and fruit groups, as illustrated in Figure 1.

Despite these efforts, the desire and capacity of ICU patients to consume food often diminish due to their deteriorating health status, making malnutrition inevitable. Thus, offering appetizing and appropriately textured foods that patients are more likely to consume can significantly increase food intake and reduce waste, serving as a crucial strategy in combating malnutrition.[10,11]

This study explores the relationship between food waste and malnutrition in ICU patients who can receive an oral diet.

Main Points

- The prevalence of malnutrition is high in intensive care unit patients.
- Intensive care patients leave approximately two-fifths of the meals served on their plates.
- In these patients, energy and nutrient intake remain below the daily recommended amounts.
- Oral enteral nutrition products are of vital importance for intensive care patients.
- Catering services and content should be improved in hospitals.
- A moderate positive significance was found between the rate of meeting the daily recommended amount of protein and hand grip strength.

METHODS

Study Desing

This cross-sectional study was conducted between November 2023 and March 2024 in the Intensive Care Unit of On Dokuz Mayıs University Adult Hospital Internal Medicine Clinic.

Ethical Approval

Ethical approval for the study was received from Ondokuz Mayıs University Clinical Research Ethics Committee (26.10.2023, No: 2023/206). Patients were informed about participation in the study, and written consent was obtained from the volunteers.

Participants

Patients aged 18 and over who were newly extubated and could achieve oral feeding, had no limb loss and could use a hand dynamometer were included in the study. To ensure patient compliance, two days after extubation, that is, on the third day of extubation, The study follow-up period started when the patient had a safe swallowing function and the ability to use his upper extremities in bed.

The patients were followed for 72 hours. During data collection, patients who were intubated, sedated, or died within 72 hours, patients whose treatment was stopped, patients who went hungry due to examination, patients whose food intake was stopped for any reason, patients who were transferred to another service, and patients who refused treatment were excluded from the study. All patients (N=124) who met the study criteria in the ward during the study period were included. Forty-five patients completed the study.

Data Collection Tools

Questionnaire: The questionnaire consists of general and health status information, hand grip strength data, and three-day food consumption records.

Data on general and health status: Information on the general and health status of the patients was obtained from hospital records. Patients with an NRS 2002 score of 3 and 4 were considered risky, and a score of 5 and above was considered high risk.[11]

Data related to hand grip strength: Hand grip strength was measured with a Camry Electronic Hand Dynamometer on the left hand, and it was repeated three times on the first and third days of the study. The patients were asked to squeeze the hand dynamometer with maximum isometric effort for five seconds in the measurements. The kg value on the LCD screen was recorded, and the measurements were averaged. The evaluation was made according to gender.

Food consumption records: Food consumption was recorded for three days (72 hours). To determine food consumption and waste amounts, the food served at meals, and the waste on the plate was measured using a Beurer KS 59 Kitchen Scale by recording the plate in grams.

The energy and nutrient intakes of the patients were analyzed with the Beslenme Bilgi Sistemi (BeBiS, İstanbul, TÜRKİYE) program and evaluated according to the rate of meeting the daily recommended intake of the Turkish Dietary Guidelines by gender. Daily recommended intake ≤66% was considered inadequate, 67-133% adequate, and >133% excessive.[12]

The energy density of the food consumed is calculated by dividing the energy (kcal) of the food by its quantity (g). The energy of the food was calculated using the BeBIS program and divided by quantity. The calculation excluded foods that have weight but do not contribute to energy intake, such as water and sugar-free drinks. The classification is very low <0.6 kcal/g, low 0.6-1.5 kcal/g, medium 1.6-3.9 kcal/g, and high 4.0-9.0 kcal/g.[13]

Statistical Analyses

The research data were analyzed with SPSS 23.0 (IBM SPSS Corp., Armonk, NY, USA) package program. General and health information of the patients, hand grip strength data, data on food consumption, and energy density values were evaluated by descriptive statistical methods. Box Plot graphs were used to evaluate the suitability of the data for normal distribution. A Paired Samples T-test was used to compare the first and third days' hand grip strength measurements. Patients' food consumption and waste rates on the plate were expressed graphically. Repeated measures ANOVA was used to compare the energy density of meals and days. A Paired Samples T-test was used to compare the food consumption of the patients with the daily recommended consumption amounts. The Pearson correlation coefficient was used to determine the relationship between energy, protein intake, and hand grip strength. The results were evaluated at a 95% confidence interval and $p<0.05$ significance level.

RESULTS

57.78% of the patients participating in the study were male. The mean age of the patients was 59.27±16.70 years. In addition to oral nutrition, 60.00% of the patients received enteral or parenteral nutrition. The daily target calorie intake was not reached in 92.60% of those receiving enteral or parenteral nutrition support. 37.78% of the patients did not consume their meals because of loss of appetite, 28.89% because the food's taste, odor, texture, and temperature were unsuitable, and 20.00% because of nausea. The distribution of information regarding the patients' general health status and anthropometric measurements is shown in Table 1.

The patients' mean NRS 2002 score was 5.38±1.28. Hand grip strength was 15.69±5.89 kg in males, 7.05±3.81 kg in females on the first day, 14.68±6.04 kg in males, and 6.30±4.06 kg in females on the third day. There was a statistically significant difference between the hand grip strength measurements on the first and third days in men ($p=0.228$).

According to the three-day food consumption records, the most common foods left on the plate by the patients were vegetables and salads (75.35%), rice-pasta-pastry-potato (57.84%), and syrup desserts (57.53%). The distribution of food left on patients' plates is shown in Figure 2. No statistically significant relationship was found between plate waste and hand grip strength ($p>0.005$).

The energy density of the foods consumed by the patients is given in Table 2. The highest energy density in meals was in breakfast ($P<0.005$). The energy density of all meals or days was low (less than 1 kcal/g/day). There was no statistically significant relationship between energy density and hand grip strength ($p>0.005$).

The average energy and nutrient intakes of the patients calculated from the three-day food consumption records and the rates of meeting the daily intake recommendations are given in Table 3. Except for sodium and vitamin B12, energy and nutrient intakes did not meet the daily recommended intake, and the results were statistically significant ($p<0.005$). A moderate positive correlation

Table 1. Distribution of information on the general, health status and anthropometric measures of patients			
General and health status		**n**	**%**
Gender	Male	26	57.78
	Female	19	42.22
Marital status	Single	10	22.22
	Married	35	77.78
Number of regular drug use	1-3	31	68.89
	4 and over	14	31.11
Reason for hospitalizations*	Oncological diseases	19	25.00
	Diseases of respiratory system	16	21.05
	Diseases of the cardiovascular system	13	17.10
	Gastroenterological diseases	8	10.52
	Diseases of the endocrine system	5	6.57
	Infection	5	6.57
	Sepsis/septic shock	3	3.94
	Diseases of the genitourinary system	2	2.63
	Hematological diseases	2	2.63
	Post-operative follow-up	2	2.63
	Diseases of the nervous system	1	1.31
Edema on the first day	Yes	19	42.22
	No	26	57.77
Nutritional routes	Oral	17	37.78
	Oral+enteral	5	11.11
	Oral+parenteral	23	51.11
Diet type	Liquid and soft diet	19	42.22
	Standart diet	26	57.78
Reason for enteral or parenteral nutiriton	Failure to reach target calories	25	92.60
	Aspiration risk	1	3.70
	Breathing problems	1	3.70
Reasons for not consuming meal	Loss of appetite	17	37.78
	Inappropriate taste, smell, texture and temperature of the food	12	28.89
	Nausea	9	20.00
	Difficulty chewing	6	13.33
	Breathing difficulties	1	2.22
Anthropometric measures		**X±SD**	
Hand grip strength	First day	12.05±6,65	
	Third day	11.15±6.70	
*More than one option is marked, the number n exceeds the sample size.			

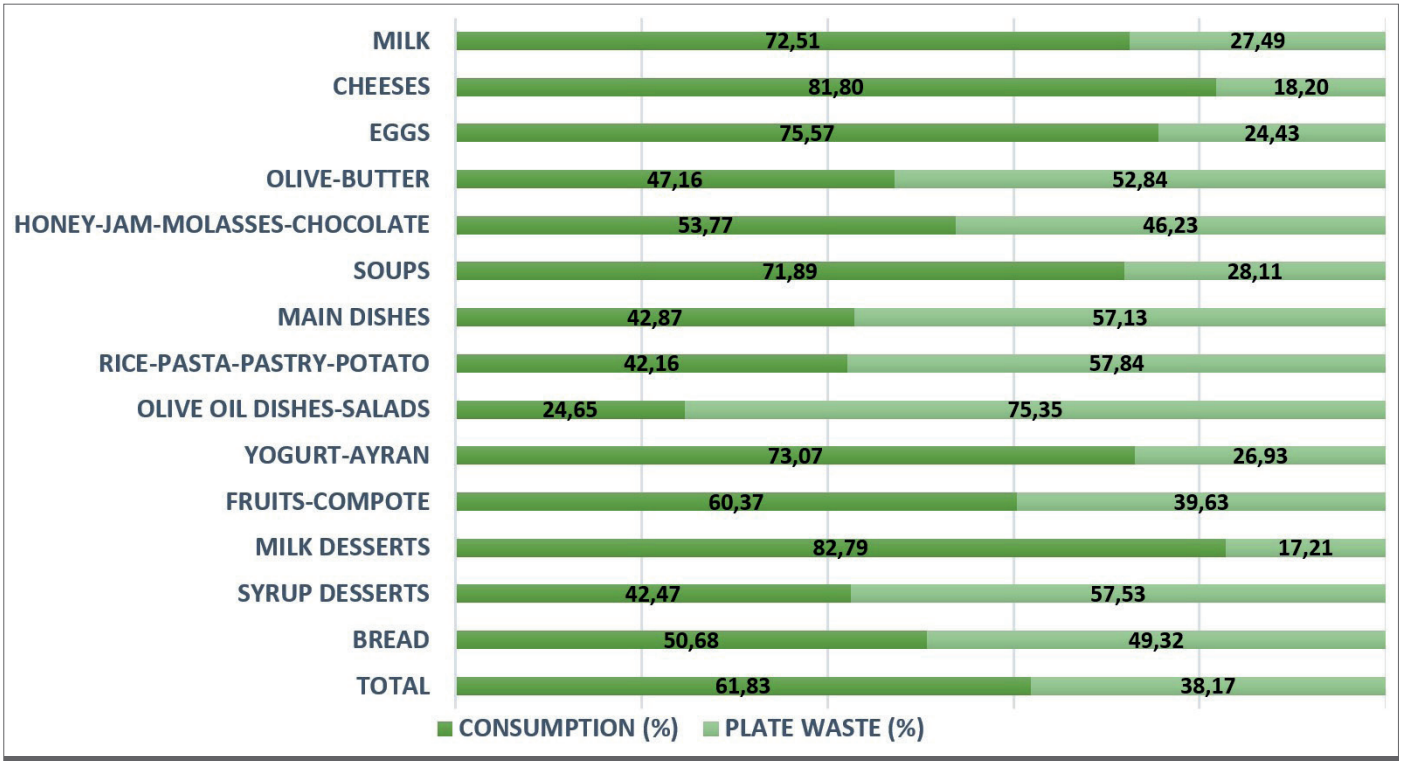

Figure 2. The distribution of food left on patients' plates

was found between hand grip strength and energy (r=413, p=0.001) and protein (r=453, p=0.001) intake, respectively.

DISCUSSION

In large-sample studies conducted in internal medicine wards and intensive care units, it has been reported that the prevalence of malnutrition is high, and one in every five patients has severe malnutrition.[14,15] In intensive care unit patients, the clinical general condition may worsen with the effect of malnutrition due to factors such as increased energy and nutrient requirements due to hypermetabolism, inflammation, trauma, and organ dysfunction.[3] In these patients, an individualized nutritional approach is required to meet the increased metabolic needs, reduce the negative effects of malnutrition, and support the healing process. Nutritional support in intensive care patients has been associated with favorable clinical outcomes, reduced complications, and improved overall prognosis.[3,10]

Table 2. The energy density of the foods consumed by the patients

		X±SD	P
Energy Density (kcal/g)	**Meals**		
	Breakfast	1.42±0.98	
	Lunch	0.71±0.27	0.001
	Dinner	0.79±0.35	
	Days		
	First day	0.98±0.40	
	Second day	0.93±0.33	0.752
	Third day	0.95±0.38	
	Total (Three days)	0.97±0.30	

Repeated Measures ANOVA

Table 3. Energy and nutrient intake calculated from a three-day diet record

Content	Total (n=45)	Male (n=26)			Female (n=19)		
	Food Consumption	Food Consumption	RDA (%)	P[1]	Food Consumption	RDA (%)	P[2]
	Mean	Mean	%		Mean	%	
Energy (kcal)	828.56	869.60	44.99	0.001	772.40	39.95	0.001
Carbohydrate (g)	84.68	90.67	32.88	0.001	76.48	27.74	0.001
Protein (g)	32.13	33.09	57.90	0.001	30.82	53.88	0.001
Fat (g)	39.56	40.97	62.42	0.001	37.64	57.37	0.001
Cholesterol (mg)	128.28	134.62	44.90	0.001	119.61	39.93	0.001
Fiber (g)	7.58	7.55	23.12	0.001	7.62	34.21	0.001
Vitamin A (µg)	520.26	520.25	58.13	0.001	520.27	73.83	0.019
Vitamin D (µg)	0.42	0.44	5.89	0.002	0.40	4.35	0.001
Vitamin E (mg)	8.71	8.52	66.46	0.001	8.97	59.79	0.001
Vitamin B1 (mg)	0.31	0.32	27.01	0.001	0.30	27.12	0.001
Vitamin B2 (mg)	0.71	0.75	58.15	0.001	0.65	59.28	0.001
Vitamin B3 (mg)	9.11	9.38	58.78	0.001	8.74	61.97	0.001
Vitamin B5(mg)	2.00	2.10	42.00	0.001	1.86	37.19	0.001
Vitamin B6 (mg)	0.48	0.50	32.81	0.001	0.46	32.09	0.001
Vitamin B7 (mg)	97.31	97.41	29.51	0.001	97.16	29.03	0.001
Vitamin B9 (µg)	14.03	14.57	48.60	0.001	13.29	44.26	0.001
Vitamin B12 (µg)	2.11	2.19	61.05	0.464	2.01	53.74	0.214
Vitamin C (mg)	20.27	20.00	22.26	0.001	20.63	27.33	0.001
Sodium (mg)	2167.81	2148.92	107.45	0.573	2193.65	109.68	0.593
Potassium (mg)	934.60	971.57	27.75	0.001	884.01	25.25	0.001
Calcium (mg)	433.40	460.72	40.31	0.001	396.02	34.21	0.001
Magnesium (mg)	107.35	111.44	27.01	0.001	101.76	31.67	0.001
Phosphorus (mg)	551.46	577.87	52.54	0.023	515.32	63.61	0.023
Iron (mg)	4.21	4.16	51.94	0.001	4.28	46.86	0.001
Copper (mg)	0.54	0.54	60.98	0.001	0.54	59.63	0.001
Zinc (mg)	5.03	5.15	47.09	0.001	4.87	60.25	0.001
Fluorine (µg)	178.27	182.22	4.56	0.001	172.86	5.70	0.001
Iodine (µg)	92.42	92.31	61.53	0.001	92.58	61.75	0.001

RDA (%): percentage of meeting the daily recommended consumption
P[1]: Comparison of male energy and nutrient intake with recommended amounts
P[2]: Comparison of female energy and nutrient intake with recommended amounts
Paired Simple T Test

The main aim of nutrition in intensive care units is to provide appropriate energy and nutrient needs according to the condition of the disease. Although meals prepared according to the patient's energy and nutrient needs are served from the hospital kitchen, the rate of leaving food on the plate is high for these patients due to loss of appetite, not liking the food, and being hungry due to the examinations performed. Gomes et al. reported that hospital food waste is 2-3 times higher than in other catering areas.[16] Kontogianni et al. reported that only 41.6% of inpatients consumed the entire meal served.[4] Schiavone et al. stated that 41.6% of the food served

to the patients was wasted, 30.4% were not hungry, and 13.6% left food on their plates because they did not like the taste of the food.[6] In this study, the main reasons why patients left food on the plate were loss of appetite (37.78%), inappropriate taste, smell, texture, and temperature of the food (28.89%), and nausea (20.00%) (Table 1).

Simzari et al. reported that the average plate waste rate for lunch and dinner during hospital stay was 37.7±29.88 and 30.4±23.61, respectively, and there was a link between plate waste and malnutrition.[6] In a study conducted in the USA, researchers reported that 32.1 percent of patients in intensive care units ate one-quarter or less of their meals. The authors found that the risk of hospital mortality was 3.24 times higher for patients who ate a quarter meal or less compared to those who ate all their meals and 5.99 times higher for patients who were allowed to eat but did not eat anything.[17] A study conducted in 2021 reported that 2 out of every five hospitalized patients were at risk of malnutrition. More than 50% of patients ate half or less of the hospital meals, and the risk of hospital mortality was up to 6 times higher in patients who ate very little or nothing.[18] In this study determined that 38.17% of the meals served to intensive care patients remained on the plate, and the most unconsumed meals were vegetable dishes and salads, with 75.35%. Regardless of the reason, consuming less or not consuming the food served in intensive care patients leads to deficiencies in energy and nutrient intake, exacerbating the disease and increasing mortality rates.[19]

Considering the tendency to eat small amounts of food in intensive care patients, serving foods with high energy density at meals is a good strategic nutrition approach. Foods with high energy density include cheeses, olives, butter, cream, hazelnut and peanut spreads, honey, jam and molasses. Enriching the meals served with these foods will increase energy intake.[13,20] In this study, the average energy density of the foods consumed daily by the patients was below 1 kcal/g. This means that the energy density is low. (Table 2). Practices such as adding cream to soup at lunch and dinner, serving pasta with cheese and olives, and dressing vegetable dishes and salads with healthy oils such as olive oil increase the energy density of the meal. The aromatic components in these foods add flavor and reduce plate waste.[12] However, if nutritional intake is less than necessary, trying to increase the energy density of the diet with meals may not be sufficient. Therefore, adding oral enteral nutrition products containing 1-1.5 g/kcal energy to the diet is vital in intensive care patients.

Authorities recommend that intensive care patients' energy intake be up to 70% of their nutritional requirement in the first week unless assessed by indirect calorimetry.[19] Wang et al. suggest that high energy intake is associated with lower mortality in patients with high nutritional risk and that at least 800 kcal/day energy intake is required to reduce mortality rates in the intensive care unit.[21] In a multicentre study by Alberda et al., the data of 2772 intensive care patients were analyzed. Although the average energy of the prescribed diets was 1794 kcal/day, it was determined that the patients received only 1034 kcal/day. The authors concluded that an energy increase of 1000 kcal daily was associated with reduced mortality.[22] A similar study by Nicolo et al. reported that the average energy consumption of 2828 patients who stayed in intensive care for four days or more was 1100 kcal, 64.1% of the prescribed amount.[23] In this study, the patient's three-day average energy consumption was 828.56 kcal/day. The percentage of meeting the daily recommended energy intake is 44.99% for men and 39.95% for women (Table 3). All of these results are below the authorities' recommendations. Additionally, this study found a moderate positive correlation between energy intake and hand grip strength.

Available data from studies conducted in intensive care units indicate that patients have low protein intake during the first two weeks of hospitalization. In their study, Alberda et al. reported that the average amount of protein in the prescribed diets was 87.5 g, and the patients consumed only 47.1 g/day.[22] In their study, Nicolo et al. reported that the average protein intake of intensive care patients was 51 g, meeting 60.5% of the prescribed amount. Researchers indicate that achieving ≥80% of prescribed protein intake reduces mortality.[23] In this study, patients' three-day average protein consumption was 32.13 g/day. The rate of meeting the daily recommended intake is 57.90% for men and 53.88% for women (Table 3). Inevitably, the protein needs of these patients cannot be met because approximately 20-30% of foods with high protein content and quality, such as milk, yogurt, cheese, eggs, and milk desserts served at meals, are left on the plate (Figure 2). In addition, one of the results showed moderate positive significance between protein intake and hand grip strength. This means that as protein intake increases, hand grip strength increases.

Micronutrient deficiencies may occur in intensive care patients due to decreased nutritional intake upon hospitalization, if not before.[24] Antioxidant micronutrients, particularly β-carotene, vitamin D, vitamin E, vitamin C, copper, iron, manganese, selenium, and zinc, tend to be lower in intensive care patients than healthy controls.[19] Similarly, in this study, there was a statistical difference between the micronutrient intakes of the patients and the recommended amounts, except for sodium and vitamin B12 (Table 3). However, essential minerals such as sodium, potassium, and magnesium are added, and fluid therapy

is applied in intensive care. This reduces micronutrient loss and meets the requirements. In addition, in patients with reduced nutritional intake, oral enteral products are an essential component of nutritional therapy to ensure daily intake of micronutrients. In standard enteral formulas, healthy individuals' recommended amount of vitamins and minerals is met when the daily enteral product intake is above 750 ml (2 kcal/g) or 1000-1500 ml (1 kcal/g). Therefore, additional enteral or parenteral vitamins and minerals should be provided if the patient cannot tolerate the enteral formulas given.[24]

Limitations

This research is one of the few studies determining food waste rates in intensive care patients. However, the amount of energy obtained from enteral and parenteral products has been neglected. In addition, there is a small number of samples, the inability to obtain biochemical findings of the individuals, and the failure to obtain anthropometric measurements of the patients due to their condition.

Malnutrition is common in intensive care patients. This study found that intensive care patients consumed only about two-fifths of the food served at meals. Plate waste increases the negative effects of malnutrition. Energy and protein intake are correlated with hand grip strength. Enriching the foods offered to these patients with cheese, olives, butter, cream, honey, and molasses, which have a high energy density, increase taste and reduce waste and malnutrition. Considering the link between plate wastage and malnutrition, there is a need to develop various strategies to reduce plate wastage rates in hospitals.

Ethical approval: The study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (2023/206 / 26.10.2023).

Informed consent: Patients were informed about participation in the study, and written consent was obtained from the volunteers.

Author contributions: Concept – K.K., M.S.; Design – K.K., M.S.; Supervision – G.T.; Resources - K.K., M.S.; Materials - K.K., M.S., G.T.; Data Collection and/or Processing – M.S., G.T.; Analysis and/or Interpretation – K.K., G.T.; Literature Search - K.K., M.S., G.T.; Writing Manuscript - K.K., M.S., G.T.; Critical Review - K.K., M.S., G.T.; Other – K.K., M.S., G.T.

Funding: This research was supported by the Scientific and Technological Research Council of Türkiye (TÜBİTAK) 2209-A University Students Research Projects Support Programme (2022/1, Project No: 1919B012206799).

Conflict of interest: The authors declare that there is no conflict of interest.

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CLINICAL SCIENCE OF NUTRITION
Original Article
DOI: 10.62210/ClinSciNutr.2024.89

Complications and factors associated with mortality in patients undergoing percutaneous endoscopic gastrostomy

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Cite this article as: Seyhan S, Tosun Taşar P, Karaşahin Ö, Albayrak B, Sevinç C, Şahin S. Complications and factors associated with mortality in patients undergoing percutaneous endoscopic gastrostomy. *Clin Sci Nutr*. 2024;6(2):97-106.

ABSTRACT

Objective: The aim of our study was to examine the factors associated with mortality in patients who underwent percutaneous endoscopic gastrostomy (PEG) and identify biomarkers that may guide clinical practice.

Methods: This retrospective observational study included adults who underwent PEG placement in our center. Demographic data, date of PEG placement, inpatient ward, PEG indication, time from admission to PEG placement, post-PEG complications, and outcome (discharge/mortality) were recorded. Logistic regression analysis was performed to identify factors associated with 90-day and 6-month mortality.

Results: Of 100 patients included in the study, 52% were men and the median age was 73 years. The most common indication for PEG was malignancy (n=25, 25%). The most common minor complication was minor peristomal bleeding and peristomal infection requiring tube removal The most common major complication was aspiration pneumonia. Thirty-eight patients (38.0%) died within 90 days and 52 patients (52.0%) died within 6 months of PEG placement. The odds of 90-day mortality were 57.5% lower per 1-unit increase in total serum protein level (odds ratio [OR]: 0.425, 95% CI: 0.230–0.888; p=0.021), 1.6% higher per 1-unit increase in serum CRP (OR: 1.016, 95% CI: 1.006–1.027; p=0.003), and 13.6 times higher in patients with aspiration pneumonia (OR: 13.631, 95% CI: 2.997–61.988; p=0.001). For 6-month mortality, a 1-unit increase in serum albumin level was associated with 81.4% lower odds (OR: 0.186, 95% CI; 0.081–0.430; p<0.001) and aspiration pneumonia with 22 times higher odds (OR: 21.984, 95% CI: 2.412–200.342; p=0.006).

Conclusion: Aspiration pneumonia, low total serum protein and albumin levels, and high CRP level were associated with higher mortality.

Keywords: PEG, indication, complication, mortality, biomarker

INTRODUCTION

Enteral nutrition (EN) is recommended for malnourished patients.[1] It is most commonly given by orogastric or nasogastric route or via a percutaneous endoscopic gastrostomy (PEG). PEG is indicated in patients who have dysphagia for any reason and have been fed by nasogastric tube for six weeks or more, have a neurological disease (such as stroke, Guillain-Barre syndrome, advanced dementia), have a diagnosis of obstructive cancer (such as head, neck, esophagus, or stomach tumor or malignant bowel obstruction), have dysphagia secondary to head trauma, or require gastric decompression.[2]

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Received: January 22, 2024 Accepted: August 8, 2024
Published: August 27, 2024

Although PEG feeding is a well-established method used for many years, studies have shown that short-term mortality after PEG can be as high as 25%.[3-5] Some patients do not benefit from this invasive and expensive procedure but instead develop complications and impaired quality of life.[6] Thus, caution should be exercised in the selection of patients with indications for PEG. In the literature, possible predictive factors for complications and mortality after PEG include hypoalbuminemia, older age, high anesthesia risk, dementia, low body mass index, and high Charlson comorbidity index.[7-10] Therefore, careful consideration and an evaluation of risk factors is warranted when PEG is indicated. The present study aimed to determine the factors associated with complications and mortality after PEG placement in Ataturk University Hospital Department of Gastroenterology.

MATERIALS AND METHODS

This retrospective observational study included patients over the age of 18 who underwent PEG in the gastroenterology department of our university between January 1, 2016 and April 1, 2022. Data were collected from the patients' medical records and the electronic records system of the hospital. Demographic data (age, sex, chronic diseases), date of PEG placement, the ward where the patient was hospitalized at the time of PEG placement, and the time from hospital admission to PEG placement (days) were noted. Complications occurring within the first 48 hours after the PEG procedure were categorized as early complications, and those occurring at least 48 hours later as late complications. Events classified as major complications included esophageal and gastric perforation, intramuscular hemorrhage in the esophagus, major bleeding-gastric wall hematoma, necrotizing fasciitis, injury to an adjacent organ, intestinal perforation, and aspiration pneumonia. Minor complications included minimal bleeding in the esophagus, minor peristomal bleeding, peristomal leakage, PEG tube dislodgement, gastric outlet obstruction, ileus, giant bezoar, tube occlusion, gastric wall necrosis, abdominal pain, abdominal distension, vomiting, diarrhea, and peristomal infection. We recorded the type of complications distinguishing them in early (occurred during the first 30 days after gastrostomy placement) and late (occurred 30 days or more after PEG placement) phases. Laboratory parameters evaluated at the time of PEG insertion, such as leukocyte, neutrophil, and platelet counts, mean platelet volume (MPV), hemoglobin, glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, CRP, erythrocyte sedimentation rate (ESR), and procalcitonin, as well as microorganisms cultured from the PEG insertion site and their antibiotic susceptibility, treatments applied, and outcome (e.g., transfer to intensive care, discharge, death) were recorded. The hospital records system and Death Notification System of the Republic of Turkey Ministry of Health were used to determine survival after PEG placement.

Main Points

- A total of 100 patients who underwent PEG included in the study.
- The most common indication for PEG was malignancy.
- The most common minor complication was minor peristomal bleeding and peristomal infection requiring tube removal
- The most common major complication was aspiration pneumonia.
- Aspiration pneumonia, low total serum protein and albumin levels, and high CRP level were associated with higher mortality.

Statistics

The data were analyzed using SPSS version 21.0 statistical software package The Kolmogorov-Smirnov assessment was used to assess whether continuous variables fit the normal distribution. Accordingly, continuous variables were presented as median (maximum–minimum values). (Categorical data were compared between groups using chi-square test or Fisher's exact test, and continuous data were analyzed using the Student's t-test or Kruskal–Wallis and Mann–Whitney U tests as appropriate Categorical and continuous variables found to be significant in terms of mortality were used to create a multivariable logistic regression model (backward: LR; entry: 0.05 and removal: 0.10). P values less than 0.05 were considered statistically significant.

Ethical approval to conduct the study was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (date: 02.06.2022, decision number: 5).

RESULTS

Patient characteristics

The study included 100 patients who underwent PEG. The patients had a median age of 73 years (range: 21-96), and 52 (52.0%) were men. The reasons for PEG application are presented in Figure 1. The most common indication for PEG insertion was malignancy (n=25, 25.0%), of which the most common were esophageal cancer (n=18, 18.0%) and head and neck tumors (n=3, 3.0%). Of the patients with cerebrovascular disease, 17 (17.0%) had cerebral infarction and 7 (7.0%) had intracranial hemorrhage.

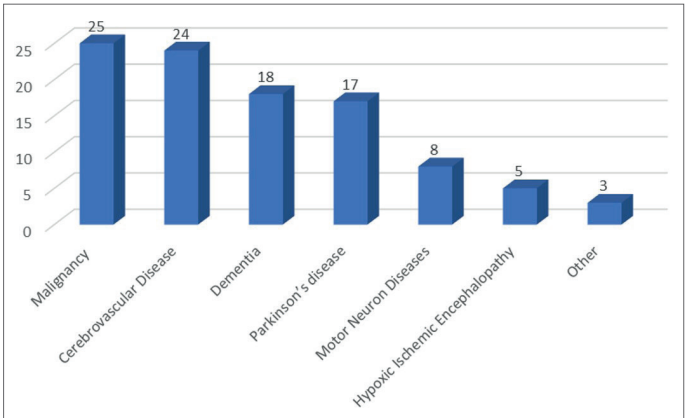

Figure 1. Indications for percutaneous endoscopic gastrostomy

The median time from hospital admission to PEG placement was 9 days (range: 1-10). The median number of diseases was 2 (range: 1-5). The patients' median Charlson Comorbidity Index score was 5 (range: 0-11). Hypertension, malignancy, and dementia were the most common chronic diseases.

Post-PEG Complications and Risk Factors

After the PEG procedure, 54 patients (54.0%) developed at least one complication and 16 patients (16.0%) developed two complications. The median ages of the patients with at least one complication and those with no complications were 74.5 years (range: 38-95) and 68.0 years (range, 21-96), respectively. Patients with at least one complication were significantly older (p=0.043). Of those who developed complications, 26 patients (48.1%) were male and 28 (51.9%) were female (p=0.404). The most common complication was aspiration pneumonia. No major complications such as necrotizing fasciitis, pneumoperitoneum, esophageal intramuscular bleeding, perforation, or adjacent organ injury were detected in any of the patients. The distribution of major, minor, and late complications after PEG placement is shown in Table 1. The most common minor complication was minor peristomal bleeding and peristomal infection requiring tube removal.

The comparison of chronic disease prevalence between patients with and without complications is shown in Table 2. There was no significant relationship between the development of complications and any chronic disease. In the complication subgroups, aspiration pneumonia was significantly more common among patients with dementia and cerebrovascular disease (p=0.010 and p=0.020, respectively). Diabetes mellitus was associated with a significantly higher rate of tube dislodgement (p=0.036). Other than these, there was no statistically significant relationship between complications and chronic diseases (p>0.05).

Table 1. Complications after PEG

Major Complications	**n (%)**
Aspiration pneumonia	14 (14.0)
Minor Complications	
Peritonitis	1 (1.0)
Minimal bleeding in the esophagus	7 (7.0)
Minor peristomal bleeding	13 (13.0)
Ileus	1 (1.0)
Tube occlusion	5 (5.0)
Late complications	
Tube dislodgement	7 (7.0)
Embedded bumper	8 (8.0)
Peristomal infection requiring tube removal	13 (13.0)

Comparisons of biomarkers evaluated at the time of PEG insertion between patients with and without post-PEG complications are shown in Table 3. Mean platelet volume and creatinine levels were significantly higher in patients with at least one complication (p=0.001 and p=0.008, respectively). Among the post-PEG complication subgroups, MPV was significantly higher in patients with minimal esophageal bleeding and minor peristomal bleeding (p=0.026 and p=0.026, respectively). We also noted significantly higher levels of CRP in patients with minimal bleeding in the esophagus (p=0.042), BUN in patients with minor peristomal bleeding (p=0.027), potassium in patients with tube occlusion (p=0.008), and sodium level and platelet count in patients with embedded bumper syndrome (p=0.033 and p=0.025, respectively).

Risk factors for 90-day and 6-month mortality after PEG

Thirty-eight patients (38.0%) died within 90 days and 52 patients (52.0%) died within 6 months of PEG placement. Comparisons of age, gender, chronic diseases, and biomarker values according to 90-day and 6-month mortality are presented in Table 4. There was no statistically significant relationship between gender and mortality. Patients who died within 6 months were significantly older (>65 year). Both 90-day and 6-month mortality were associated with longer median time from hospital admission to the PEG procedure. The 90-day mortality rate was significantly higher among patients with dementia and cerebrovascular disease, whereas the 6-month mortality rate was significantly higher in the presence of hypertension, COPD, and dementia and lower in the presence of Parkinson's disease. Among the biomarkers evaluated on the day of PEG placement, total protein and albumin were significantly lower in both the 90-day and 6-month mortality groups, while CRP, ESR,

Table 2. Distribution of chronic diseases according to the development of at least one complication and selected complication subgroups

Comorbidities	Complication, n (%)		p
	No (n=46)	Yes (n=54)	
Comorbidities	No (n=46)	Yes (n=54)	p
Hypertension	11 (26.1)	24 (44.4)	0.057
Diabetes mellitus	6 (13.0)	6 (11.1)	0.767
Coronary artery disease	7 (15.2)	13 (24.1)	0.270
Congestive heart failure	1 (2.2)	6 (11.1)	0.085
Chronic obstructive pulmonary disease	2 (4.3)	3 (5.6)	0.576
Dementia	10 (21.7)	13 (24.1)	0.782
Parkinson's disease	8 (17.4)	10 (18.5)	0.884
Cerebrovascular disease	9 (19.6)	16 (29.6)	0.247
Chronic liver disease	-	1 (1.9)	0.540
Peripheral vascular disease	-	2 (3.7)	0.289
Chronic kidney disease	1 (2.2)	1 (1.9)	0.711
Hypothyroidism	2 (4.3)	2 (3.7)	0.628
Hyperthyroidism	2 (4.3)	2 (3.7)	0.628
Malignancy	14 (30.4)	13 (24.1)	0.475
Amyotrophic lateral sclerosis	5 (10.9)	3 (5.6)	0.272
Multiple sclerosis	-	1 (1.9)	0.540
Huntington's disease	1 (2.2)	-	0.460
Major depression	1 (2.2)	1 (1.9)	0.711
Hypoxic ischemic encephalopathy	1 (2.2)	5 (9.3)	0.144
	Aspiration pneumonia, n (%)*		
	No (n=86)	Yes (n=14)	p
Dementia	16 (18.6)	7 (50.0)	0.010
Cerebrovascular disease	18 (20.9)	7 (50.0)	0.020
	Tube dislodgement, n (%)*		
	No (n=93)	Yes (n=7)	p
Diabetes mellitus	9 (9.7)	3 (42.9)	0.036

*Only statistically significant differences in chronic diseases between complication subgroups are presented.

and procalcitonin were significantly higher. Moreover, 6-month mortality was associated with significantly lower sodium and hemoglobin levels.

A comparison of complication rates according to mortality is presented in Table 5. Both 90-day and 6-month mortality were associated with statistically significantly higher rates of aspiration pneumonia. Tube displacement was significantly less frequent in patients with mortality at both 90 days and 6 months.

In order to determine independent risk factors for 90-day mortality after PEG placement, a multivariable logistic regression model was created with the presence of significant dementia and cerebrovascular disease, the development of aspiration pneumonia, and total protein, albumin, CRP, ESR, and procalcitonin values. It is presented in Table 6. The odds of 90-day mortality were 57.5% lower per 1-unit increase in total serum protein level (odds ratio [OR]: 0.425, 95% CI: 0.230–0.888; p=0.021), 1.6% higher per 1-unit increase in serum CRP (OR: 1.016, 95% CI: 1.006–1.027; p=0.003), and

Table 3. Comparisons of biomarkers evaluated at the time of PEG insertion between patients with and without post-PEG complications

Biomarker	At least one complication, median (range)		p
	No (n=46)	Yes (n=54)	
Leukocyte count (x10^3/µL)	7000 (2500 - 16800)	7080 (4030 - 20140)	0.616
Neutrophil count (mcL)	4980 (1700 - 15000)	4600 (2660 - 16420)	0.986
Lymphocyte count (mcL)	1335 (300 - 2920)	1510 (500 - 5750)	0.103
Platelet count (x10^3/µL)	216500 (21300 - 578000)	239500 (56000 - 532000)	0.213
Mean platelet volume (fL)	9.35 (6.10 - 12.20)	10.25 (6.80 - 14.20)	**0.001**
Hemoglobin (g/dL)	11.8 (7.6 - 16.9)	12.3 (7.7 - 15.5)	0.641
Glucose (mg/dL)	96.5 (61 - 226)	101 (63 - 354)	0.212
CRP (mg/L)	16.36 (4.21 - 36.4)	19.16 (3.74 - 36.92)	0.068
Creatinine (mg/dL)	0.47 (0.14 - 1.19)	0.62 (0.20 – 3.00)	**0.008**
Sodium (mg/dL)	138 (136 - 150)	138 (126 - 155)	0.773
Potassium (mmol/L)	3.94 (2.5 - 5.23)	4.03 (2.53 - 5.31)	0.686
AST (IU/L)	18.5 (6 - 100)	24 (6 - 631)	0.451
ALT (IU/L)	10.5 (2 - 94)	15.5 (1 - 172)	0.655
Total Protein (g/dL)	6.0 (4.2 - 8.2)	6.1 (4.6 - 8.4)	0.711
Albumin (g/dL)	3.01 (1.82 - 4.76)	3.05 (2.16 - 4.9)	0.790
CRP (mg/L)	25.95 (0.20 - 276.90)	21.25 (0.90 – 219.00)	0.879
ESR (mm/h)	31 (1 - 124)	33 (5 - 120)	0.594
Procalcitonin (ng/mL)	0.13 (0.01 - 1.40)	0.16 (0.02 - 16.78)	0.222
	Esophageal bleeding*		
	No (n=93)	Yes (n=7)	
Mean platelet volume (fL)	10.00 (6.10 – 14.20)	11.00 (9.30 – 11.90)	0.026
CRP (mg/L)	23.4 (0.2 – 276.9)	92.7 (19.1 – 134.4)	0.042
	Minor peristomal bleeding*		
	No (n=87)	Yes (n=13)	
Mean platelet volume (fL)	9.90 (6.10 – 14.20)	11.60 (9.30 – 11.90)	0.026
CRP (mg/L)	16.8 (3.7 – 36.9)	20.0 (8.8 – 33.4)	0.027
	Tube occlusion *		
	No (n=95)	Yes (n=5)	
Potassium (mmol/L)	4.00 (2.50 – 5.23)	4.58 (3.98 – 5.31)	0.008
	Embedded bumper syndrome*		
	No (n=92)	Yes (n=8)	
Sodium (mg/dL)	138 (124 – 155)	142 (136 – 147)	0.033
Platelet count (x10^3/µL)	221500 (21300 – 578000)	325000 (181000 – 532000)	0.025

*Only statistically significant differences in biomarkers between complication subgroups are presented.
MPV: Mean platelet volume, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IU: International unit

Table 4. Comparison of age, gender, chronic diseases, and biomarker values according to 90-day and 6-month mortality with bivariate analysis

	90-day mortality, n (%)		p	6-month mortality, n (%)		p
	No (n=62)	Yes (n=38)		No (n=48)	Yes (n=52)	
Age, median (range)	72.5 (21 – 94)	74 (48 – 96)	0.245	70.5 (21 – 93)	76.5 (48 – 96)	0.016
Gender, n (%)						
Male	33 (53.2)	19 (50.0)	0.754	29 (60.4)	23 (44.2)	0.078
Female	29 (46.8)	19 (50.0)		19 (39.6)	29 (44.2)	
Days from admission to PEG, median (range)	7 (1 – 210)	12 (2 – 156)	**0.018**	5.5 (1 – 210)	12 (1 – 156)	**0.015**
Chronic disease, n (%)						
HT	22 (35.5)	14 (36.8)	0.891	11 (22.9)	25 (48.1)	**0.009**
DM	9 (14.5)	3 (7.9)	0.323	6 (12.5)	6 (11.5)	0.882
CAD	15 (24.2)	5 (13.2)	0.181	11 (22.9)	9 (17.3)	0.484
CHF	4 (6.5)	3 (7.9)	0.784	1 (2.1)	6 (11.5)	0.069
COPD	1 (1.6)	4 (10.5)	0.067	-	5 (9.6)	**0.035**
Dementia	9 (14.5)	14 (36.8)	**0.010**	6 (12.5)	17 (32.7)	**0.017**
Parkinson's disease	14 (22.6)	4 (10.5)	0.103	14 (29.2)	4 (7.7)	**0.005**
CVD	11 (17.7)	14 (36.8)	**0.032**	10 (20.8)	15 (28.8)	0.245
Chronic liver disease	1 (1.6)	-	0.620	1 (2.1)	-	0.480
PVD	1 (1.6)	1 (2.6)	0.618	1 (2.1)	1 (1.9)	0.732
CKD	1 (1.6)	1 (2.6)	0.618	-	2 (3.8)	0.268
Hypothyroidism	4 (6.5)	-	0.110	3 (6.3)	1 (1.9)	0.279
Hyperthyroidism	4 (6.5)	-	0.110	2 (4.2)	2 (3.8)	0.660
Malignancy	16 (25.8)	11 (28.9)	0.731	9 (18.8)	18 (34.6)	0.059
ALS	7 (11.3)	1 (2.6)	0.119	5 (10.4)	3 (5.8)	0.313
MS	1 (1.6)	-	0.620	1 (2.1)	-	0.480
Huntington's disease	1 (1.6)	-	0.620	1 (2.1)	-	0.480
Major depression	1 (1.6)	1 (2.6)	0.618	1 (2.1)	1 (1.9)	0.732
HIE	5 (8.1)	1 (2.6)	0.258	4 (8.3)	2 (3.8)	0.301
Biomarker, median (range)						
Leukocytes (x10^3/µL)	6895 (2500 - 20140)	7495 (4130 - 16800)	0.143	6860 (4030 - 20140)	7345 (2500 - 16800)	0.285
Neutrophils (mcL)	4225 (1700 - 16420)	5230 (2110 - 15000)	0.053	4180 (2530 - 16420)	4905 (1700 - 15000)	0.092
Lymphocytes (mcL)	1480 (300 - 5750)	1375 (320 - 2860)	0.398	1535 (300 - 5750)	1335 (320 - 2860)	0.081
Platelets (x10^3/µL)	206500 (21300 - 519000)	239500 (82000 - 578000)	0.238	216500 (21300 - 519000)	236000 (56000 - 578000)	0.661
MPV (fL)	10.05 (6.1 - 14.2)	9.9 (6.9 - 12.4)	0.589	10.15 (6.1 - 14.2)	9.9 (6.8 - 12.4)	0.874
Hemoglobin (g/dL)	12.5 (7.6 - 15.8)	11.05 (7.7 - 16.9)	0.053	13.25 (7.6 - 15.8)	11 (7.7 - 16.9)	**0.003**
Glucose (mg/dL)	99 (63 - 354)	100 (61 - 187)	0.859	98 (68 - 354)	101.5 (61 - 239)	0.684
BUN (mg/dL)	18.23 (3.74 - 36.92)	17.53 (5.14 - 36.4)	0.798	18.98 (3.74 - 33.40)	16.58 (5.14 - 36.92)	0.467
Creatinine (mg/dL)	0.60 (0.18 - 3)	0.60 (0.14 - 1.55)	0.499	0.6 (0.18 - 1.3)	0.6 (0.14 - 3)	0.983
Sodium (mg/dL)	138 (126 - 147)	139 (124 - 155)	0.929	139 (131 - 147)	137 (124 - 155)	**0.016**
Potassium (mmol/L)	4.04 (2.74 - 5.23)	3.89 (2.5 - 5.31)	0.201	4.13 (2.74 - 4.82)	3.84 (2.5 - 5.31)	0.120
AST (IU/L)	19.5 (6 - 283)	19 (6 - 631)	0.720	19 (9 - 283)	19.5 (6 - 631)	0.661
ALT (IU/L)	12.5 (1 - 172)	13 (2 - 153)	0.969	12.5 (1 - 172)	13 (2 - 153)	0.727
Total protein (g/dL)	6.25 (4.7 - 8.4)	5.8 (4.2 - 7.6)	**0.001**	6.30 (4.88 - 8.40)	5.85 (4.20 - 7.6)	**<0.001**
Albumin (g/dL)	3.32 (2.24 - 4.9)	2.76 (1.82 – 4.00)	**<0.001**	3.50 (2.24 - 4.76)	2.78 (1.82 - 4.9)	**<0.001**
CRP (mg/L)	16.8 (0.2 - 165.5)	56.1 (3.0 - 276.9)	**<0.001**	8.1 (0.2 - 165.5)	33.85 (2.3 - 276.9)	**<0.001**
ESR (mm/h)	27 (2 - 114)	34 (1 - 124)	**0.044**	24 (2 - 114)	35 (1 - 124)	**0.004**
Procalcitonin (ng/mL)	0.12 (0.01 - 1.4)	0.19 (0.05 - 16.78)	**<0.001**	0.10 (0.01 - 1.4)	0.12 (0.03 - 16.78)	**<0.001**

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, PVD: Peripheral vascular disease, CKD: Chronic kidney disease, ALS: Amyotrophic lateral sclerosis, MS: Multiple sclerosis, HIE: Hypoxic ischemic encephalopathy, MPV: Mean platelet volume, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IU: International unit

Table 5. Comparison of complication rates according to mortality in bivariate analysis

Complication, n (%)	90-day mortality, n (%)		p	6-month mortality, n (%)		p
	No (n=62)	Yes (n=38)		No (n=48)	Yes (n=52)	
At least one complication	34 (54.8)	20 (52.6)	0.830	24 (50.0)	30 (57.7)	0.441
Major Complication						
Aspiration pneumonia	3 (4.8)	11 (28.9)	**0.001**	1 (2.1)	13 (25.0)	**0.001**
Minor Complication						
Peritonitis	1 (1.6)	-	0.620	1 (2.1)	-	0.480
Minimal bleeding in the esophagus	2 (3.2)	5 (13.2)	0.071	2 (4.2)	5 (9.6)	0.253
Minor peristomal bleeding	9 (14.5)	4 (10.5)	0.401	6 (12.5)	7 (13.5)	0.562
Ileus	-	1 (2.6)	0.380	-	1 (1.9)	0.520
Tube occlusion	4 (6.5)	1 (2.6)	0.368	2 (4.2)	3 (5.8)	0.538
Late Complication						
Tube dislodgement	7 (11.3)	-	**0.031**	6 (12.5)	1 (1.9)	**0.044**
Embedded bumper	7 (11.3)	1 (2.6)	0.119	6 (12.5)	2 (3.8)	0.110
Peristomal infection requiring tube removal	10 (16.1)	3 (7.9)	0.191	6 (12.5)	7 (13.5)	0.886
Late necrotizing fasciitis	-	1 (2.6)	0.380	-	1 (1.9)	0.520

Table 6. Last row of logistic regression models for 90-day and 6-month mortality risk factors

90-day mortality *	B	Standard error	Odds ratio	95% CI for EXP(B)		P
				Lower	Upper	
Constant	3.157	2.119	23.502			0.036
Total protein	-.794	.345	0.425	0.230	0.888	0.021
CRP	.016	.005	1.016	1.006	1.027	0.003
Aspiration pneumonia	2.612	.773	13.631	2.997	61.988	0.001
6-month mortality**						
Constant	5.041	1.330	154.646			<0.001
Albumin	-1.681	0.427	0.186	0.081	0.430	<0.001
Aspiration pneumonia	3.090	1.127	21.984	2.412	200.342	0.006

Omnibus tests; *Model chi-square: 33.992, degrees of freedom: 3, p<0.001 **Model chi-square: 33.481, degrees of freedom: 2, p<0.001 Hosmer and Lemeshow tests; * Model chi-square: 2.006, degrees of freedom: 8, p=0.981 **Model chi-square: 6.056, degrees of freedom: 8, p=0.641

13.6 times higher in patients with aspiration pneumonia (OR: 13.631, 95% CI: 2.997–61.988; p=0.001). Similarly, a multivariable logistic regression model was created with the presence of significant dementia and COPD, development of aspiration pneumonia complications, sodium, hemoglobin, total protein, albumin, CRP, ESR, and procalcitonin levels to predict 6-month mortality after PEG placement. In this model, a 1-unit increase in serum albumin level was associated with 81.4% lower odds (OR: 0.186, 95% CI; 0.081–0.430; p<0.001) and aspiration pneumonia with 22 times higher odds (OR: 21.984, 95% CI: 2.412–200.342; p=0.006).

DISCUSSION

PEG is a safe and effective method for the enteral feeding of patients experiencing dysphagia for various reasons. In our study including 100 patients with an average age of 73 years, we determined that high serum CRP and low total protein were independent risk factors for 90-day mortality, while low serum albumin was an independent risk factor for 6-month mortality after undergoing PEG. Both 90-day and 6-month mortality were associated with longer median time from hospital admission to the PEG

procedure. Moreover, the development of aspiration pneumonia was a strong risk factor for both 90-day and 6-month mortality.

There are different observations in the literature regarding major and minor complications of PEG. The rate of major complications was reported by Richards et al. as 8.7% in their study of patients with malignancy[11] and as 7.4% by Grant et al. in a meta-analysis of patients diagnosed with head and neck cancer.[12] In studies conducted in patient groups other than cancer, the rate of major complications varies between 1% and 9%.[13-15] It has been debated in the literature whether aspiration pneumonia should be considered a complication or a result of the underlying disease.[16] Previous studies also showed that aspiration pneumonia was more common in patients with dementia.[17] In our study, aspiration pneumonia was classified as a major complication and was common (14%). It was significantly more frequent among patients with dementia and cerebrovascular disease. While it remains unclear whether this complication is associated with the PEG procedure itself or the underlying disease, the presence of aspiration pneumonia was identified as an independent risk factor for both 90-day and 6-month mortality.

The most common minor complications of PEG are minor peristomal bleeding and peristomal infection requiring tube removal, which occurred in our study at rates of 13% and 7%, respectively. Major bleeding was not observed in any of our patients. In the literature, bleeding rates vary between 1.2% and 3.3%.[18-20] A recent study reported that 0.4% of bleeding was directly attributable to PEG, while other bleeding occurred secondary to gastric or duodenal ulcer, the biopsy site, or nasogastric trauma.[20] The use of H2 blockers or proton pump inhibitors (PPI) in patients with low bleeding risk has been proposed as an explanation.[18] Although prior use of H2 blockers or PPIs was not investigated in our study, our results showed that CRP values were higher in patients with minimal esophageal bleeding and BUN values were higher in patients with minor peristomal bleeding. The relatively high bleeding rates in our study can be explained by the patients' worse general condition and greater likelihood of bleeding in patients with uremia.

Studies have shown that 30-day mortality after PEG is lower in Eastern countries compared to Western countries. Rates of 2.3% to 4% have been reported in studies conducted in Eastern countries.[21-25] This has been attributed to a potential cultural barrier to PEG feeding in Eastern countries, as the PEG procedure is considered too invasive for older patients.[26,27] In a study of patients with cerebrovascular disease, the 30-day post-PEG mortality rate was found to be 2.4%.[18] In another study conducted in Turkey, Karasahin et al. reported a 30-day mortality rate of 28.3%.[28] In our study, 38% of the patients died within 90 days and 52% within 6 months. Our high mortality rates can be explained by the fact that a large proportion of our patients had malignancy and comorbidities were common.

Albumin and CRP levels are used as acute and short-term prognostic indicators in patients undergoing PEG.[29,30] In a study conducted by Blomberg et al., CRP level higher than 10 mg/L and albumin level lower than 3.0 g/dL were shown to be independent risk factors for post-PEG mortality. In the same study, a mortality rate of up to 20.5% was reported in patients with both elevated CRP levels and hypoalbuminemia.[29] Similarly, another study demonstrated that mortality was up to 60% among patients with CRP level higher than 21.5 mg/L and albumin level lower than 3.15 g/dL.[18] It was also reported that CRP levels over 50 mg/L after PEG increased mortality by up to 18%. In that study, albumin levels lower than 2.8 g/dL were shown to be an independent risk factor for mortality in patients with dementia.[31] Similarly, in the Turkish study conducted by Karasahin et al., CRP level higher than 78.3 mg/L and albumin level lower than 2.71 g/dL were found to be independent risk factors for mortality.[28] Consistent with the literature, our results indicated that a 1-unit increase in albumin level reduced the risk of 6-month mortality by 0.186 times, while a 1-unit increase in CRP level increased the risk of 90-day mortality by 1.016 times. Hypoalbuminemia may be associated with anorexia resulting from cytokine release in chronic inflammatory conditions. There is also evidence in the literature associating the coexistence of hypoalbuminemia and CRP with numerous diseases.[32,33]

The European Society for Clinical Nutrition and Metabolism (ESPEN) does not recommend PEG in patients with short life expectancy, terminal cancer, or advanced dementia.[6] Likewise, the European Society of Gastrointestinal Endoscopy (ESGE) does not recommend PEG for patients with a life expectancy of less than 30 days.[34] It is also important to determine the medical and ethical indications of the patients. A reduction in quality of life has been demonstrated after the PEG procedure in people with serious comorbidities. Although the relationship between PEG and mortality has been examined in the literature, the timing of the procedure may also be important. Dietrich et al.[35] reported that early PEG placement could help prevent weight loss and the catabolic process. The ESGE guideline (2021) also recommends that PEG be performed in patients with chronic degenerative diseases or some malignancies who have weight loss despite oral nutrition therapy.[34] However, in patients with severe malnutrition or advanced disease, PEG is risky and increases mortality. In addition, several studies have shown that survival is longer in those

with high serum albumin levels.[18,30,36,37] This information is consistent with our findings that lower serum albumin levels and longer time from hospital admission to PEG were associated with higher mortality at both 90 days and 6 months.

Although this study is among the few examining PEG complications and their relationship with on mortality in our country, it has certain limitations. Firstly, the study was conducted retrospectively with a small number of patients from a single center. In addition, although we suspect the low total protein levels may be associated with malnutrition, the study did not include a malnutrition screening or assessment. Furthermore, this study does not clearly establish whether aspiration pneumonia occurs as a result of PEG or the underlying condition that led to PEG placement. To better understand this relationship, patients who developed aspiration pneumonia after PEG should be examined in more detail in terms of their underlying diseases and history of aspiration pneumonia before PEG. Finally, parameters such as body mass index and preoperative American Society of Anesthesiologists (ASA) score, which may also be associated with mortality, were not analyzed.

CONCLUSION

In this study, mortality was found to be negatively associated with albumin level at the time of PEG placement and positively associated with the development of aspiration pneumonia. Hypoalbuminemia caused by malnutrition and is considered an indication for PEG. Post-PEG mortality is higher in patients at high risk of aspiration. Those diagnosed with cerebrovascular disease and dementia should be monitored closely.

Ethical approval: The study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (5/02.06.2022).

Informed consent: Since our study was a retrospective study, written consent was not obtained from the patients.

Author contributions: Concept – P.T.T., O.K.; Design – P.T.T., O.K.; Supervision – P.T.T., S.S.; Resources – S.S., C.S., B.A.; Materials – S.S.,B.A.; Data Collection and/or Processing – S.S., C.S.; Analysis and/or Interpretation – S.S., O.K.; Literature Search – S.S., P.T.T., O.K.; Writing Manuscript – S.S., P.T.T., O.K.; Critical Review – P.T.T., S.S.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

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CLINICAL SCIENCE OF NUTRITION
Review Article
DOI: 10.62210/ClinSciNutr.2024.86

Investigation of potential effects of quercetin on COVID-19 treatment: a systematic review of randomized controlled trials

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Cite this article as: Beşler ZN, Bayraktar DZ, Koçak MC, Kızıltan G. Investigation of potential effects of quercetin on COVID-19 treatment: a systematic review of randomized controlled trials. *Clin Sci Nutr*. 2024;6(2):107-117.

ABSTRACT

Objectives: The COVID-19 pandemic has rapidly become a global health crisis. Currently, there are no proven, reliable, specific treatments for COVID-19. Alongside drug interventions, supportive treatments are implemented during the disease. Quercetin, recognized for its antiviral, anti-inflammatory, anti-aging, and antioxidant properties, is under evaluation in this study for its potential impact on preventing, influencing the course, and mitigating the severity of COVID-19.

Methods: A thorough search was conducted across scientific databases, including PubMed, Embase, Web of Science, SAGEpub, Copernicus, Cochrane Library, ScienceDirect, Elsevier, Scopus, Google Scholar, EBSCOhost, Crossref, Ovid-LWW, and DergiPark databases, between 1 November 2021 and 1 April 2022 to ensure a comprehensive inclusion of relevant studies.

Results: Thirteen randomized controlled clinical trials (five published, eight unpublished) were identified. Existing literature supports quercetin's role as a potent free radical scavenger with robust antioxidant properties. It exhibits anti-inflammatory characteristics by inhibiting lipid peroxidation and restraining pro-inflammatory enzymes such as lipoxygenase and phospholipase A2. Scholarly discourse suggests that quercetin supplementation within the 500-1500 mg range leads to favorable outcomes, including quicker patient discharge, reduced inflammation, increased respiratory rate, accelerated viral clearance, and an improved disease prognosis. However, it is noted that intervention durations vary across studies.

Conclusions: The analysis of the studies suggested that quercetin is a promising therapeutic agent that can cause a decrease in disease symptoms, frequency of hospitalization, hospital stay, need for non-invasive oxygen treatment, need for intensive care, and mortality. Nonetheless, more clinical studies are needed to better understand quercetin's curative effects on COVID-19 infection.

Keywords: Quercetin, COVID-19, randomized controlled trials

INTRODUCTION

Coronaviruses, which are a large family of viruses, involve many subspecies, ranging from those that cause mild infection, such as a common cold, to those that cause severe respiratory syndrome and severe infections. The outbreak of COVID-19 (SARS-CoV-2), a novel type of coronavirus that emerged in Wuhan, China in December 2019, has spread rapidly around the world and has become a pandemic.[1] According to the data from the World Health Organization, 774,954,393 cases have been detected worldwide since the first reported case, and as of 17 March 2024 and 7,040,264 of these cases have resulted in death.[2] COVID-19 can be asymptomatic and have a wide clinical spectrum, ranging from mild symptoms similar to upper respiratory tract infection to life-threatening signs of sepsis in a person.[3]

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Received: February 26, 2024 Accepted: April 30, 2023
Published: May 25, 2024

Currently, there are no specific treatments for COVID-19 that have been proven to be reliable and effective. However, since the data obtained from SARS and influenza suggest that it is more useful to start antiviral treatment early, it is recommended that antiviral drugs should be started as early as possible.[4] In addition to drug treatment during the course of the disease, some supportive treatment practices may also be included. As part of the studies evaluating the use of vitamins and minerals in the COVID-19 process, it has been suggested that the use of vitamin C and zinc in pharmacological doses may also benefit. In addition, it is thought that some bioactive compounds such as phytochemicals with antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties may have a positive effect on the disease.[5,6]

When studies related to phytochemicals are considered as subheadings, the existence of studies conducted with quercetin was found to be attractive.[7-9] Quercetin is a flavonoid found in various foods such as apples, onions, grapes, berries, blueberries, strawberries, cilantro, dill, coffee, tea, oranges, lettuce, potatoes, and tomatoes.[10-13] Quercetin has been reported to exhibit antiviral, anti-inflammatory, anti-aging, and antioxidant bioactivity.[11-13] It exerts its antioxidant effect by removing free radicals and maintaining oxidative balance, and its anti-inflammatory and anti-allergic effects by inhibiting the lipoxygenase and cyclooxygenase pathway.[12,14]

In clinical studies, quercetin has been shown to have antiviral[15,16] and anti-inflammatory effects[16], relieve respiratory symptoms[16], prevent poor prognosis[17] and reduce hospitalization[18] in COVID-19 patients.

Quercetin inhibits the entry of the virus into the cell by blocking the angiotensin-converting enzyme-2 (ACE2) receptor in patients with SARS and MERS, as well as resists the coronavirus by regulating the cell unfolded protein response (UPR), inhibiting the cell cycle, and lowering the level of interleukin-(IL) 6.[8,9,12,19]

The aim of this study is to understand the relationship between quercetin and COVID-19 more decisively and to comprehend the effect of quercetin supplementation on the course of COVID-19 disease through a systematic review in which promising potential therapeutic properties of quercetin are handled based on the clinical studies where quercetin and COVID-19 infection were examined together.

Main Points

- Quercetin demonstrates potent antioxidant and anti-inflammatory properties in COVID-19 treatment.
- Favorable outcomes with quercetin supplementation, including quicker patient discharge and improved disease prognosis.
- Quercetin though further clinical studies are warranted for a comprehensive understanding of its efficacy against COVID-19.

METHOD

This systematic review was written as a result of scrutinizing the up-to-date randomized controlled clinical trials conducted to investigate the effect of quercetin on the treatment of COVID-19 infection. During this review, the effect of antiviral, anti-inflammatory, antioxidant, and immunomodulatory activities of quercetin on disease prophylaxis, course and severity was evaluated. This study was conducted in accordance with the PRISMA-P protocol (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols)[20] and the Covidence systematic review design, which is a key component of the Cochrane review production tools.[21]

Inclusion and Exclusion Criteria

The studies included in this systematic review are randomized controlled clinical trials conducted on individuals aged 18 years and over in 2020 and later published in English or Turkish. Case-control, case series, cross-sectional studies, in vivo, in vitro, animal studies, in silico studies, review studies, and clinical trials in which quercetin and different phytochemicals were evaluated together, as well as studies on a nutrient extract and its quercetin content, were not included in this systematic review.

Participants

Of the five studies handled in the current systematic review, participants in 2 studies investigating the prophylactic effect of quercetin were volunteers aged 18 years and over without allergic response to quercetin. The 11 studies evaluating the effect of quercetin on disease course and severity were conducted with COVID-19 positive patients aged 18 years and older without allergic response to quercetin. No restrictions were made on gender, ethnicity, and the region in which the study was conducted.

Ways of Intervention

In the studies, participants were given between 500-1000 mg of quercetin orally or 500-1500 mg of quercetin phytosome (500 mg of quercetin phytosome contains 200 mg of quercetin) in addition to standard treatment in the intervention groups.

Preliminary Results

The preliminary results from randomized controlled trials examining the efficacy of quercetin in the prophylaxis,

course and severity of COVID-19 disease indicate a reduction in the development of disease symptoms, frequency of hospitalization, length of hospital stay, need for non-invasive oxygen treatment, need for intensive care and mortality.

Literature Search

In this systematic review, a comprehensive search was conducted on PubMed, Embase, Web of Science, SAGEpub, Copernicus, Cochrane Library, ScienceDirect, Elsevier, Scopus, Google Scholar, EBSCOhost, Crossref, Ovid-LWW, and DergiPark databases between 1 November 2021 and 1 April 2022. Unpublished studies have also been identified from clinical trial registration platforms (http://clinicaltrials.gov/). In addition, a manual search was conducted for reference lists of extended studies. Literature searching was conducted with the keywords [(quercetin OR kuarsetin) AND (COVID-19 OR COVID19 OR SARS-CoV-2 OR SARS-COV-2 OR Koronavirüs OR Coronovirus)]''. The PRISMA flow charts of the published and unpublished literature search processess were shown in Figure 1.

Selection and Evaluation of Studies

To determine the studies to be included in the review, three authors (D.Z.B., Z.A., and M.C.K.) independently reviewed the titles, abstracts and full texts of the obtained articles to assess their suitability (Figure 1). All studies are clinical trials examining the effect of quercetin supplementation on the COVID-19 infection. Individuals included in the studies were people who were actively receiving treatment for COVID-19 infection or receiving prophylactic support against COVID-19 infection. Since the group with the highest level of evidence among the clinical trials was randomized controlled trials, these studies were included in the current systematic review. The randomized controlled trials selected by the three authors were compared and the overlapping studies were eliminated.

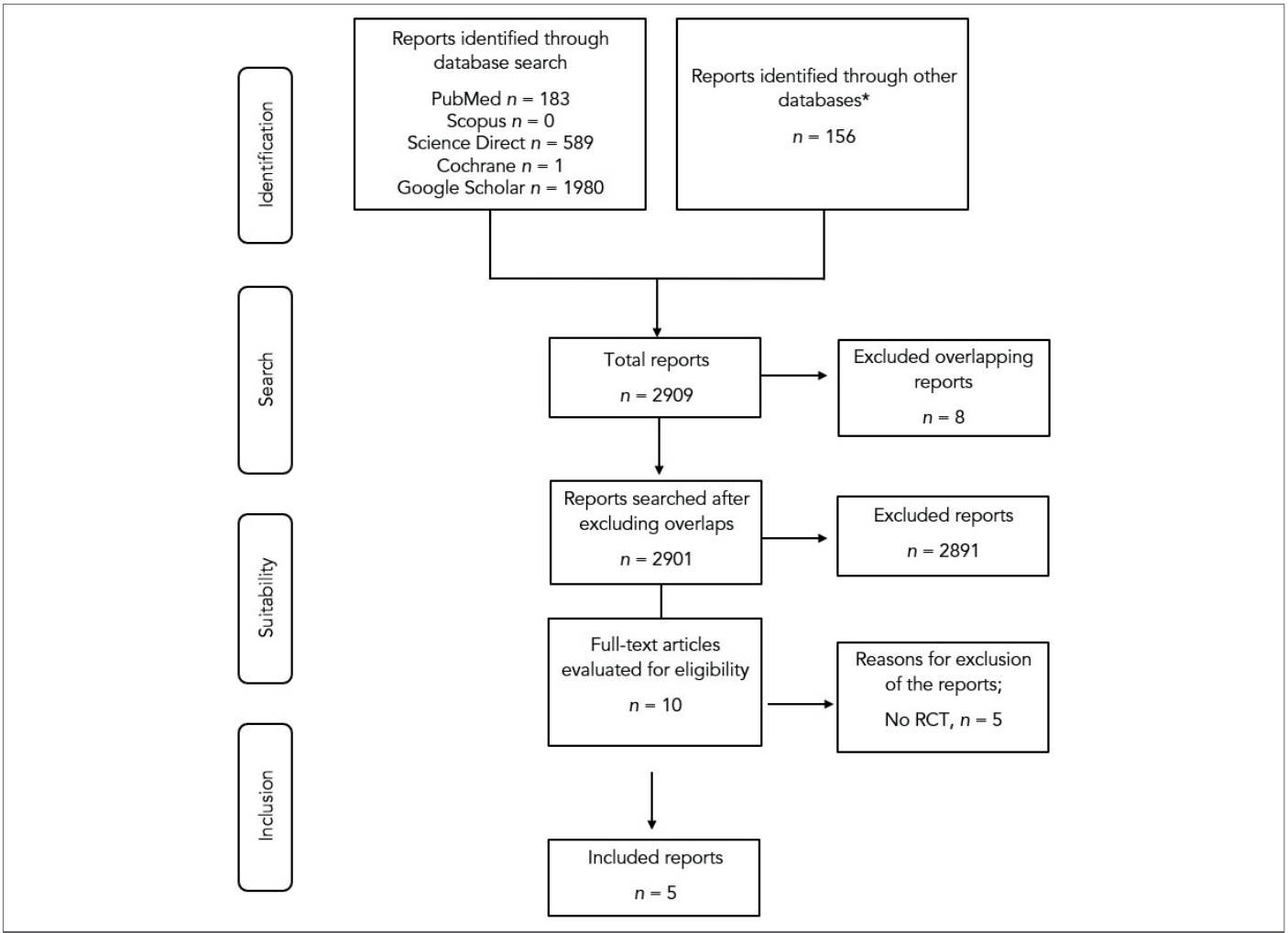

Figure 1. PRISMA flow chart of the literature search process for published clinical studies
*Crossref, Web of Science, SAGEpub, Copernicus, Ovid-LWW, Elsevier, EBSCOhost, DergiPark

Conducting a meta-analysis instead of a systematic review with selected randomized controlled trials would be the most appropriate way to quantitatively analyze the clinical trials included in the current study. However, because the number of studies obtained as a result of a literature search is less and the results of some of these studies have not yet been published, it is decided that the best way to analyze the data is to conduct a qualitative analysis after consulting several expert statisticians.

Risk of Bias

To eliminate the risk of bias in the selection of published and unpublished studies to be included in the review, the studies selected by three authors (D.Z.B., Z.A., and M.C.K.) were subjected to the evaluation of the fourth author (G.K.).

RESULTS

In the results section, we focused on the characteristics of patients, clinical, laboratory, treatment data and outcomes of the studies. The results of 5 studies included in this systematic review were summarized in Table 1. The coding table of the studies comprises the authors of the study, the year of the study, the region/country where the study was conducted, the sampling groups [test (T) and control (C) groups], mean age/range of age, intervention dose, intervention duration, investigated parameters and the main results of the studies.

Characteristics of Studies

A total of 803 patients (ranging from 60 to 429) participated in the 5 studies included in this systematic review.[7,18,22-24] All studies involved participants older than 18 years. Of the five studies, two were from Pakistan[7,22], one was from Italy[23], one was from Turkey[24] and one was from Iran.[18] The treatments were administered orally. Doses of quercetin range from 200 mg/day[23] to 1000 mg/day.[18] In one study, apart from quercetin, vitamin C and bromelain were given as additional supplements.[24] The duration of treatment was different in all studies (from 7 days to 3 months or during the follow-up period) (Table 1).

The findings of five suitable studies included in the systematic review were shown in Table 1. Shohan et al.[18] conducted a randomized controlled trial on 60 patients with severe COVID-19. Those given quercetin alongside antiviral drugs showed significantly lower fatigue and weakness symptoms, reduced levels of inflammatory markers, and a shorter hospital stay compared to the control group ($p<0.05$). Di Pierro et al.[22] conducted two trials, one on outpatients and another on hospitalized patients. In both trials, quercetin supplementation alongside standard treatment led to better clinical outcomes, reduced virus persistence, and lower hospitalization rates compared to the control groups ($p<0.05$). Rondanelli et al.[23] studied healthcare workers without COVID-19 infection. Those supplemented with quercetin had a lower risk of contracting COVID-19 compared to the control group, with one participant showing higher clinical remission ($p<0.05$). Önal et al.[24] studied hospitalized adults with COVID-19. Quercetin supplementation alongside standard treatment led to significantly reduced inflammation markers and improved blood parameters, although it did not reduce the frequency of severe events like respiratory failure ($p<0.05$).

Clinical Symptoms

Two studies that examined the effect of quercetin on COVID-19 infection, involving 162 participants, reported that quercetin significantly decreases the duration of conversion from positive to negative and reduces the severity of symptoms.[22,23] In a study conducted with 429 participants, there was no difference between the groups in terms of the frequency of events, while pulmonary findings were better in the quercetin group.[24] Three studies conducted on 254 participants reported a decrease in fatigue[7,18,22] and 2 studies involving 194 participants reported a decrease in fatigue and an improvement in appetite.[7,22]

Laboratory Data

Some studies reported that quercetin supplementation reduced serum CRP levels significantly in individuals with COVID-19[18,24], decreased serum ferritin levels significantly[22,24] and reduced LDH levels ($p<0.05$).[18,22] Although the values were within the normal range, a study reported that serum hemoglobin levels were partially increased in the quercetin group compared to the control group ($p<0.05$).[18] In another study, no significant difference was found in terms of serum hemoglobin values between quercetin and control groups.[22] In one of the two studies examining serum platelet and lymphocyte levels after quercetin intervention, a slight but non-significant decrease in lymphocytes was observed, while there was no difference in platelet levels ($p>0.05$).[22] In another study, it was reported that the increase in the number of platelets and lymphocytes was significantly higher in the quercetin-receiving group ($p<0.05$).[24]

Duration of Hospitalization

Two studies involving 212 participants showed that quercetin intake was associated with shorter hospitalization.[7,18]

Intensive Care Requirement and Mortality

The effect of quercetin on intensive care needs and mortality was investigated in 3 studies. In two studies, there were no significant differences in terms of mortality, duration of admission to the ICU and the number of

Table 1. Results of randomized controlled trials included in the present systematic review

Authors and Year	Region/Country where the study was conducted	Sampling (T/C)	Age (I/C)	Intervention	Duration	Researched Parameters	Results
Shohan et al.[18], 2022	Ahvaz Razi Training Hospital, Iran	60 (30/30)	I:52.7±13.1 C:50.9±10.3	C: Standard treatment I: 1000 mg Quercetin orally + standard treatment	7 days	Clinical symptoms IL-1β, TNF-α, and IL-6 BUN, Cr, SGOT, SGPT, Total/Direct Bilirubin, ALP, LDH, quantitative CRP, ESR, D-dimer, CK-mb, and quantitative Troponin saturation, pulse, respiratory rate, body temperature, blood pressure, and the hospital stay duration	Quercetin was significantly associated with relatively early discharge and low serum levels of ALP, q-CRP, and LDH ($p<0.05$), There was a significant increase in hemoglobin level and respiratory rate (values within the normal range) ($p<0.05$), no significant differences in mortality, ICU hospitalization frequency, and ICU hospitalization duration in patients receiving Quercetin ($p>0.05$).
Di Pierro et al.[22], 2021a	King Edward University, Department of Medicine, Pakistan	42 (21/21)	42.5 ± 3.3 56.2 ± 3.3	C: Standart treatment I: 1500 mg Quercetin phytosome orally + standard treatment for 7 days, then 1000 mg Quercetin phytosome orally + standard treatment for the next 7 days	14 days	RT-PCR, CRP, LDH, ferritin, D-dimers, hemoglobin, WBC, platelets, neutrophils, lymphocytes, the course of symptoms related to COVID-19, need for hospitalization, compliance with treatment, tolerability and side effects	After 1 week of treatment, the SARS-CoV-2 test was negative in 16 patients in the Quercetin group, all the symptoms of 12 patients were mitigated, and the SARS-CoV-2 test result of 2 patients in the control group was negative, and the symptoms of 4 patients were partially recovered. At week 2, the remaining 5 patients of the Quercetin group returned negative in SARS-CoV-2 test results, while 17 of the remaining 19 patients in the control group turned negative at week 2, one at week 3, and one patient continued to be positive ($p<0.05$). Quercetin significantly ($p<0.05$) reduced LDH (%-35.5) and ferritin (35.5% and 40%, $p<0.05$%), Quercetin reduced CRP and D-dimer but was not statistically significant ($p>0.05$).

T: Test group; C: Control group; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; BUN, blood urea nitrogen; Cr, creatinine; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; ALP, alkaline phosphatase; LDH, Lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CK-mb, creatine kinase-mb; ICU, intensive care unit; RT-PCR, real time-PCR; WBC, white blood cells.

Table 1. Results of randomized controlled trials included in the present systematic review

Authors and Year	Region/Country where the study was conducted	Sampling (T/C)	Age (I/C)	Intervention	Duration	Researched Parameters	Results
Di Pierro et al.[7], 2021b	Liaquat University of Medicine and Health Sciences, Pakistan	152 (76/76)	18-80	C: Standard treatment I: 1000 mg Quercetin phytosome orally + standard treatment	30 days	Length of hospital stay, need for non-invasive oxygen treatment, need for ICU hospitalization, mortality, compliance, tolerability, and side effects	There was a decrease in the frequency and duration of hospitalization ($p=0.001$), the need for non-invasive oxygen treatment ($p<0.05$), progression to ICU, and mortality in the Quercetin-receiving group ($p<0.05$).
Rondanelli et al.[23], 2022	Pavia, Italy	120 (60/60)	T:50.8±12.1 C:47.7±13.6	C: Placebo (food ingredient) I: 500 mg Quercetin phytosome orally	3 months	RT-PCR COVID symptoms Mortality	In COVID-19 infection, Quercetin was 14% more protective than placebo ($p<0.05$).
Önal et al., 2021	Kanuni Sultan Süleyman Training and Research Hospital, Turkey	429 (49/380)	T: 30-90 C: 18-100	C: Standard treatment I: 1000 mg Quercetin, 1000 mg vitamin C, 100 mg bromelain orally + standard treatment	During the follow-up period	COVID symptoms, Lymphopenia, thrombocytopenia, CRP, LDH, D-Dimer, ferritin, Procalcitonin, Hgb Pulmonary findings, Hospital follow-up duration, discharge rate, and case rate	While the decrease in CRP and ferritin levels was significantly higher in the Quercetin group ($p<0.05$), the increase in the platelet and lymphocyte counts was significantly higher ($p<0.05$), and the case frequency was not found different between the groups ($p<0.05$), Quercetin had a positive effect on pulmonary findings and laboratory parameters ($p<0.05$).

T: Test group; C: Control group; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; BUN, blood urea nitrogen; Cr, creatinine; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; ALP, alkaline phosphatase; LDH, Lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CK-mb, creatine kinase-mb; ICU, intensive care unit; RT-PCR, real time-PCR; WBC, white blood cells.

cases admitted to the ICU.[18,24] Another study reported that the results of ICU hospitalization and mortality were significantly better in the quercetin group, however, it was not statistically significant when patients with comorbidity were excluded and healthy individuals were evaluated. This may be due to the small number of patients.[7]

Respiratory Rate, Non-Invasive and Invasive Mechanical Ventilation

Although the values measured in a study were between the normal ranges, the respiratory rate was partially increased in the quercetin group compared to the control group ($p<0.05$).[18] Di Pierro et al.[7] reported that the need for oxygen treatment of a patient in the control group was 13 times higher than that of a patient in the quercetin group.

Tolerance and Side Effects

Two studies involving 194 participants reported that compliance with treatment was high, quercetin supplementation was well tolerated and no specific side effects were reported by patients.[7,22]

DISCUSSION

This systematic review examining the effects of quercetin supplementation on COVID-19 prophylaxis and the treatment process in patients diagnosed with COVID-19 are that quercetin prevents the formation and progression of the disease and reduces the levels of inflammatory markers related to the pathogenesis of the disease.

Quercetin acts as a free radical scavenger, and both in vitro and in vivo studies have shown that quercetin is a powerful antioxidant.[25] Quercetin supplementation in the diet of mice infected with the influenza virus was observed to significantly reduce levels of both superoxide radicals and lipid peroxidation products, suggesting that the use of quercetin as an antiviral treatment to mitigate the cytopathological effects of virus infections may be useful.[26] In addition, quercetin has been reported to have anti-inflammatory properties that include inhibitory effects on lipid peroxidation and proinflammatory enzymes such as lipoxygenase and phospholipase A2. It has been suggested that this anti-inflammatory effect is partially mediated by flavonoid activity on arachidonic acid metabolism and related leukotriene/prostaglandin pathways. In addition, quercetin has been shown to reduce the release of lipopolysaccharide-stimulated TNF-α, IL-6, and IL-1 from macrophages.[27] Inhibition of proinflammatory cytokines may be especially important in the pulmonary phase of COVID-19 (cytokine storm). CRP is an inflammatory biomarker for IL-6 that reflects proinflammatory cytokine levels and is one of the most important prognostic markers in patients with COVID-19 infection.[28,29] Quercetin exhibits important immunomodulatory properties in people with COVID-19 infection.[30] However, quercetin has a similar effect to anti-COVID-19 drugs due to its inhibitory effect on platelet aggregation and mast cell activation.[31]

In a phase-II clinical trial, isoquercetin, a quercetin derivative with 5 times higher intestinal absorption, significantly reduced D-Dimer levels by inhibiting disulfide isomerase which activates clotting factors and by preventing blood clotting in metastatic late-stage cancer patients.[31] The practical use of quercetin, like most polyphenols, is limited by its low solubility and oral absorption. Recently, it has been shown that quercetin (Quercetin Phytosome®) coated with sunflower lecithin reaches plasma levels up to 20 times higher in humans, without any noticeable side effects.[32] Phytosome is a technological form developed in order for phytochemicals to resemble the cell membrane structure by forming complexes with phospholipids and thereby increasing bioavailability by facilitating their absorption.[33] In addition, Quercetin Phytosome® has a strong safety profile.[33] Interaction between Quercetin Phytosome® and the human microbiota has also been elucidated.[34] The Quercetin Phytosome® formulation was found to be more stable than the non-formulated quercetin after interaction with the intestinal microbiota.[35] Phytosome slows down the intestinal microbial degradation of quercetin, allowing it to have more time and better dispersion for absorption of the free molecule.[34] Of the 5 studies included in the current systematic review, three utilized the Quercetin Phytosome®[7,22,23] and two utilized the quercetin.[18,24]

NLRP3 inflammation is defined as an uncontrolled inflammatory weapon that is considered an important therapeutic target associated with COVID-19 infection.[36] Shohan et al.[18], discussed in the present review, considered the inhibitory effect of quercetin on NLRP3 inflammation in a randomized controlled trial and conducted a treatment method based on a combination of quercetin with antiviral drugs in severe COVID-19 patients. According to the results of the study, intake of 1000 mg/day of quercetin for 1 week in addition to antiviral drugs was associated with a reduced length of hospital stay, lower serum levels of q-CRP, LDH, and ALP and a statistically significant increase in respiratory rate and serum hemoglobin level in the intervention group.[18] A study revealed that quercetin, which is from the flavonoid family, is able to regulate the expression of 85% of the structural proteins of the COVID-19 virus.[37] The viral S-protein of SARS-CoV-2 infects the human cell by binding the angiotensin-converting enzyme-2 (ACE-2) receptor. In a study, quercetin and Epicatechin were able to form an interaction with ACE through both the zinc ion of ACE and the amino acids of ACE. The study also showed that the presence of a

catechol group on the flavonoid increases its power to inhibit ACE. Therefore, quercetin is noted to have the greatest capacity to inhibit ACE among all flavonoids.[38] Other studies have reported that quercetin may lead to the prevention of COVID-19 entry into host epithelial cells as an inhibitor of the acid sphingomyelinase ceramide system which plays an important role in the entry of the virus into respiratory epithelial cells during COVID-19 infection.[39-41] In addition, in a molecular docking study, quercetin was shown to effectively reduce lytic replication of the COVID-19 virus by binding to 3CL and PL proteases and inhibiting the COVID-19 replication cycle.[42] In addition, it has been suggested that quercetin suppresses TNF/TNFR and NLRP3 downstream signals such as Nf-kB and IL-1" and shows inhibitory activity on S protein-ACE2 interaction in rhACE2 cells in vitro.[6,27,43]

The use of immunomodulatory nutraceuticals such as vitamin C and quercetin is also recommended as adjuvant treatment in COVID-19 patients.[44] The prophylactic and therapeutic use of quercetin in combination with bromelain and vitamin C is indicated to be appropriate to increase the bioavailability of antiviral drugs and quercetin.[24] In a case series study, researchers reported that the intake of 800 mg/day of quercetin, 50 mg zinc acetate, 165 mg bromelain, and 1000 mg vitamin C supplements with antiviral medication by patients with COVID-19 infection was safe and improved the course of the disease.[17] It has also been shown to act as a zinc ionophore and increase the entry of zinc into cells to inhibit viral intracellular replication.[45]

According to the results of a randomized controlled trial by Di Pierro et al.[22] discussed in the current review, they observed that the intake of 1500 mg/day of quercetin Phytosome® in the first week and 1000 mg/day of quercetin in the second week (corresponding to 600 mg and 400 mg of quercetin per day, respectively) in addition to standard treatment for 2 weeks disclosed the ability to clear the COVID-19 virus and improve clinical symptoms, and statistically shortened the rate of conversion of RT-PCR test from positive to negative.[22] The shortening of the conversion rate of the RT-PCR test from positive to negative was consistent with the recording of complete clinical remission in the quercetin and placebo groups on the 7th and 17th days, respectively, in the study of Rondanelli et al.[23]. Quercetin supplementation significantly reduced LDH, ferritin, CRP, and D-dimer levels as another result of this study, similar to other studies. Regarding the safety of quercetin use, its hepatic safety was confirmed by stating that it is very well tolerated and not caused different side effects compared to the control group receiving standard treatment.[22,24] The study of Di Pierro et al.[22] has some possible limitations because the sample size of the study is small, it is not performed in double-blind and placebo-controlled conditions. However, the authors reported that this study is a preliminary study. Although the authors reported that quercetin positively affects LDH, ferritin, and some COVID-19 biomarkers, they did not know the reason why other biomarkers did not change significantly with treatment. In another randomized controlled trial in which 152 patients were given a Quercetin Phytosome® supplement of 1000 mg/day for 30 days and included in this review, Di Pierro et al.[7] associated quercetin supplementation with a significant reduction in length of hospitalization, oxygen need, intensive care unit need and mortality, which are consistent with previous studies.

In the study by Önal et al.[24], included in the current review, quercetin supplementation resulted in a significant reduction in acute phase reactants, despite more advanced lung involvement and COPD. The decrease in serum CRP and ferritin levels was significantly higher in the intervention group than in the control group. It is also suggested that quercetin supplementation has a role in increasing the number of platelets and lymphocytes.[24] The increase in acute phase reactants in COVID-19 is thought to be due to the exaggerated release of proinflammatory cytokines from "hyper-reactive" monocytes.[46] Monocytes play a critical role in the inflammatory response. Active monocytes act on the immune system by providing the secretion of essential cytokines such as IL-6, IL-1, IL-8, and TNF-α, which are pro-inflammatory cytokines.[47,48] Different mechanisms may play a role in the abnormal activation of monocytes in chronic diseases.[47] Flavonoids have the ability to modulate macrophages from pro-inflammatory phenotypes and potentially contribute to the improvement of predetermined inflammatory processes. These findings can be explained by the fact that flavonoids contribute to the transformation of the immunomodulatory effects on macrophages into pro-anti-inflammatory phenotypes.[49]

Among the studies included in this systematic review, the study of Rondanelli et al.[23] is the only study in which the prophylactic effect of quercetin was evaluated. This study indicated that quercetin supplementation was significantly protective against symptomatic coronavirus infection for over a 3-month period. These results are consistent with the results of the study which found that 3 months of quercetin supplementation in healthcare workers was significantly protective.[50] In addition, according to the analyzes conducted in the 5th month of this study, the risk of infection was found to be 99.8% in participants taking quercetin supplements and 96.5% in the control group. It was observed that the quercetin group has 14% more protection factors to prevent contracting COVID-19 infection than the placebo group.[23] In a study of 113 people conducted by Margolin et al.[15], an experimental group of 53 people was given 25 mg of zinc, 10 drops of henna leaf extract, 1000 mg of vitamin C, 1000 IU (25

μg) of vitamin D3, 400 IU of Vitamin E and 500 mg of l-lysine orally for 20 weeks. As a result of the study, the development of symptoms of the disease was found to be significantly less in the group receiving supplements than in the group not receiving them. However, they participated in a long-term experiment and could regularly use the supplements given separately, thus it can be considered that the people in the experimental group were more cautious about the disease also had an impact on the outcome. It was reported that quercetin is a senolytic agent that can alleviate the course of the disease with the early elimination of aging cells in the management of COVID-19. It is assumed that quercetin is involved in the initial stage of countering cytokine storm and cell aging by activating the immune system. Lee et al.[51] concluded that quercetin can alleviate COVID-19-related pulmonary disorders and systemic inflammation during an active infection, and even alleviate chronic post-infection damage of long-term COVID-19 disease due to its senolytic activity. Limitations of the study discussed in this review were the lack of evaluation of the immune response and cytokine production, the small sample size, the short duration of the intervention, and the inclusion of only health workers.[23]

In conclusion, this systematic review shows that quercetin is promising as a therapeutic agent and may potentially lead to reduced disease symptoms, hospitalization rates, length of hospital stay, need for noninvasive oxygen therapy, need for intensive care, and mortality. Due to the complex pathophysiology of COVID-19 infection, which has not yet been clearly elucidated, further clinical studies are needed to be able to definitively talk about the curative effect of quercetin on COVID-19 infection.

Limitations of the Study

The few number of available studies and the fact that the study designs were not exactly the same constituted the limitations of the study.

Author contributions: Concept – Z.N.B., D.Z.B., M.C.K., G.K.; Design – Z.N.B., D.Z.B., M.C.K., G.K.; Supervision – Z.N.B., D.Z.B., M.C.K., G.K.; Resources – Z.N.B., D.Z.B., M.C.K., G.K.; Materials – Z.N.B., D.Z.B., M.C.K., G.K.; Data Collection and/or Processing – Z.N.B., D.Z.B., M.C.K., G.K.; Analysis and/or Interpretation – Z.N.B., D.Z.B., M.C.K., G.K.; Literature Search – Z.N.B., D.Z.B., M.C.K., G.K.; Writing Manuscript – Z.N.B., D.Z.B., M.C.K., G.K.; Critical Review – Z.N.B., D.Z.B., M.C.K., G.K.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

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CLINICAL SCIENCE OF NUTRITION
Case Report
DOI: 10.62210/ClinSciNutr.2024.84

A case of nutritional management and challenges after esophageal cancer surgery*

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*This case was presented in KEPAN 10 VAKA online case competition. It received first price.

Cite this article as: Tuncay P, Doğanay M. A case of nutritional management and challenges after esophageal cancer surgery. *Clin Sci Nutr*. 2024; 6(2):118-121.

ABSTRACT

Malnutrition and cachexia are common in cancer patients. Malnutrition rates of cancer patients vary according to the location of the tumor. In esophageal cancer, severe cachexia and sarcopenia are seen at the time of diagnosis. The defense of nutritional therapy (NT) against cancer, especially gastrointestinal cancer, is very difficult. NT should start with the diagnosis of the disease. The aim of NT should be to prevent cancer cachexia, related complications, and mortality. In Türkiye, squamous cell esophageal cancer is often seen, especially due to dietary habits (hot drinks, meat-based diet low in vegetables). This is a case report of a 55-year-old male patient who had lots of challenges during the nutritional management after esophageal cancer surgery. The patient's complaints did not improve after neoadjuvant therapies and minimally invasive esophagectomy (MIE) was performed. Inflammation and fistula were seen after major abdominal surgery. As long as the fistula and drainage were continued, parenteral nutrition (PN) remained the only option for NT allowing the bowel to rest in the presence of a fistula. In case of contraindication to oral or enteral nutrition (EN), PN was started on day 6 of MIE. Since it was thought that oral or EN could not be started for more than 10 days, a central catheter was placed, and the patient was fed with CPN (central parenteral nutrition). After the insertion of a stent and a nasojejunal (NJ) tube, EN combined with CPN could be applied. Because of anastomotic leakage, oral nutrition couldn't be continued. Short-term peripheral parenteral nutrition (PPN) therapy was continued until the leakage stopped. The patient was discharged with oral and oral nutritional supplements. Two years after the MIE, no significant difference from previous radiological reports was found and there were no problems with oral nutrition.

Keywords: Enteral, esophagus cancer, nutrition, parenteral

INTRODUCTION

Esophageal cancer is one of the most common cancers worldwide. There are two types of esophageal cancer, squamous cell carcinoma and adenocarcinoma.[1,2] Dysphagia and weight loss are typical symptoms of malnutrition.[3,4] Nutritional screening and assessment are the most important part of esophageal cancer therapy.[5] Nutritional screening should performed in all patients and specific tools are needed. Nutritional screening should be done immediately and repeated at intervals according to the guidelines established by the European Society for Clinical Nutrition and Metabolism (ESPEN), the Academy of Nutrition and Dietetics, the American Association for Parenteral and Enteral Nutrition, and the American Society for Parenteral and Enteral Nutrition (ASPEN).[5-7] ESPEN frequently recommends the use of NRS-2002 in cancer patients.[8]

In the postoperative phase of total esophagectomy, oral or EN therapy should be preferred over PN therapy, if there is no contraindication. In case of postsurgical complications, such as anastomotic leakage, etc., may cause some difficulties in nutritional treatment.

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Received: August 7, 2023 Accepted: March 13, 2024
Published: April 24, 2024

Nutritional interventions, such as EN combined PN therapy, should be applied instantly to improve patient outcomes and limit further complications. A high number of complications arise from surgery, many of which affects nutrition. Malnutrition and cachexia are exacerbated as a result of this intensive surgery. The impact of malnutrition is multifactorial, and regardless of the patient's body-mass index unintentional weight loss of more than 10% in the preceding six months poses a significant risk of morbidity and mortality in cancer patients. Despite the difficulties, the aim is to correctly assess nutritional status and provide appropriate NT. NT is better performed with the cooperation of a multidisciplinary nutrition team. Although EN after esophagectomy is accepted as a standard of NT, the timing and method of delivering EN remain questionable. This report aims to show the timing and type of EN solution after esophagectomy.

CASE REPORT

The patient, who had complaints (chest pain and difficulty swallowing solid foods) in 2017, had a weight loss of 15 kg in the last six months. After the diagnosis of esophageal squamous cell cancer, he received chemotherapy and radiotherapy in an external hospital. With a weight of 64 kg and height of 1.70 m, the fifty-year-old male was admitted to our general surgery outpatient clinic complaining of esophageal cancer for a minimally invasive esophagectomy (MIE) operation in 2018 (Table 1). He had no history of smoking, alcohol, or co-morbidities. There is no information about the patient's preoperative nutritional status and NT.

We work as consultants in the clinical nutrition unit (CNU). The patient was referred to the CNU 6 days after MIE. He had a cough and sputum. His fever was 38.7°C and CRP (C-Reactive Protein) was 394 mg/L. The fistula was detected on a postoperative thorax-CT scan. Drainage was provided with an inserted tube thoracostomy. After the nutritional assessment, we observed that the patient, who had a weight loss of > 5% and reduced food intake, was cachectic. The nutritional status was evaluated with NRS-2002. The nutritional score was 4 and NT was planned. His daily energy and protein requirements were 1600-1920 kcal (25-30 kcal/kg/day) and 77-128 gr (1.2-2 g/kg/day), respectively. PPN (peripheral parenteral nutrition) was started on the 6th day of MIE and continued for 9 days. Parenteral solutions were prepared in a compounder. During the first 4 days of PPN therapy, 900 kcal 1500 mL solutions were prepared. On the 15th day of MIE, a central catheter was inserted. For the first 6 days of the central catheter, 1600 kcal 2084 mL parenteral solutions were prepared. Until the 26th day 1800 kcal 2356 mL parenteral solution was given. On the 27th day of MIE, the patient's temperature was 38°C, and the catheter was changed due to central catheter infection. Consequently, 1400 kcal 2406 mL PPN solution was administered on the 27th day of MIE. The flow from the tube thoracostomy decreased and a stent was inserted due to leakage in the gastric stapler line. The patient was continued to recieve 1800 kcal 2336 mL parenteral solution on the 27-29th day of MIE. On the 30th day, a nasojejunal (NJ) tube was inserted after the stent and EN combined with CPN therapy (on the first 4 days 1400 kcal 2047 mL and on the 5th day 1000 kcal 1428 mL was performed until the daily EN intake was 60 % of daily energy requirement) was continued with semi-elemental enteral solution (1mL/1 kcal) at a rate of 10 mL/hour. EN was given for 20 hours per day (4 hours rest) with a continuous enteral pump, and the rate was increased by 10 mL every 24 hours. He reached the targeted EN dose on the 39th day. Tube thoracostomy was removed on the 44th day and antibiotherapy was continued because of fever. Regimen 1-2 transition diet (tea, diluted yogurt, fruit juice, smooth compote, smooth soup) was given on the 62nd day. The stent and NJ tube were removed 2 days after oral nutrition. However, oral nutrition was stopped due to anastomotic leakage. PPN (1000 kcal 1440 mL commercial solution) was given for 11 days (Table 1). Then, oral nutrition was improved, and he was discharged on the 86th day with oral nutritional supplements.

Main Points

- Nutrition is an important therapy as much as medical treatment in cancer.
- Enteral nutrition should optimal feeding route after esophagectomy.Early enteral nutrition can improve postoperative recovery.
- Multidisciplinary approach is necessary in enteral nutrition timing and type of enteral nutrition selection.

Table 1. Postoperative nutrition history

Day of MIE	Nutrition Therapy Way and Energy İntake
6-14th	900 kcal 1500 mL PPN
15-21th	1600 kcal 2084 mL CPN
21-26th	1800 kcal 2356 mL CPN
27th	1400 kcal 2406 mL PPN
28-30th	1800 kcal 2336 mL PPN
31-34th	1400 kcal 2047 mL PPN + semi-elemental enteral solution
35th	1000 kcal 1428 mL PPN + semi-elemental enteral solution
36-59th	100 mL/hour EN (2000 kcal)
62-64th	Oral nutrition (regimen1-2)

The patient was admitted to the hospital with nausea and vomiting 2 days after discharge. He was advised to eat small snacks. Because of the COVID pandemic, he could not come to the hospital for one year. After a year, endoscopy was performed. Stenosis, fistula (with diffuse wall thickening measuring 7 mm at its thickest part), and bleeding were observed at the anastomosis site, and hemoclips were discarded. No significant difference was found compared to the early postoperative radiological reports.

He lost 20 kg in 19 months of therapy period and was diagnosed with cachexia due to systemic inflammation. His final body weight was 60 kg and his body-mass index was 20.7 kg/m^2. He has no problems with food consumption and swallowing. He continues regular check-ups in the oncology outpatient clinic.

DISCUSSION

The esophagus is the center of the gastrointestinal system. It is a transporter of nutrients between the mouth and the stomach. If this mechanism is damaged due to any reason (e.g. ingestion of corrosive agents, hot drinks, etc.), it can lead to malnutrition, dehydration, electrolyte depletion, and starvation.

Due to both damage and obstruction of the esophagus, patients undergo modern multimodal therapies that require chemoradiation or chemotherapy before surgery. As the only curative option, surgery after neoadjuvant treatment is the mainstay of therapy in this setting. However, many patients are at risk for developing postoperative complications related to the complexity of the surgical procedure.[3] Because of complications (e.g., anastomotic leakage, pneumonia, chylothorax, etc.), the timing and type of postoperative feeding remains a matter of debate. Three major nutrition therapies are described in the literature: EN, PN and combined NT. Thirty randomized controlled trials demonstrated that there was no difference in mortality between PN and EN, whereas PN was associated with increased infectious complications, catheter-related infections, and longer hospital stays.[9] Since the patient was referred to our clinical nutrition unit for nutritional treatment only 4 days after the MIE operation, the insertion of the stent may not have provided an advantage in terms of earlier administration of the enteral route and prevention of the septic complications associated with parenteral nutrition.

Anastomotic leakage after MIE was another major complication seen in this case. Possible after postoperative fistula development and PN was the only option. After 12 days of CPN therapy, a central catheter infection developed and the catheter was replaced with a new one. Conservative non-invasive approaches include nil by mouth, antibiotics, placement or maintenance of a nasogastric tube, maintenance of drains if effective, and NT.[10] A nasojejunal tube was placed after the stent insertion, and combined NT was started with antibiotherapy. Combined NT (EN and PN) may be an option to achieve recommended energy and protein goals. EN alone is often insufficient to achieve energy and protein targets in the acute phase of critical illness.[11,12]

ESPEN recommends that the total energy expenditure of cancer patients be assumed to be similar to that of healthy subjects, generally ranging between 25 and 30 kcal/kg/day with 1.5-2.0 g/kg/day protein.[13] According to the recommendation, 1600-1920 kcal/day energy and 96-128 g/day protein were planned to supply with NT. However, it cannot be possible during PPN (because of the osmolarity limit maximum energy and protein were 1400 kcal-62,72 g respectively). Since adequate macro and micronutrients could not be provided, combined NT could be achieved with the NJ tube inserted at the time of stent placement. Oral intake was not feasible due to anastomotic leakage, which occurred on the 2nd day after the removal of the stent and NJ, necessitating the continuation of PPN.

This patient is one of the unique cases of a successful NT, which was still significant two years after discharge. Every patient diagnosed with cancer should be evaluated nutritionally before and during treatment. When cancer cachexia develops, irreversible severe muscle and fat loss can occur and difficulties in NT can be experienced. A multidisciplinary approach should be employed in treatment..

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

Author contributions: Concept – P.T.,M.D.; Design – P.T.,M.D.; Supervision – P.T.,M.D.; Resources – P.T.,M.D.; Materials – P.T.,M.D.; Data Collection and/or Processing – P.T.,M.D.; Analysis and/or Interpretation – P.T.,M.D.; Literature Search – P.T.,M.D.; Writing Manuscript – P.T.,M.D.; Critical Rev iew – P.T.,M.D.

Funding: The authors declare the study received no funding.

Conflict of interest: The authors declare that there is no conflict of interest.

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