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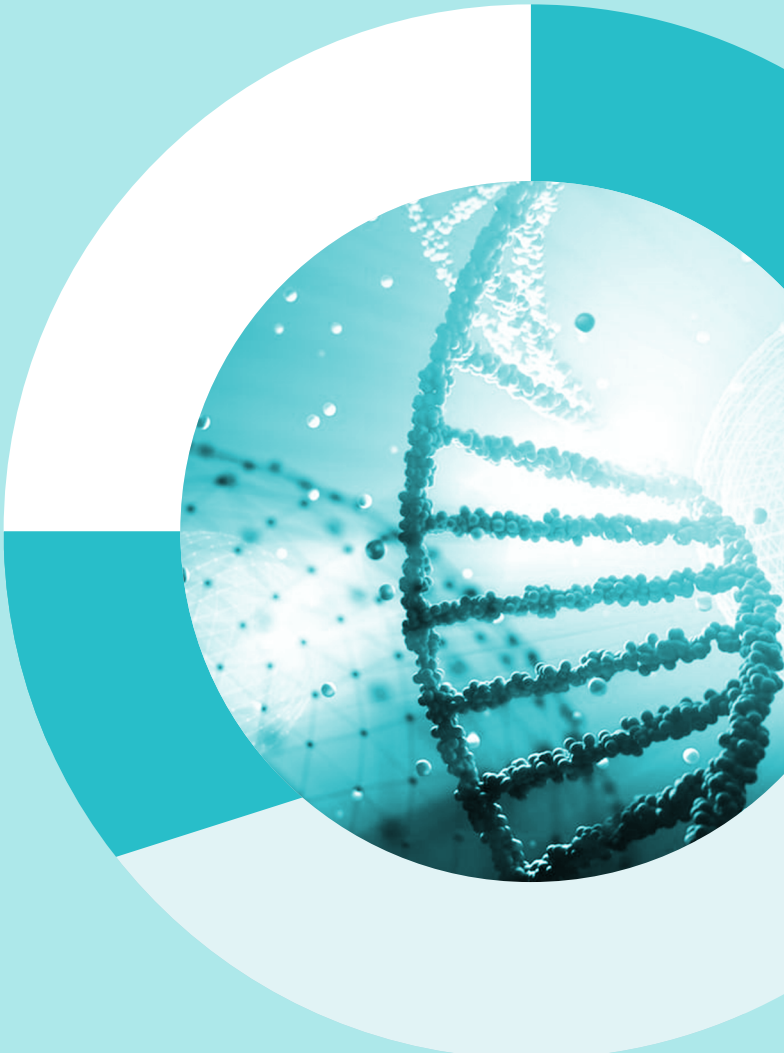

Official Journal of Cyprus Turkish Medical Association

galenos yayınevi

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Cyprus Journal of Medical Sciences (Cyprus J Med Sci), the official organ of Cyprus Turkish Medical Association.

This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles. As of 2022, the journal has become a bimonthly publication, publishing in February, April, June, and August, October and December. The journal's publication language is English. (E-ISSN:2536-507X)

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http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

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As of 1 January 2019, a data sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual deidentified participant data will be shared

- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

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- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be

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

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Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
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Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

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

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Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

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

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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

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

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

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REVIEW

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A Review: Are Some Diet Models Beneficial or Harmful for Type II Diabetes Mellitus?

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Abstract

Diabetes mellitus (DM) is a chronic disease affecting millions worldwide. According to the current literature, type II DM is linked with some currently trending diet models such as high-protein, low-carbohydrate (CHO), ketogenic, gluten-free (GF), intermittent fasting (IF) nutrition models, the Mediterranean diet (MD), etc. The purpose of this review article was to shed light on the relationships between some currently trending diet models and type II DM, their potential effect mechanisms and any complications according to evidence from the current literature. High-protein, low-CHO, ketogenic, GF and IF nutrition models can potentially decrease inflammation and body weight, improve the lipid profile and gut microbiota, increase the secretion of incretin hormones and regulate immune responses and thus increase insulin sensitivity in tissues. However, these currently trending diet models may result in acute or chronic complications such as; hypoglycemia, fatigue, lethargy, nutrient deficiencies, acute abnormalities or other related chronic disorders. Some of these complications may be critical for life. Conversely, the MD has very important beneficial effects on the prevention of type II DM and there is no evidence in the literature which shows this diet model has any side effects. In conclusion, applying optimal nutritional principles is the most recommended nutritional approach in order to reduce risk and manage type II DM.

Keywords: Diabetes mellitus, high-protein/low-CHO diet, gluten-free diet, intermittent fasting, Mediterranean diet

INTRODUCTION

Diabetes mellitus (DM) is an endocrinopathy which is characterized by hyperglycemia which develops as a result of an insufficiency or lack of insulin production from the pancreas and peripheral insulin resistance (IR).[1] DM is a chronic disease with a rapidly increasing prevalence, and according to International Diabetes Federation's 2021 data, 537 million people between the ages of 20 and 79 have been diagnosed with type II DM. Approximately 10% of health expenditure is spent on the treatment of diabetes and diabetes-related diseases. Most countries try to control DM due to its socio-economic burden on both society and the population. Nutritional habits are a very important factor for both the prevention and management of DM.[2] Over the years, different nutritional models have been developed to prevent and manage chronic diseases such as obesity and DM, which have both reached epidemic proportions. It is possible to classify these different nutrition models under three basic groups: nutritional models with altered nutrient distribution [low-carbohydrate (CHO), fat, etc.], food or food group restriction [gluten-free (GF) diet, etc.] and altered meal timings [intermittent fasting (IF), etc.].[3] In the literature, there are some important comprehensive studies about these nutrition models with regards to DM (Table 2). The "A Secondary Analysis of the Dietary Intervention Randomized Controlled Trial" study aimed to examine the metabolic effects of three dietary patterns which they described as healthy: a low-fat diet model with restricted calories, a Mediterranean diet (MD) model with restricted calories and a low-CHO diet model with restricted calories. According to the results of that study, decreases in body weight (kg) and fasting plasma insulin levels (pmol/L) were observed after the first six months in all three dietary model intervention groups. However, the following 24-month results showed that there was an increase in both parameters but they did not go back to their initial values.[4]

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In addition to diabetic risk factors, such as age, family, history and physical inactivity, the presence of obesity is another important risk factor which contributes to the development of diabetes (especially type II DM).[5] Therefore, while examining the effects of different nutritional models which are directly related to diabetes on metabolic parameters, their effects on body weight control should also be considered. Generally, knowledge in the current literature related to the effects of low-calorie diets (LCDs) on obesity and diabetes supports the idea that LCDs have beneficial effects on plasma glucose levels, HbA1c levels, Homeostatic Model Assessment for Insulin Resistance Index (HOMA-IR) measurements and body weight in diabetic and obese individuals. Evaluating the effectiveness of low-CHO nutrition models as a medical nutrition therapy for diabetes, obesity and cardiovascular diseases is a current research topic.[6] However, increasing the rate of energy from fat in low-CHO nutrition models also brings into question the applicability of these models. Although low-CHO/high-fat nutritional models, such as the Atkins diet, the Zone diet and the ketogenic diet (KD), have positive effects on insulin sensitivity and DM management in the short term, the long-term effects on health have not yet been fully demonstrated.[7] The literature emphasizes that low-CHO, low-glycemic index, low-energy and high-dietary fiber diet models are effective in providing ideal body weight and glycemic regulation. However, there is no single nutritional model which can be considered to be the best for the medical nutrition therapy of obesity and diabetes. Instead of a single general approach, individualized medical nutrition therapy with a patient-centered multidisciplinary approach is recommended.[8]

From this starting point, this current review aimed to examine the potential effects of some different nutrition models on body weight, certain blood parameters such as; HbA1c, fasting plasma glucose level, HOMA-IR, etc., and thus, to determine their effectiveness in both the prevention and management of type II DM.

Nutrition and Type II Diabetes Mellitus

According to the World Health Organization, nutrition has an important role in ensuring healthy growth and development, in prolonging life expectancy and in preventing non-communicable chronic diseases (NCDs), such as cardiovascular diseases, hypertension, diabetes, obesity, pulmonary diseases, cancer, etc., in every physiological process of life from the maternal period to old age.[9] Unhealthy eating habits are the most important modifiable risk factor contributing to the development of NCDs. The literature has drawn attention to the fact that there is an inverse relationship between the risk of NCDs and healthy eating models which contain high consumption rates of vegetables and fruits, whole grain products, legumes and nuts. On the other hand, high-fat foods, processed meats and meat products and the high consumption of saturated fat, salt and sugar (e.g., the Western diet) are associated with the risks of NCDs.[8] About 90% of all diabetes diagnoses are type II diabetes, which is a preventable type of DM because it has modifiable risk factors such as obesity, physical inactivity and unhealthy nutritional habits.[9] Studies showing the efficacy of lifestyle change in the prevention of diabetes are included in the Da Qing study, the Finnish Diabetes Prevention Study the Diabetes Prevention Program and the Malmö study. These studies showed that, for individuals with high type II DM risk, clinical type II DM development can be reduced by 58% as a result of increased physical activity, healthy eating habits, obesity management and behavior change interventions.[9-11]

The Nutrition Therapy Guidelines summarize the metabolic goals of individualized medical nutrition therapy (preferably applied by an experienced dietitian) in the treatment of type II diabetes as follows;

- HbA1c (glycated hemoglobin) <7%,
- Blood pressure (BP) <140/80 mmHg,
- Low-density lipoprotein-C <100 mg/dL,
- Triacylglycerol < (TAG) 150 mg/dL,
- High-density lipoprotein-C >40 mg/dL,
- Maintain/achieve ideal body weight,
- Delay/prevent diabetic complications.[12]

Although medical nutrition therapy is among the treatment components in the treatment of type II DM, there is no single nutritional model which is recommended. According to the American Diabetes Association's position statement, one of the following low-fat, low-CHO, vegetarian, Mediterranean or Dietary Approaches to Stop Hypertension diet models, which include cultural and individual preferences, can be applied.[13]

Diet Models and Type II Diabetes Mellitus

High-Protein and Low-Carbohydrate Diet Models

In the last decade, high-protein and low-CHO diet models have been more popular than low-fat diet models. In addition to the effects of high protein, a limited amount of CHO may increase the effects of these diet models on human health.[14] Although there are many studies in the literature about the effects of these diet models on weight loss,[15,16] it is also possible to find studies which aimed to determine the effects on DM, cardiovascular diseases, etc.[17,18] There are various types of high-protein diet models as well.[19] The most popular types and their contents are shown in Table 1.

According to the literature, some potential mechanisms between high-protein and low-CHO diet models and type II DM have been put forward. As shown in Figure 1, low-CHO diets (providing <130 g CHO per day) may decrease plasma insulin levels and low plasma insulin helps weight loss and protects the body from issues with fatty liver. These potential effects may help reduce IR in human tissues.[24]

In addition, amino acids, especially branched-chain amino acids, produce some bioactive peptides (BPs) during their digestion.

Table 1. The most popular high-protein diet models and their contents

Diet model	CHO (%)	Protein (%)	Fat (%)	Reference
Zone	36	34	29	[20]
Atkins	6	35	59	[21]
Stillman	3	64	33	[22]
High-protein, optimal CHO	50	20	30	[23]

CHO: Carbohydrates.

These BPs are potential inhibitors of the incretin system.[25] BPs potentially inhibit dipeptidyl peptidase IV (DPP-IV), alpha-amylase and alpha-glucosidase enzymes, which have important roles in the development of type II DM. DPP-IV has a key role in releasing incretin gut hormones such as glucagon-like peptide I and glucose-dependent insulinotropic peptide. Alpha-glucosidase and alpha-amylase are enzymes which help the digestion of CHO in the human digestive system. When BPs inhibit these enzymes, they potentially help to decrease the plasma glucose and the glucose-dependent plasma insulin levels.[26] Because of these mechanisms, high-protein and low-CHO diet models have potentially positive effects on type II DM. There are some studies regarding this subject in the literature which report its effects on the both prevention and management of type II DM. According to the results of these human studies, this diet model can decrease HbA1c levels both for diabetic and non-diabetic obese patients. Furthermore, a high-protein/low-CHO diet can be beneficial in weight loss.[17,18,27] However, Larsen et al.[27] reported this nutritional model was not beneficial for type II DM in the long term. Although these potential effects exist, low-CHO diets with the use of some medical drugs such as insulin, oral anti-diabetics, etc. may cause hypoglycemia in the acute period[28] those wishing to decrease the risk of microvascular complications through glycemic control inevitably face an increased risk of hypoglycemia, often without warning symptoms and potentially with severe consequences. This is especially true for those with type I DM, but also for some with type II DM (Figure 1). Additionally, these diet models have negative effects on human health in the long term. It is possible to say these diet models may cause some complications such as atherosclerosis, endothelial dysfunction, ischemia-inducted arrhythmias, cardiac contractile function impairment, sudden death, osteoporosis, kidney damage, cancer, etc.[19,28]

Ketogenic Diet

The KD model is the most common treatment model for childhood epilepsy in the acute term (when patients have persistent symptoms). Additionally, it has started to be used as a therapeutic approach for obesity and type II DM.[29]

The KD is characterized by high fat, moderate protein and low CHO intake. It contains 55-60% of energy in the form of fats, 30-35% in protein and 5-10% in CHO.[30] In addition, KD has some potentially beneficial effects on cardiovascular diseases, the gastrointestinal system and cancer.[31] KD causes ketosis, which is related to increased ketone bodies, in the human body and shows some potentially beneficial effects on health via them.[32] However, these ketone bodies are related to many complications which may even cause death.[33] According to the current literature on the potential effects of KD on type II DM, it may positively affect intestinal microbiota, decrease inflammation in the pancreas and liver and thus increase insulin sensitivity on the related cells and improve mitochondrial impairment which is very important in decreasing IR. In addition, KD potentially benefits weight loss. Due to these potential effects, KD is a potentially effective nutrition model which decreases plasma glucose and HbA1c levels and increases insulin sensitivity.[29,31] These mechanisms are shown in Figure 1. The meta-analysis results showed that KD was an effective diet model for the reduction of HbA1c, TAG and body weight in diabetic patients.[34-36] Choi et al.[34] observed that the KD was more beneficial for diabetic patients than for non-diabetics. The detailed methods and results of these studies are shown in Table 2. However, in addition to these beneficial effects, "keto-flu" with fatigue, lethargy and headache are the most common complications of KD at the beginning. Furthermore, constipation, low-grade acidosis, hypoglycemia, dehydration, dyselectrolytemia and dyslipidemia may occur in the short term. Growth retardation for children, hyperuricemia, kidney damage, osteoporosis, sudden death etc. are the long-term critical complications of KD.[28,33,37-39]

Gluten-Free Diet

Another popular nutrition model nowadays is the GF diet. The GF diet is necessary for some diseases, such as celiac disease, wheat allergy and non-celiac gluten sensitivity.[40] Gluten is a protein found primarily in grains.[41]

All natural cereal products, except corn, rice, buckwheat, etc., include gluten.[40] Some GF products are available in supermarkets for people who cannot or do not want to consume gluten.[42] In addition to disorders of the lower gastrointestinal system, the GF diet may be effective in treating metabolic syndrome, obesity, cardiovascular health and type II DM.[43-45] On the other hand, there are some negative effects of GF diets on overall health. GF diets may cause obesity, dysbiosis of the gut microbiota, dyslipidemia, non-insulin-dependent DM, etc.[46] The GF diet has some potential effects on type II DM (Figure 1). The GF diet may improve gut microbiota and provide biosis so it can decrease glucose absorption via the strengthening of tight junctions and regulate the immune system.[47] It may also reduce pro-inflammatory cytokines, such as TNF-α and adipokines in our bodies. Thus, it may decrease the stress levels of pancreatic beta cells and IR on muscle cells.[45] These potential effects are related to the absence of gluten proteins. On the other hand, the GF diet is mainly related to limited cereal or simple CHO intake, which is an important approach for type II DM prevention and management.[48] Table 2 shows relevant current studies about this subject. Zong et al.[48] found that higher gluten intake with dietary fiber consumption was not a risk factor for type II DM in healthy people. On the other hand, some studies observed that gluten-related increased type II DM risk. Furthermore, these studies showed that there is a bidirectional relationship between the GF diet and obesity. Ehteshami et al.[44] observed a decrease in waist circumference while Tortora et al.[49] observed an increase in this anthropometric measurement. Although there are some beneficial effects of the GF diet, this diet model has some complication risks. It is possible to classify these complications into two groups, namely nutrient deficiencies and chronic diseases. Dietary fiber, protein, essential amino acids, vitamins A, D, E, K and the B group of vitamins, calcium, iron, magnesium and zinc deficiencies may be observed.

In addition, obesity, dysbiosis of gut microbiota, dyslipidemia and non-insulin-dependent DM are some of the GF diet-related chronic diseases in the long term.[46,50-52]

Intermittent Fasting

IF is one of the effective nutritional models in the treatment of obesity and obesity-related metabolic disorders. It is thought that this nutrition model, which is based on energy restriction at certain time intervals, can yield more successful results when the circadian rhythm hypothesis is taken into account[53] which may present independent health benefits. However, the number of diet books advising how fasting can be incorporated into our daily lives is several orders of magnitude greater than the number of trials examining whether fasting should be encouraged at all. This review will consider the state of current understanding regarding various forms of intermittent fasting (e.g. 5:2, time-restricted feeding and alternate-day fasting. The circadian rhythm theory argues that a well-adjusted IF model will optimize the physiological processes occurring in the peripheral, fat,

muscle and skeletal tissues and may be effective in preventing obesity and cardiometabolic disorders. It is thought that IF approaches which restrict food intake, especially late in the evening, may have positive effects on IR and glycemic regulation.[18,54] The following are the four most common types of IF models;

- 5:2 Fasting model: two days fasting, five days libitum,

- Alternate-day fasting model: fasting days alternated with libitum eating,

- Time-restricted fasting model: <8 h/day fasting model,

- Religious fasting model (Ramadan): 12-16 h/day fasting during the Ramadan month.[4,55]

IR is a pathological disorder which contributes to the development of type II diabetes. A time-restricted IF model has been reported to cause an increase in adiponectin levels. Increased adiponectin levels stimulate the AMP-activated protein kinase (AMPK) signaling pathway. Thus, it contributes to the regulation of the glucose metabolism, lipolysis and insulin sensitivity.[56]

In addition to IF's direct effects on glucose and the insulin metabolism, it is thought to be effective in the prevention of type II DM by suppressing pro-inflammatory cytokines and peptides such as interleukin-6, C-reactive protein and homocysteine[57] (Figure 1). According to Table 3, a study on lean healthy men reported that Ramadan IF decreased HbA1c levels and proinflammatory mediators.[58] Another study showed IF (fasting 18-20 hours/day) had positive effects on both IR and body weight in diabetic patients.[55] In addition, a positive relation was determined between 18 hours of fasting and IR in overweight, prediabetic men.[59] These beneficial effects are noted in the "Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus report- 2019" which lists IF models among the different diets. However, the report emphasizes that the evidence is insufficient to recommend an IF diet as one of the nutritional therapy methods for diabetes or pre-diabetes.[13] Furthermore, these diet models may cause side effects of hypoglycemia, ketonemia, dizziness and fatigue.[60,61]

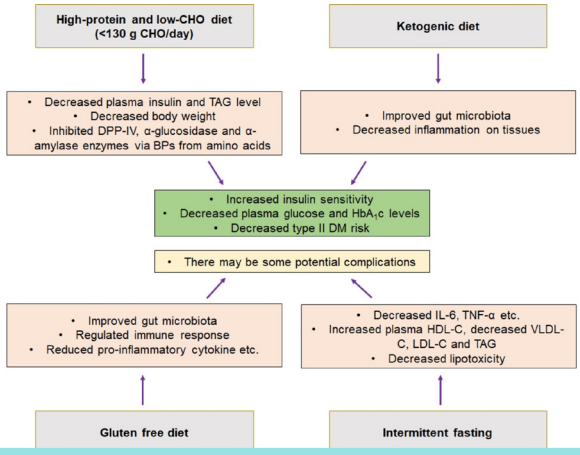

Figure 1. Potential effects of some diet models on type II DM.[24-26,31,45,47,62-64]

DM: Diabetes mellitus, CHO: Carbohydrates, TAG: Triacylglycerol, DPP-IV: Dipeptidyl peptidase IV, BP: Blood pressure, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-alpha, HDL-C: High-density lipoprotein, VLDL-C: Very low-density lipoproteins, LDL-C: Low-density lipoprotein, TAG: Triacylglycerol.

The MD was developed by Ancel Keys in the 1960s. This is a dietary model which is characterized by plant-based nutritional habits.[65] The MD includes low saturated fatty acids, high monounsaturated fatty acids-MUFA (from olive oil), dietary fiber, complex CHOs, etc. Bach-Faig et al.[66] developed a pyramid which shows MD-specific nutritional habits and this pyramid was later revised by Serra-Majem et al.[67] This diet model is related to a high consumption of olive oil, whole grains, legumes, seeds, nuts, vegetables and fruits, a moderate consumption of fish, red wine and dairy products and a limited consumption of poultry, red meat and processed red meat products.[65,66] As shown in Figure 2, the MD has some potentially positive effects on human health as a result of the beneficial nutrients and nutritional substances it includes.[68]

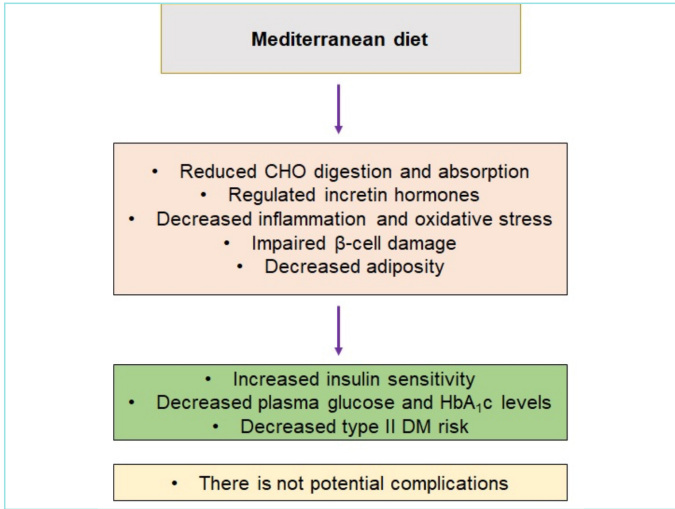

Figure 2. Potential effects of the Mediterranean diet on type II DM.[69-71]

DM: Diabetes mellitus, CHO: Carbohydrates, HbA1c: Hemoglobin A1c.

Mediterranean Diet

The MD includes a lower amount of CHO than other diet models and complex CHOs. Thus, the MD may reduce the digestion and absorption of CHOs, increase glucose uptake into cells and regulate incretin hormones. Additionally, the MUFA and polyunsaturated fatty acids-PUFA in the MD have anti-inflammatory roles. Thus, they may increase insulin sensitivity in tissues.[31] Some micronutrients and phytochemicals in the MD have antioxidant and anti-inflammatory effects. Also, they may impair β-cell damage and increase insulin secretion. At the same time, the MD provides an adequate amount of energy and may decrease the prevalence of obesity, which is a risk factor for DM.[32] Dietary fiber is high in the MD and can delay gastric emptying and decrease the absorption of glucose. Thus, it can regulate plasma glucose levels.[69] The MD is characterized by moderate red wine consumption. Red wine includes resveratrol, which is a polyphenol. It has anti-inflammatory and anti-oxidant roles and thus may help decrease IR in tissues.[71] Studies on healthy people showed that there is an inverse relationship between the MD and type 2 DM risk. Higher adherence to the MD could decrease type 2 DM risk.[72,73] In line with this, Esposito et al.[74] noted the importance of the MD to delay the need for DM medications in type II diabetic obese patients. Detailed information about these studies is

shown in Table 2. When the literature was researched by the authors, no study was found which showed any side effects of the MD.

"High protein, low-CHO diets", "KD", "GF diet", "IF", "MD" and "type II DM" were used as keywords to search the PubMed and ScienceDirect databases. Only diabetic and non-diabetic human studies (including case-controlled, epidemiological and meta-analyses) were included and the results of some current studies are shown in Table 2 for each trending diet model separately.

CONCLUSION

This review found some trending diet models to have potentially beneficial effects. Although the results of some original articles support the idea that high-protein, low-CHO, ketogenic, GF, and IF nutrition models have beneficial effects on the prevention and management of type II DM, neither the side effects nor the long-term negative effects of these should be disregarded. Additionally, it can be said that the MD includes nutrients and nutritional substances which may have potentially positive effects on type II DM development. According to the current literature, the MD nutrition model does not have any side effects. Thus, the adaption of the principles of the MD can be recommended in order to prevent the development type II DM and other NCDs.

MAIN POINTS

- Nutritional habits are a modifiable risk factor in the etiopathogenesis of chronic non-communicable diseases.
- Different dietary patterns may affect the metabolic parameters associated with type II diabetes.
- Although some of the trending nutrition models have positive effects on the metabolic parameters associated with type II diabetes, the effects of long-term practices on health need to be examined in more detail.

Table 2. Some literature examples about the effects of these diet models on type II DM

	Authors	Year	Sample of features	Methods	Results
High-protein low-CHO diets	Larsen et al.[27]	2011	**Sample size** 99 type II DM-diagnosed patients **Backgrounds of participants** Age: 30-75 years BMI: 27-40 kg/m^2 HbA1c: 6.5-10.0% If they had another significant disease, they were excluded.	**There were two study groups** (HP & high CHOs-HC) HP (n=53): 30% of energy from fats, 30% protein, 40% CHOs HC (n=46): 30% fats, 15% protein, 55% CHOs Time: 12 months (data was collected in the first three months and then at the end of the research)	1. HbA1c levels decreased in both groups with no statistical significance. 2. There was no highly beneficial effect of the HP diets on type II DM in the long term. 3. Body weight and plasma TAG levels decreased in both groups but there was no statistical significance.
	Evangelista et al.[17]	2021	**Sample size** 76 overweight and obese patients **Backgrounds of participants** Age: 57.7±9.7 years old BMI: 36.2±7.1 kg/m^2 HbA1c: 7.2±1.3%	**There were two study groups** (HP & SP) HP (n=33): 30% of energy from fats, 30% protein, 40% CHOs SP (n=43): 30% fats, 15% protein, 55% CHOs Each group consumed >25 g of dietary fiber per day Time: Three months (data was collected at the end of the research)	1. HP decreased plasma HbA1c and TAG levels statistically significantly more than SP. 2. Both diet models were effective for weight loss.
	Dong et al.[18]	2020	**Meta-analysis** Nine different types of research There were 418 type II DM-diagnosed patients	**There were nine different types of research papers** Time of the studies: Four-24 weeks Protein contents of diet: 25-32% of energy for SG and 15-20% for CG	1. HP diets decreased plasma HbA1c levels with a statistical significance. 2. They did not affect plasma fasting glucose levels significantly. 3. There was no difference between lipid levels.
Ketogenic diet	Choi et al.[34]	2020	**Meta-analysis** 14 different research studies	**There were 14 different research papers** No age restriction There were diabetic and non-diabetic patients in the studies. The studies included compared the effects of KD on glycemic regulation according to CG (low-fat diets).	1. KD had greater effects on the HbA1c levels of diabetic participants than low-fat diets. 2. According to the comparison of diabetic and non-diabetic participants, KD was more effective for diabetic patients. 3. KD showed significant beneficial effects on the diabetic participant's plasma TAG level and body weight.
	Yuan et al.[35]	2020	**Meta-analysis** 13 different research studies There were 567 type II DM-diagnosed patients	**There were 14 different research studies** Included studies compared the before-after effects of KD.	1. Plasma fasting glucose and HbA1c levels decreased after the KD intervention. 2. KD improved plasma lipid profile and provided weight loss.
	Alarim et al.[36]	2020	**Meta-analysis** Six different research studies	**There were six different research papers** There were type II DM-diagnosed participants for each study. The studies included had to have a control group.	1. KD had statistically significant effects on plasma fasting glucose and HbA1c levels. 2. Effects of the KD on the HbA1c levels were greater than for the plasma fasting glucose.

Table 2. Continued

	Authors	Year	Sample of features	Methods	Results
Gluten-free diet	Zong et al.[48]	2018	**Sample size** 202,114 participants **Backgrounds of participants** Age: 24-75 years	Time: At least 22 years (It was a cohort study) Researchers aimed to determine the relationship between gluten intake and type II DM. Physicians screened participants to diagnose type 2 DM, nutritionists determined their gluten intake with a food frequency questionnaire-FFQ every 2-4 years.	1. Higher gluten intake was related to higher starch and cereal dietary fiber intake. 2. Higher Gluten intake with dietary fiber sources did not show any harmful effects on the development of type II DM. 3. Simple CHOs sources were related to the development of type II DM. 4. Researchers found that gluten intake did not increase the risk of type II DM in this study.
	Ehteshami et al.[44]	2018	**Sample size** 45 metabolic syndrome-diagnosed patients **Backgrounds of participants** Age: 25-70 years BMI: 25-35 kg/m^2	**There were two study groups** (GF diet & RD) GF: <2 g/day gluten RD: Participants' nutritional habits	1. There were statistically positive differences between the groups for waist circumference, plasma fasting glucose, and TAG levels. 2. There was no statistical difference for the HOMA-IR index.
	Tortora et al.[49]	2015	**Sample size** 98 coeliac-diagnosed patients	Time: 12 months Data was collected at the beginning and end of the study (after one year).	1. GF diet had increased patients' plasma fasting glucose and TAG levels significantly at the end of the year. 2. BMI and waist circumference increased after one-year of GF diet intervention.

DM: Diabetes mellitus, CHO: Carbohydrates, BMI: Body mass index HbA1c: Hemoglobin A1c, HP: High protein, TAG: Triacylglycerol, SP: Standard protein, SG: Study groups, CG: Control group, KD: Ketogenic diet, FFQ: Food frequency questionnaire, GF: Gluten-free, RD: Regular diet, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance Index.

Table 3. A study on lean healthy men reported

	Authors	Year	Sample of features	Methods	Results
Inter-mitten diets	Harder-Lauridsen et al.[58]	2017	**Sample size** Ten lean healthy men	28 days Ramadan IF	1. Ramadan IF decreased HbA1c. 2. Decreased TNF-α, IL-6, and IL-10 were found to be related to Ramadan IF
	Antoni et al.[55]	2017	**Sample size** 20 type II DM-diagnosed people **Backgrounds of participants** Age: 18-65 years	2-week standard diet model 2-week IF model (fasting 18-20 hours/day) 2-weeks follow up	1. Researchers reported decreased CRP, HOMA-IR, and waist circumference
	Sutton et al.[59]	2018	**Sample size** Eight overweight men diagnosed with prediabetes	18 hours of fasting for five weeks	IF was found to be related with: 1. Increased insulin sensitivity, 2. Increased insulinogenic index, 3. Decreased insulin resistance
Mediterranean diet	Esposito et al.[74]	2014	**Sample size** 215 newly diagnosed type II DM overweight patients	**There were two study groups** (Low CHO MD-LCMD & Low-fat diet) Time: Four years	1. LCMD was more effective at decreasing patients' HbA1c levels. 2. It helped in further delaying the need for DM medications
	Ahmad et al.[72]	2020	**Sample size** 25,317 healthy women	Time: 20 years Adherence to the MD is determined by a special questionnaire. Physicians screened them for type 2 DM regularly	1. High adherence to the MD reduced by 30% the risk of type II DM such as insulin resistance, adiposity, and inflammation
	Khalili-Moghadam et al.[73]	2019	**Sample size** 2,139 healthy adults	168-item FFQ was used to determine the participant's nutritional habits. Traditional MD scores were used to evaluate their adaptation status to this diet	1. Recommended consumption of MD patterns such as fish, legumes, nuts, and olive oil can decrease the risk of type II DM. 2. An inverse relationship between the MD and the risk of type II DM was found in this study

LCMD: Low carbohydrate Mediterranean diet, DM: Diabetes mellitus, IF: Intermittent fasting, IL: Interleukin, TNF: Tumor necrosis factor, MD: Mediterranean diet, CHO: Carbohydrates, FFQ: Food frequency questionnaire, HbA1c: Hemoglobin A1c, CRP: C-reactive protein, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance Index.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.D.; Design: T.D., S.Ö.; Data Collection and/or Processing: T.D., S.Ö.; Analysis and/or Interpretation: T.D., S.Ö.; Literature Search: T.D., S.Ö.; Writing: T.D., S.Ö.

DISCLOSURES

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RESEARCH ARTICLE

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Cardiac Functions and Peripheral Arterial Stiffness in Patients with Polycystic Ovary Syndrome: A Cross-Sectional Study

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Abstract

BACKGROUND/AIMS: Polycystic ovary syndrome (PCOS) patients have been described as having subclinical cardiac and vascular damage; nevertheless, research data is contradictory. We aimed to assess global cardiac functions, peripheral arterial stiffness (AS), and the relationships between echocardiographic and AS measurements in patients with PCOS.

MATERIALS AND METHODS: We enrolled 42 consecutive PCOS patients and 32 age- and body mass index (BMI)-matched healthy controls. All participants underwent a comprehensive two-dimensional echocardiographic examination. Applanation tonometry was utilized to determine peripheral AS [carotid-radial pulse wave velocity (PWV) and augmentation index (AIx)] in each participant. In addition, we evaluated the correlation between AS and echocardiographic parameters.

RESULTS: The PCOS and control groups had similar ages and BMIs. Right ventricular (RV) and left ventricular (LV) diameters, LV mass, and LV ejection fraction were similar between the groups. Considering the pulse wave and tissue Doppler parameters of the cardiac functions, the LV septal S', LV Tei index, RV S', RV Tei index, and E/E' ratio were comparable between the two groups. Peripheral AS parameters including, PWV and AIx were higher in those patients with PCOS [19.3±12.5 vs. 12.5±9.6; p=0.01 and 5 (4.7-5.5) vs. 4.4 (4.2-4.8); p=0.0001, respectively]. AS parameters were not correlated with echocardiographic parameters.

CONCLUSION: Despite normal echocardiographic LV and RV functions, women with PCOS had increased AS. There was no correlation between echocardiographic and AS parameters in these patients.

Keywords: Diastolic and systolic right ventricular functions, diastolic and systolic left ventricular functions, peripheral arterial stiffness, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrinopathies in young females, characterized by excessive androgen levels, multiple cysts in the ovaries, and ovulatory failure.[1,2] PCOS is associated with accelerated atherosclerotic cardiovascular (CV) disease due to the high incidence of CV risk factors, including elevated mean blood pressure, dyslipidemia, and impaired response to insulin.[3] Nevertheless, the presently available data does not validate that PCOS independently increases the risk of a CV event.[4-6] Several studies have

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been conducted using various methods, such as echocardiography and the evaluation of arterial stiffness (AS), and it has been shown that these patients have both structural and functional abnormalities.[7-14] It is generally supposed that these changes may be linked to CV risk factors rather than the presence of PCOS.

AS is a surrogate measure of early morphological and functional changes in vasculature and it is a powerful predictor of subsequent CV outcomes and death rates.[15] PCOS has been linked with increased AS in various studies using AS measurements, including the common carotid artery stiffness index, carotid-femoral pulse wave velocity (PWV) and the augmentation index (AIx), the cardio-ankle vascular index, and brachial-ankle PWV.[11-14] Data on the associations between PCOS and carotid-radial (peripheral) AS is limited.

Previous studies also demonstrated that PCOS is linked with left ventricular (LV) diastolic and systolic abnormalities.[9,10] Echocardiographic findings suggest impaired LV relaxation and early remodeling in PCOS patients. However, there is not enough data on the global right ventricular (RV) functions in PCOS patients.

Thus, we aimed to assess the stiffness of peripheral arteries using applanation tonometry and compare the LV and RV echocardiographic findings of young women with PCOS with control subjects using comprehensive two-dimensional (2D) echocardiography, PW, and tissue Doppler (TD) imaging. We also aimed to determine correlations between echocardiographic measurements and AS parameters.

MATERIALS AND METHODS

Subjects

The calculation of the number of subjects to be included in this study was performed using the G*Power 3.1 program. For 90% statistical power and α=0.05 significance level, the smallest sample size required to determine the d=0.50 effect size for independent groups according to the t-test was calculated as 33 for the 1st group and 15 for the 2nd group, a total of 48. This study consisted of 42 consecutive PCOS patients and 32 healthy controls with normal menstrual cycles who were matched for age and body mass index (BMI). The exclusion criteria were: smoking; pregnancy; the previous or present use (up to the preceding 3 months) of combined hormonal contraceptives, statins, anti-androgens, or hypoglycemic drugs; a history of hypertension, diabetes mellitus, hyperlipidemia, autoimmune diseases, thyroid disease, chronic renal disease, chronic liver disease, hyperprolactinemia, chronic pulmonary disease, and acute infection. PCOS was determined consistent with the revised 2003 Rotterdam consensus criteria with the rejection of other etiologies.[2]

All participants provided their written informed consent. Our study was authorized by the Dokuz Eylül University Ethical Examination Board (approval number: 2022/33-11, date: 19.10.2022).

Echocardiographic Examination

An experienced cardiologist performed all echocardiographic examinations using a Philips Affinity 50 ultrasound system (Philips, Andover, MA, USA) using a 3.2 MHz transducer. The American Society of Echocardiography's guidelines for standard 2D echocardiographic measures were followed.[16] LV linear measurements were obtained using a parasternal long-axis view. Interventricular septum, posterior wall thickness, LV end-diastolic diameter, LV end-systolic diameter, and left atrium (LA) diameter were recorded. The Devereux formula was used for the LV mass calculation. LV volumes and ejection fraction (LVEF) were determined using the biplane summation-of-disks method. The left atrial (LAA) and right atrial (RAA) areas were calculated at end-systole from the apical four-chamber (4C) view. The RV-focused apical 4C view was used for the linear longitudinal end-diastolic dimension of RV (RVd). RV fractional area change (RVFAC) was calculated as (end-diastolic area-end-systolic area)/(end-diastolic area) x 100%.[17] In the apical 4C view, an M-mode cursor was placed down the RV free wall to the lateral tricuspid annulus. The maximum length of tricuspid annulus movement during systole was specified as tricuspid annular plane systolic excursion (TAPSE).

PW Doppler was utilized for measuring the mitral flow velocities. The early diastolic peak E wave (E), atrial contraction wave (A), and E wave deceleration time (EDT) were measured and the E/A ratio was calculated. TD imaging was utilized to record the velocities of the mitral and tricuspid annulus. LV systolic (LV S') and LV diastolic (LV E') velocities were recorded. For diastolic LV filling performance, E/E' was calculated. RV systolic (RV S') and RV diastolic (RV E') velocity waveforms were also recorded.

TD velocity waveforms were also used to calculate the Tei indices. The RV Tei index was determined by dividing the ejection duration by the sum of the contraction time and isovolumetric relaxation duration.[17] A similar method was also used for the determination of the LV Tei index.

Measurement of Arterial Stiffness

SphygmoCor applanation tonometry was used to measure the waveforms of the radial artery pressure (AtCor Medical, West Ryde, NSW, Australia). The apparatus automatically measured central aortic pressure, pulse pressure (PP), AIx, and aortic pressure augmentation.[18] Aortic pressure augmentation was divided by PP to calculate AIx. By sequentially recording carotid and radial artery waveforms which were electrocardiography-gated, the same device determined the aortic pulse wave velocity (AoPWV). The length of the pathway was measured with a tape measure. The length pathway was measured as (the distance between the radial artery and the suprasternal notch) - (the distance between the carotid artery and the suprasternal notch). The AoPWV was calculated by dividing this length by the transit duration. Echocardiographic examination and AS measurements were made consecutively in each participant during the morning fasting period.

Statistical Analysis

SPSS version 26 from SPSS Inc., Chicago, IL, was used for statistical analysis. Histograms and the Kolmogorov-Smirnov test were used for assessing normal distribution. Continuous variables are represented as means ± standard deviations and medians (interquartile range). To analyze between-group differences, the Mann-Whitney U test was used when the data were not normally distributed, and Student's t-test was used when the data were normally distributed. Correlations between echocardiographic data and AS parameters were determined by Pearson correlation analysis. All tests were two-sided, and $p<0.05$ was considered statistically significant.

RESULTS

The demographics and laboratory findings of the PCOS and control groups are shown in Table 1. Age, BMI, diastolic and systolic arterial pressure, and laboratory findings were similar between the two groups (p>0.05 for all).

The echocardiographic findings of the two groups are shown in Table 2. Among the conventional 2D echocardiographic parameters, LV diameters, LVEF, LV mass, LAA, RV diameter, RV FAC, and RAA were similar between the two groups (Table 2). Also, among the TD and PW Doppler findings; LV S', RV S', LV and RV Tei indices, and E/E' were similar between the groups (Table 2).

Table 3 shows the AS parameters in the PCOS and control groups. AIx and AoPWV were elevated in the PCOS group compared to the controls [19.3±12.5 vs. 12.5±9.6; p=0.01 and 5 (4.7-5.5) vs. 4.4 (4.2-4.8); p=0.0001, respectively].

The correlation between the AIx and echocardiographic parameters in the PCOS group is presented in Figure 1. Among the global LV function parameters, no correlation was found between AIx and LVEF (r=0.14, p=0.37), LV Tei index (r=-0.27, p=0.07), E/A (r=-0.23, p=0.14) and E/E' (r=0.21, p=0.17). Similarly, AIx was not correlated with RV FAC (r=-0.02, p=0.88), TAPSE (r=0.08, p=0.61), RV S' (r=0.19, p=0.22), and RV Tei index (r=0.03, p=0.81).

Table 1. Baseline clinical characteristics and laboratory findings

	PCOS, (n=42)	Controls, (n=32)	p-value
Age†	23 (21-25)	23 (21-27)	0.74
Body mass index*	24.5±5.3	23.7±5.2	0.77
Systolic blood pressure† (mmHg)	110 (98-125)	110.5 (104-129)	0.21
Diastolic blood pressure† (mmHg)	70.5 (68-80)	73 (70-80)	0.57
Glucose* (mg/dL)	93±5	91.7±6.8	0.07
Creatinine* (mg/dL)	0.8±0.12	0.78±0.12	0.54
AST† (U/L)	22 (16-29)	23 (16-30)	0.94
ALT† (U/L)	30 (25-35)	28 (25-31)	0.25
LDL-C* (mg/dL)	92.3±13.7	88.2±15.6	0.48
HDL-C† (mg/dL)	51 (45-60)	53.5 (48-62)	0.42
Total cholesterol* (mg/dL)	167±19	172±15	0.23
Triglycerides† (mg/dL)	117 (89-132)	122.5 (98-137)	0.16
Hemoglobin† (mg/dL)	12.8 (12.3-13.4)	12.7 (11.8-13.1)	0.42

*: Mean ± standard deviation, †: Median (interquartile range), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL-C: Low-density lipoprotein-cholesterol, HDL: High-density lipoprotein-cholesterol, PCOS: Polycystic ovary syndrome.

Table 2. Comparison of echocardiographic parameters between PCOS and control groups

	PCOS, (n=42)	Controls, (n=32)	p-value
LVEDD† (mm)	42 (41-44)	44 (40-47)	0.09
LVESD† (mm)	26 (25-28)	27 (25-31)	0.10
LVEF* (%)	64.7±6.3	62.7±7.8	0.21
LV mass* (gr)	111.7±27.6	111.8±25.8	0.20
LV E/A*	1.4±0.2	1.5±0.2	0.08
LV EDT† (msn)	190 (177-217)	193 (165-217)	0.72
LV E/E' ratio*	6.5±1.3	7.0±1.9	0.18
LV S'† (cm/s)	10.9 (10.4-11.2)	10.8 (10.3-12)	0.77
LV Tei index* (%)	39±8	40±8	0.50
Left atrial area† (cm^2)	16.1 (14.9-18.6)	18 (14.9-21)	0.20
RVd† (mm)	24 (23-26)	25 (24-26)	0.21
RV FAC* (%)	52.8±6.4	55.1±5.3	0.10
TAPSE* (mm)	22±2.7	22±2	0.94
RV S'* (cm/s)	16.6±2.5	17.4±3.7	0.25
RV Tei index* (%)	30±10	28±6	0.38
RV E'* (cm/s)	17.6±3.3	16.9±3.7	0.23
Right atrial area* (cm^2)	13.4±2.5	13.6±2.8	0.41

*: Mean ± standard deviation, †: Median (interquartile range). LVEDD: Left ventricular end-diastolic diameter, LVESd: Left ventricular end-systolic diameter, LVEF: Left ventricular ejection fraction, LV: Left ventricle, E: The early diastolic peak E wave, A: Atrial contraction wave, EDT: E wave deceleration time, S': Systolic velocity, RV: Right ventricle, E': Diastolic velocity, FAC: Fractional area change, TAPSE: Tricuspid annular plane systolic excursion, PCOS: Polycystic ovary syndrome.

The correlation between the AoPWV and echocardiographic parameters in the PCOS group are presented in Figure 2. Among the LV parameters, AoPWV was not correlated with LVEF (r=0.06, p=0.69), the LV Tei index (r=0.24, p=0.12), E/A (r=-0.24, p=0.12) or E/E' (r=-0.15, p=0.34). Similarly, AoPWV was not correlated with RV FAC (r=-0.16, p=0.32), TAPSE (r=0.04, p=0.79), RV S' (r=0.008, p=0.96), or the RV Tei index (r=-0.01, p=0.50).

DISCUSSION

Our study revealed that PCOS patients have increased peripheral AS despite preserved echocardiographic LV and RV functions even without the frequently associated traditional CV risk factors. AS parameters and echocardiographic measurements were not correlated among the PCOS subjects.

Previous reports have suggested that PCOS is linked with larger LA diameter, increased LV mass index, increased EDT, and E/E' ratio.[7-10]

Table 3. Comparison of arterial stiffness parameters between groups

	PCOS, (n=42)	Controls, (n=32)	p-value
AIx* (%)	19.3±12.5	12.5±9.6	0.01
AoPWV† (m/sn)	5 (4.7-5.5)	4.4 (4.2-4.8)	0.0001

*: Mean ± standard deviation, †: Median (interquartile range), AIx: Augmentation index, AoPWV: Aortic pulse wave velocity, PCOS: Polycystic ovary syndrome.

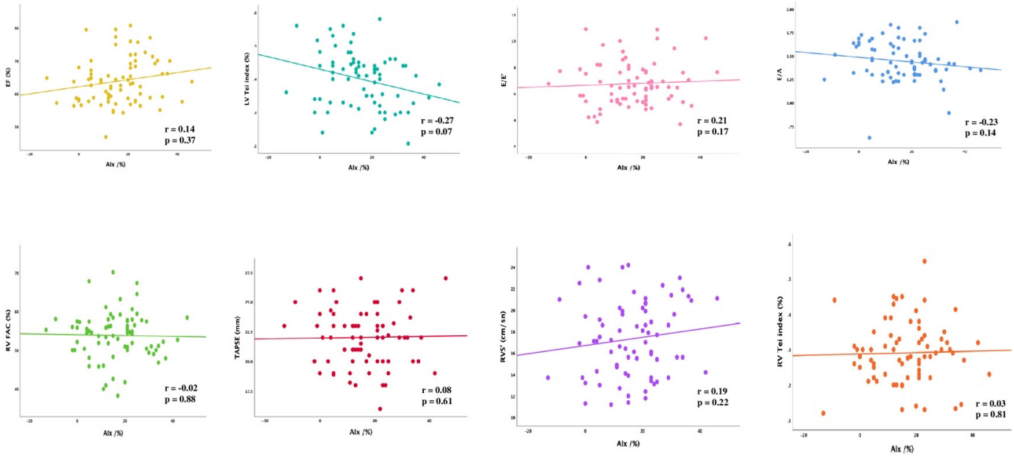

Figure 1. Correlations between AIx and LV and RV systolic and functions.

AIx: Augmentation index, LV: Left ventricular, RV: Right ventricular, FAC: Fractional area change, RV S': RV systolic, A: Atrial contraction wave, E: The early diastolic peak E wave, E': Diastolic velocity.

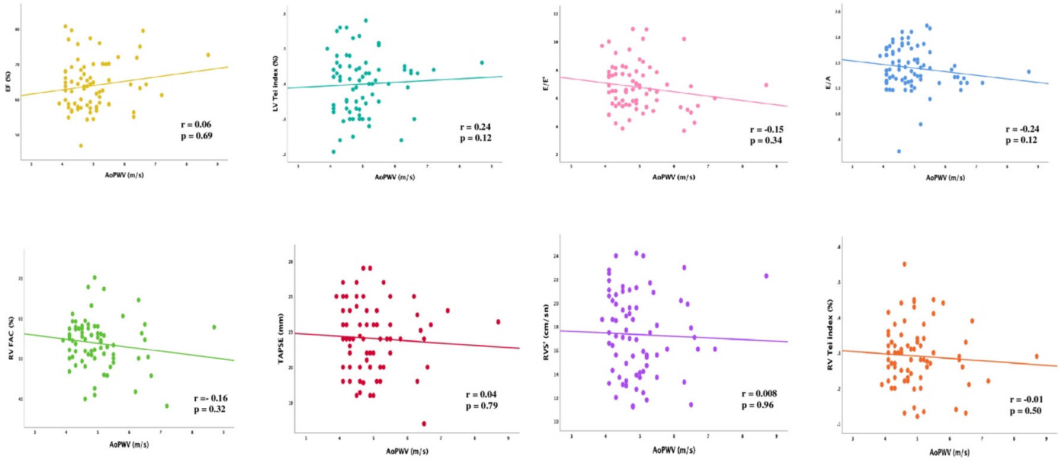

Figure 2. Correlations between AoPWV and LV and RV systolic and diastolic functions.

AoPWV: Aortic pulse wave velocity, LV: Left ventricular, RV: Right ventricular, FAC: Fractional area change, RV S': RV systolic, A: Atrial contraction wave, E: The early diastolic peak E wave, E': Diastolic velocity.

These changes in echocardiographic findings suggest abnormalities in the diastolic filling of the LV and impaired LV relaxation. Wang et al.[8] concluded that these women's increased LV mass index may correspond to early remodeling before overt cardiac dysfunction. However, similar to our discoveries, Tekin et al.[19] and Selcoki et al.[20] demonstrated no significant discrepancies in LV and LA diameters, LVEF, EDT, or E/A ratio between patients with PCOS and controls. The discrepancies between these results may have been associated with the underlying differences in BMI and insulin resistance in the different studies.

Previous research has demonstrated that BMI is a reliable predictor of LV E' dysfunction[21] and a reduction in BMI is linked to a substantial decrease in E' velocity and the LA volume index.[22] As the mean BMI in the patients of our study is lower than in the previous reports,[9,10] this may explain the conflicting results in impaired diastolic function in the PCOS group. We noted no differences in respect to LV mass between the PCOS and the control groups. Rashid et al.[7] revealed that non-obese, normotensive PCOS patients had considerably larger LV mass and LV mass index than the control group, but they also found considerable overlap in the values of serum insulin and impaired response to insulin and LV mass index. They concluded that the elevated LV mass index values in PCOS patients might be explained by the direct mitogenic effect of insulin.[7] The CARDIA Women's study[8] showed that LV mass index was increased in PCOS patients in comparison to controls, but the BMI values in that cohort were higher than in our population and the diagnostic criteria of PCOS were also different.

It has been shown that the Tei index is an easily measured and reliable method for evaluating both LV and RV S' and diastolic myocardial performance.[17,23] Unlike previous reports, we demonstrated that LV and RV Tei indices were similar between the PCOS and control groups. We also showed that RV functions in terms of RVFAC, RV S', RV E', and TAPSE were comparable between the two groups. To the best of our knowledge, this is the first preliminary report suggesting that both LV and RV E' and systolic functions were similar in PCOS patients and control subjects.

Controversial data exist concerning whether PCOS raises CV disease risk. A meta-analysis including more than 100,000 individuals suggested that PCOS was linked to elevated CV disease risks.[4] Additionally, a population-based retrospective analysis also showed that PCOS was associated with more ischemic heart disease.[5] In contrast, a discrete meta-analysis proposed that PCOS was linked to an elevated stroke risk but after adjusting for BMI, this observation was not statistically significant.[6] Based on the available data, PCOS should be regarded as an important CV risk factor.[24] AS has been demonstrated to be a robust biomarker of CV disease risk.[25,26] Measurements of AS demonstrate the earliest adverse functional and morphological abnormalities in the arterial wall. There are various methods in the literature to examine AS. Independent of other well-known CV factors, greater AoPWV has been demonstrated to be related to an elevated risk for future CV events.[26] Previous studies investigating AS in women with PCOS have demonstrated discordant results. In studies which adjust AS for blood pressure and BMI, the relationship between PCOS and increased AS was not statistically significant.[27,28] We demonstrated that peripheral AS was elevated in those subjects with PCOS in comparison to controls. Other studies which are in line with our results have revealed increased AS in subjects with PCOS.[11-14] The exact reasons for the differences between these results are not well-defined. Firstly, specificity and sensitivity to identify impaired vascular function in subjects with PCOS may differ depending on the measurements and indices. Secondly, slightly increased blood pressure levels in PCOS subjects may have affected the findings. Thirdly, other factors including insulin resistance and elevated plasma aldosterone are associated with vascular stiffness.[29] Finally, as the carotid-femoral PWV has the best predictive value for predicting future CV events and is the gold standard for AS assessment,[30] AS in PCOS patients may differ between carotid-femoral (central) and carotid-radial (peripheral) arteries, which might have resulted in these discrepant results.

In this present study, we showed that both carotid-radial PWV and AIx were elevated in the PCOS group. In a previous work conducted by Fruzzetti et al.[31], peripheral PWV and radial AIx were comparable between adolescent PCOS patients and control subjects. However, the patients included in their study were younger, which might explain the different results. PWV is recognized to linearly rise with advanced age and increased blood pressure in the general population.[32] Moreover, diabetes and metabolic syndrome are correlated with increased PWV.[33,34] The most important predictors of AS in PCOS patients were demonstrated to be hyperandrogenism and impaired response to insulin.[11,35] In this present study, we were unable to identify the possible mechanisms involved in increased peripheral AS in the PCOS group. Additional studies are warranted to demonstrate the associations between increased peripheral AS and PCOS.

Our results showed that AS parameters including AIx and AoPWV were not correlated with RV and LV E' and systolic functions in subjects with PCOS. A study conducted by Higashi et al.[36] concluded that in atherosclerosis-free healthy subjects, AS measured by brachial-ankle PWV and carotid AIx was significantly associated with E' in both males and females and E/E' solely in females. The participants in our study were younger than those in the prior study, had lower values of AIx, and had lower diastolic and systolic blood pressures. These divergencies in baseline features and AS parameters might account for the differences in correlations.

Study Limitations

The limitations of this study were as follows; firstly, our study cohort had low BMI, younger age, normal diastolic and systolic blood pressures, and low plasma lipids, which may not represent an exact PCOS patient population. Secondly, as we used a cross-sectional sample, we could only establish an association between AS and PCOS. Thirdly, the echocardiographic data were limited to 2D, PW, and TD measurements and did not include more reliable speckle-tracking echocardiography and volumetric measurements. Fourthly, we could not demonstrate the effects of androgens, sex hormones, or ovulation time on AS parameters. Finally, the lack of assessment of insulin resistance and central AS may have affected our results. However, radial AIx was strongly correlated with carotid AIx in apparently healthy subjects, and radial AIx is a potential alternative marker of CV disease.[37]

CONCLUSION

This research revealed that females with PCOS have normal LV and RV diastolic and systolic functions, specifically presented with LV and RV Tei indices. These women also have increased peripheral AS despite the lack of commonly associated traditional CV risk factors and obesity. Future research is warranted to determine if PCOS individuals with higher peripheral AS and no risk factors are at an elevated risk of future CV events.

MAIN POINTS

- This study demonstrated that both left ventricular and right ventricular global (both systolic and diastolic) functions are preserved in young, cardiovascular risk factors-free PCOS patients with respect to control subjects.
- This is the first study which applies both left and right ventricular myocardial work quantification by echocardiography through the Tei index in PCOS patients.
- The literature presents limited data on the associations between PCOS and carotid-radial (peripheral) arterial stiffness. We studied carotid-radial (peripheral) arterial stiffness in PCOS patients and compared both arterial stiffness and echocardiographic parameters with control subjects.
- We also revealed correlations between peripheral arterial stiffness and echocardiographic parameters.

ETHICS

Ethics Committee Approval: Our study was authorized by the Dokuz Eylül University Ethical Examination Board (approval number: 2022/33-11, date: 19.10.2022).

Informed Consent: All participants provided their written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç., M.E.Ö., R.E.O., Z.K., E.Ö., Concept: A.Ç., M.E.Ö., E.Ö., Design: A.Ç., Z.K., E.Ö., Data Collection and/or Processing: A.Ç., R.E.O., E.Ö., Analysis and/or Interpretation: A.Ç., E.Ö., Literature Search: A.Ç., M.E.Ö., R.E.O., Z.K., E.Ö., Writing: A.Ç., R.E.O.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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Patient Measure of Safety Scale: The Study of Adapting the 30 and 10-Item Form to Turkish

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Abstract

BACKGROUND/AIMS: Patients are an important source of information in reducing preventable harm that improves healthcare. Therefore, it is important to know the perceptions and thoughts of patients regarding the safety of health services. The aim of this study was to adapt the 10 and 30-item forms of the Patient Safety Precautions Scale (PMOS) to Turkish culture.

MATERIALS AND METHODS: The methodologically-designed study was conducted with 426 patients. To adapt PMOS to Turkish culture, language and content validity and construct the validity of scale were examined, and then reliability coefficients were calculated.

RESULTS: The overall Cronbach's alpha coefficient of scale was found to be 0.933 for PMOS-30 and 0.835 for PMOS-10. The mean scores of items ranged from 3.38±1.31 to 4.65±0.65. The item-total correlation values of items in the scale ranged from 0.427-0.883 for PMOS-30 and 0.435-0.859 for PMOS-10. The structure formed for PMOS-30 and PMOS-10 forms explains 76.620% and 57.260% of the total variance, respectively.

CONCLUSION: The Turkish version of the PMOS-10 and 30 scale is a valid and reliable tool. Hospitals can plan initiatives for safety improvements based on the findings from the PMOS-30 and PMOS-10 questionnaires.

Keywords: Patient safety, safety culture, patient involvement, patient feedback, hospital safety

INTRODUCTION

For all health systems in the world, patient safety is a crucial global public health issue. It is the basis of healthcare delivery and necessary to advance to a universal level of healthcare.[1] Patient safety requires intense organizational responsibility to prevent possible errors or when an error occurs, to identify, analyze, and correct them. All employes are responsible for identifying high-risk situations and reducing the hazards of undesirable incidents before errors occur.[2] Together with the responsibilities of healthcare professionals concerning patient safety, patient feedback and patient satisfaction regarding their care are crucial for ensuring patient safety and healthcare quality.[3,4] Patients can provide a unique perspective on safe care in hospitals. The relationship between hospitals' quality and safety practices (e.g. provision of resources, processes, practices, hospitalization, readmission, mortality, etc.) with patients' perceptions of care is very significant and becoming increasingly important for health systems to plan their interventions toward quality goals.[5,6]

It has been suggested in literature that current patient safety initiatives tend to reflect a narrow perspective that does not include perspective of patients and that there may be an inconsistency between these two.[7] Recent studies examining patients perspective on patient safety have shown that safety is different in their perspective.[8,9] Qualitative research has been conducted in hospitals to investigate the meaning of feeling safe to learn patients' perspectives, perceptions and experiences with respect to clinical safety. Results of these studies showed that patients' understanding of safety was different from that of health professionals. Safety for patients encompasses not only "error-free" but also continuity of care, psychological support, trust, effective communication and

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information to ensure safety in the clinical setting.[10,11] Therefore, it is critical to involve patients and their relatives in patient safety practices in order to increase awareness of patient safety issues and to raise public awareness.[12] However, public knowledge of patient safety is insufficient. Recently, the role of patients, who are most directly affected by patient safety, on patient safety has begun to be investigated. For example, patients must ensure that their medications are prescribed correctly for drug safety. They should be informed about the effects and side effects of drugs. Research has shown that the patient involvement is effective in preventing medication errors and side effects.[13] The Healthcare Research and Quality Agency has provided guidelines to patients to prevent medication errors and medication side effects as well as to minimize the risk of medical errors during hospitalization and surgery.[14]

To support patient participation, which is very important in ensuring patient safety and developing existing patient safety practices, it is necessary to determine the perception of safety of patients first. Patient participation in safety is receiving increasing attention internationally and is an evolving field. In recent years, various tools and guidelines have been developed to improve patient safety using a patient-centered perspective.[15] To increase patient safety in the hospital environment, most of these tools and guidelines are designed to evaluate patient feedback.[16] In Türkiye, there is no tool for patients to evaluate the health care they received. The Patient Safety Precautions Scale (PMOS) is the first questionnaire structured to measure patient perception of safety. PMOS was originally developed as 44 items.[4,16] Two shorter versions of the scale were created by Louch et al.[17]: PMOS-10 and PMOS-30. In this context, the aim of the research is to adapt the 10 and 30-item forms of the Patient Measures of Safety Scale to Turkish culture.

MATERIALS AND METHODS

Study Design

The methodologically designed study was conducted in two public hospitals located in the southern region of Türkiye. Research data were collected between February and June 2022.

Participants

All services except intensive care units, psychiatry, and coronavirus disease-2019 (COVID-19) isolation services were included in the research in the institutions where the research was conducted. In scale adaptation studies, it is recommended to take 10-15 people per item, or the sample should be at least 300-500 people according to International Test Commission guidelines. In this study, the scale consisted of 30 items, and 426 people participated in the study.

Inclusion criteriawere at least 18 years old and able to speak Turkish and patients hospitalized for at least three days.

Exclusion criteria: patients with cognitive impairment, psychiatric, and terminal illness were not included in the study.

Data Collection Forms

Patient Measures of Safety-PMOS-30-10 is a newly structured questionnaire designed to measure patient safety perception.[17] The questionnaire consists of three parts; the first part contains the Turkish version of Patient Measures of Safety-30 and 10 questionnaires. Scale, 30 items and organization and care planning; access to resources; communication and teamwork; ward type and layout; information flow; staff roles and responsibilities; staff education; equipment and delays consists of eight sub-dimensions with main headings. All items were measured using a 5-point Likert scale. The "I prefer not to answer/I do not know" option is also available. Items 4, 9, 15, 16 18, 19, 22, 23 and 29 in the scale are negative and reverse-coded. The patient's perceptions of patient safety are high when there is an increase scores of scale and sub-dimension. In addition, 30-item scale has a short form of 10 items (items 3, 4, 5, 11, 13, 14, 19, 25, 28 and 29) and consists of one dimension. The second part consists of two other items that are not included in the scale. It evaluates patients general perception of safety with two direct questions and one open-ended question; "How do you evaluate safety of this hospital?"; "Have you noticed any incidents that may harm patients?" (yes or no); "If yes, please explain" (open-ended question). In the third section, there is a socio-demographic characteristic form.

Language and Scope Validity

To avoid problems that may be related to translation, scale items were translated into Turkish by the researchers and three native English language experts who are fluent in both languages, knowledgeable in culture and terminology, and in Turkish. Researchers selected the most appropriate expressions from Turkish translations of questionnaire items and created a Turkish questionnaire and presented it to 10 experts. Language suitability, clarity, and intelligibility of each item for Turkish society were evaluated by the experts. The PMOS was given its final form in line with recommendations of the experts. For this, the original and its Turkish translation of the scale was presented to the expert group, and experts were asked to select one of the answers "not suitable (1)", "the item needs to be adjusted (2)", "appropriate but a small change is required (3)" or "very suitable (4)". The Davis technique was used to calculate the content validity ratios of scale items and content validity index of scale. In this index, content validity rates of items and content validity index of scale are expected to be above 0.80. In this study, the scope validity index value was found to be "0.90" for 7 items and "1" for the other 23 items. Scale was translated back into English by a Turkish linguist who had not seen the English version of the questionnaire before, knew both languages and cultures well, and was sent back to Gemma Louch and her approval was obtained. After going through the stages, it took its final form in Turkish.

Data Collection

During the data collection process, researchers visited hospitals every week and evaluated each clinic every three days, and patients who were hospitalized for at least three days were included in the study. Patients were requested to sign an informed consent form. Questionnaires were collected by the researcher in the form of distribution and retrieval using the sealed envelope method.

Ethical Considerations

First, permission was obtained from the scale owner, Gemma Louch. Ethics board permission was received from the Ethics Committee of the Akdeniz University Faculty of Medicine (approval number: KAEK-871, date: 01.12.2021) and permission of the institutions where the study was to be conducted was obtained. In addition, informed consent was obtained from patients who were to participate in the study.

Statistical Analysis

SPSS 23.0 and AMOS 20.0 package programs were used in data analysis. The mean and standard deviations for each item of the Turkish version of the questionnaire and weighted average were calculated. The Davis technique was used to calculate the language content validity index of the scale; exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were used for construct validity; and the Cronbach's alpha value was used for the internal consistency reliability test. The confidence interval was set at 95% and the significance level was $p<0.05$.

RESULTS

Socio-Demographic Results

The average age of the participants in the study is 35.80±9.98, 59.2% were women, 24.4% were primary school graduates, 57.4% lived in the district, 65.3% had income equal to their expenses, and 62.4% did not work. 46.9% of the participants rated safety of the hospital as good, and two people stated that they noticed an incident that could harm patients (Table 1).

Table 1. Some descriptive features of the participants (n=426)

Specifications	n	%
Gender		
Woman	252	59.2
Male	174	40.8
Educational status		
Literate	70	16.5
Primary school	104	24.4
Middle school	84	19.7
High school	92	22.6
University	76	17.8
Where he/she lives		
Province	8	1.9
District	330	77.4
Village	88	20.7
Income status		
Income less than expenses	24	5.6
Income equals expense	278	65.3
Income more than expenses	124	29.1
Employment status		
Working in the public/private sector	88	20.7
Self-employed	72	16.9
Unemployed	266	62.4
Overall patient perception of safety		
Bad	34	8.0
Sufficient	192	45.1
Good	200	46.9
Have you noticed any events that could have caused harm to patients?		
No	424	99.5
Yes	2	0.5
	Min.-Max.	**Mean ± SD**
Age	19-60	35.80±9.98

Min.: Minimum, Max.: Maximum, SD: Standard deviation.

Item Analyses

Within the scope of adapting PMOS to Turkish culture, construct the validity of scale was first examined and then the reliability coefficients were calculated. The item analysis results of PMOS are shown in Table 2. The mean scores of items ranged from 3.38±1.31 to 4.65±0.65. The item-total correlation values of items in the scale vary between 0.427-0.883 for PMOS-30 and 0.435-0.859 for PMOS-10. Overall Cronbach's alpha coefficient of scale was determined as 0.933 for PMOS-30, and when item was deleted, Cronbach's alpha coefficients varied between 0.926 and 0.934. Cronbach's alpha coefficient for PMOS-10 was determined as 0.835, and when item was deleted, it was seen that Cronbach's alpha coefficients varied between 0.783 and 0.835.

Table 2. Item analysis results of patient measure of safety (PMOS-30 and 10)

		PMOS-30		PMOS-10	
Items	**Mean ± SD**	**Item total correlation**	**When the item is deleted Cronbach' alpha**	**Item total correlation**	**When the item is deleted Cronbach' alpha**
Item 1	4.62±0.68	0.598	0.930		
Item 2	4.33±0.78	0.574	0.931		
Item 3	4.25±0.59	0.534	0.931	0.628	0.825
Item 4	4.12±1.14	0.480	0.931	0.458	0.833
Item 5	4.60±0.60	0.661	0.930	0.797	0.816
Item 6	4.15±1.23	0.817	0.927		
Item 7	4.63±0.68	0.570	0.931		
Item 8	**4.65±0.65**	0.615	0.930		
Item 9	4.21±0.95	0.561	0.931		
Item 10	4.61±0.70	0.570	0.931		
Item 11	4.59±0.72	0.565	0.931	0.681	0.811
Item 12	4.42±0.78	0.856	0.928		
Item 13	4.43±0.77	0.883	0.928	0.859	0.783
Item 14	4.35±1.11	0.576	0.930	0.635	0.829
Item 15	3.66±1.22	0.579	0.931		
Item 16	3.75±1.32	0.527	0.931		
Item 17	**3.38±1.31**	0.564	0.931		
Item 18	3.53±1.30	0.578	0.931		
Item 19	3.81±1.20	0.569	0.931	0.435	0.835
Item 20	4.15±1.27	0.813	0.927		
Item 21	4.14±1.28	0.817	0.926		
Item 22	3.62±1.28	0.427	0.934		
Item 23	3.76±1.27	0.435	0.933		
Item 24	4.26±1.17	0.715	0.928		
Item 25	4.16±1.21	0.749	0.928	0.795	0.815
Item 26	4.28±1.18	0.674	0.929		
Item 27	4.13±1.30	0.717	0.928		
Item 28	4.21±1.29	0.647	0.929	0.641	0.827
Item 29	3.90±1.15	0.619	0.929	0.683	0.810
Item 30	4.10±1.22	0.787	0.927		

PMOS-30: Patient Safety Precautions Scale-30, SD: Standard deviation.

Exploratory Factor Analysis

Adequacy of the research sample for factor analysis was tested with Kaiser-Meyer-Olkin (KMO) analysis, and its suitability for factor analysis was tested with Bartlett's test of Sphericity (BTS) analysis. The KMO coefficient was 0.939 for PMOS-30 and 0.891 for PMOS-10, and the BTS result was found to be significant (p=0.001). EFA was performed to examine the factor structure of the scale after determining these data were applicable to factor analysis. According to factor rotation results in the investigation of PMOS-30, it was determined that there were eight components with an eigenvalue above 1 for 30 items. For PMOS-10, there was only one structure with eigenvalue greater than 1 and scale items showed single-factor structure. Structure formed for PMOS-30, and PMOS-10 forms explains 76.620% and 57.260% of total variance, respectively. Factor loads of the sample ranged from 0.565-0.947 for PMOS-30 and 0.623-0.895 for PMOS-10 (Table 3).

Table 3. Explanatory factor analysis results regarding the patient measure of safety (PMOS-30 and 10)

	PMOS-30 item								PMOS-10 item
KMO	0.939								0.891
χ^2 (15)	16994.650								12948.016
p	0.001								0.001
Items	F1	F2	F3	F4	F5	F6	F7	F8	F1
Item 1	0.920								
Item 2		0.923							
Item 3	0.924								0.729
Item 4		0.878							0.830
Item 5					0.615				0.817
Item 6						0.935			
Item 7							0.932		
Item 8								0.947	
Item 9				0.778					
Item 10				0.733					
Item 11				0.722					0.766
Item 12						0.797			
Item 13	0.823								0.895
Item 14							0.785		0.746
Item 15				0.744					
Item 16				0.565					
Item 17				0.626					
Item 18				0.704					
Item 19	0.615								0.635
Item 20						0.867			
Item 21								0.891	
Item 22		0.656							
Item 23			0.584						
Item 24	0.890								
Item 25		0.924							0.850
Item 26						0.887			
Item 27			0.898						
Item 28	0.910								0.783
Item 29			0.702						0.623
Item 30					0.863				
Explained variance (%)				76.620				57.260	

PMOS-30: Patient Safety Precautions Scale-30, KMO: Kaiser-Meyer-Olkin.

Confirmatory Factor Analysis

In CFA, the eight-factor structure of PMOS-30 and the one-factor structure of PMOS-10 were tested and the goodness of fit statistics were examined. The goodness of fit index values in the sample are given in Table 4 for both forms of the scale and it is seen that the established models give acceptable goodness of fit index values.

Reliability Analysis

Participants mean PMOS-30 score was 125.61±18.86 and mean PMOS-10 score was 42.84±6.08. In study, Cronbach's alpha values for eight sub-dimensions of PMOS-30 were determined as between 0.660 and 0.936. Cronbach's alpha value for the total scale was 0.933; the PMOS-10 Cronbach's alpha value was determined as 0.835 (Table 5). Pearson correlation coefficient between long and short forms of the scale was 0.964 (p=0.001). All reciprocal correlations of total and eight sub-dimensions of the PMOS-30 scale were medium and high, positive and statistically significant (p<0.001) (Table 6).

DISCUSSION

The current study investigated the reliability and validity of the Patient Safety Measures-PMOS:30 and 10 Item-Form, a tool that allows patients to identify safety risks in hospital settings. The results of the study show that scales have acceptable validity and reliability and that each construct is adequately represented. Patient safety is a multidimensional concept. PMOS-30 assesses eight key areas of patient safety.[16]

Table 4. Confirmatory factor analysis results of PMOS-30 and PMOS-10

Fit indices	χ^2/df	p	CFI	SRMR	RMSEA	TLI
PMOS-30	4.812	<0.001	0.948	0.047	0.051	0.935
PMOS-10	4.125	<0.001	0.954	0.041	0.046	0.961
Good fit	<2	-	>0.97	<0.05	<0.05	>0.95
Acceptable fit	<5	-	>0.90	<0.08	<0.08	>0.90

PMOS-30: Patient Safety Precautions Scale-30, CFI: Comparative fit index, SRMR: Standardized root mean square residual, RMSEA: Root mean square error of approximation,TLI: Tucker-Lewis Index.

Table 5. Sub-dimensional values and reliability analysis results of patient measure of safety (PMOS-30 and 10)

Variables	Question number	Total, Mean ± SD	Item, Mean ± SD	Cronbach's alpha
PMOS-30	30	125.61±18.86	4.18±0.62	0.933
Communication and teamwork	6	25.97±3.51	4.32±0.58	0.812
Organization and care planning	4	16.53±2.73	4.13±0.68	0.660
Access to resources	3	11.80±2.67	3.93±0.89	0.723
Ward type and layout	7	27.78±4.50	3.96±0.64	0.871
Information flow	2	8.71±1.66	4.35±0.83	0.851
Staff roles and responsibilities	4	17.01±4.15	4.25±1.03	0.936
Staff training	2	8.99±1.68	4.49±0.84	0.898
Delays	2	8.79±1.72	4.39±0.86	0.791
PMOS-10	10	42.84±6.08	4.28±0.60	0.835

PMOS-30: Patient Safety Precautions Scale-30, SD: Standard deviation.

Table 6. Sub-dimensional correlation values of the Patient Safety Perception Scale

Scales		1	2	3	4	5	6	7	8	9	10
PMOS-30 items	r	-									
	p										
Communication and teamwork	r	0.953									
	p	0.001									
Organization and care planning	r	0.852	0.763								
	p	0.001	0.001								
Access to resources	r	0.837	0.750	0.744							
	p	0.001	0.001	0.001							
Ward type and layout	r	0.740	0.632	0.715	0.637						
	p	0.001	0.001	0.001	0.001						
Information flow	r	0.844	0.838	0.633	0.655	0.574					
	p	0.001	0.001	0.001	0.001	0.001					
Staff roles and responsibilities	r	0.869	0.876	0.622	0.680	0.580	0.905				
	p	0.001	0.001	0.001	0.001	0.001	0.001				
Staff training	r	0.747	0.699	0.539	0.658	0.676	0.650	0.632			
	p	0.001	0.001	0.001	0.001	0.001	0.001	0.001			
Delays	r	0.870	0.859	0.613	0.606	0.625	0.842	0.881	0.830		
	p	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001		
PMOS-10 items	r	0.964	0.948	0.802	0.804	0.744	0.844	0.851	0.784	0.875	-
	p	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	

PMOS-30: Patient Safety Precautions Scale-30.

Construct validity was used for the validity of the scales in our study. Therefore, EFA and CFA were performed. Before EFA, the KMO value and Bartlett test results were examined in terms of sample adequacy. If KMO measurements of 0.80 and above are obtained, this result shows that the sample adequacy of the factor analysis data is sufficient. The results of the Bartlett test show that items in scale are suitable for factor analysis.[18] Accordingly, the KMO test results for PMS-30 and PMS-10 were found to be 0.939 and 0.891, respectively, and the BTS test results were found to be significant in this study, showing that the sample size of the study was sufficient for factor analysis. The varimax rotation technique, which is one of the most commonly used vertical rotation techniques were used in EFA.[19] Higher the total variance explained by the factors in the analysis, stronger factor structure of the scale.[20] At least 30% of the total variance is expected to be explained in single-factor scales. It should be higher than 30% in multi-factor structures.[19] The eight-factor structures that arise on the PMOS-30 scale (76.62%) and one-factor structures that arise on the PMOS-10 scale (57.26%) account for the majority of the total variance. Therefore, it can be said that the factor structure is strong. The first criterion of factor analysis is that load values of items in factors are high. In the literature, it is stated that items with a correlation value below 0.30 are insufficient, items with a correlation value between 0.30-0.40 can be included in the scale, and items with a value above 0.40 have good distinguishing features.[21] In our study, it was found that there was no item with correlation value less than 0.30 and the lowest value was 0.565 for PMS-30 and 0.623 for PMS-10. In the next step, CFA was applied and the eight-factor structure of the PMOS-30 measurement tool and the one-factor structure of the PMOS-10 were tested. CFA provides information about whether the factors have sufficient relationships, whether the factors are independent from each other, which variables are related to which factors, and whether the factors are sufficient to explain the model.[19,22] In this respect, the eight-factor structure of the PMOS-30 is in an acceptable level in general with the collected data, and the eight-factor structure of the scale is confirmed. It is understood that the single-factor structure of PMOS-10 shows acceptable level of agreement with the collected data and this structure is confirmed.

Reliability analysis determines how accurately the scale measures the concept it represents and how consistent the answers given to the scale items are.[22] Cronbach's alpha coefficient was calculated to test internal consistency for reliability. The higher alpha coefficient, the higher internal consistency of the scale. The alpha coefficient should be between 0.60 and 0.80 to verify the reliability of the scale. However, if the alpha coefficient is between 0.80 and 1.00, the scale has a high level of reliability. A coefficient close to 1 indicates that the scale has a high level of internal consistency reliability.[19] The fact that the Cronbach's alpha value was 0.83 in both scales in this study indicated that the study was highly reliable. The two subdimensions with the lowest alpha coefficient are "Organization and maintenance planning" (0.660) and "Access to resources" (0.723). It can be said that these two subdimensions are quite reliable. In the original study of the scale, PMOS-30, (α=0.89) and PMOS-10 (α=0.79) were found to have good internal reliability. Measurements performed showed good reliability and validity and retained the psychometric properties of the original scale.[17] The validity and reliability of the PMOS questionnaire has been confirmed in studies in Australia,[5] Italy[23] and Iran.[24] The Persian version of PMOS validated in Iran has been identified as an appropriate tool for patients in Persian communities to assess their safety.[24]

In general, according to the results of the PMOS-30 questionnaire, the lowest average was "Temperature" (item: 17, mean: 3.38) and all averages were 4 except for "access to resources" (3.93) and "ward type

and layout" (3.96) fields. In the study, patients mostly agreed with the item "My treatment/procedure/operation always happened on time". The rate of patients' agreement with the item "Temperature" is at the lowest level. It is suggested that such a result was obtained because the institutions where the research was conducted are in the hottest region of Türkiye (summer average 40-45 °C). In the study, the general safety perception of patients was at a satisfactory level. Only 34 patients rated safety as badorvery bad. They cited 20 incidents that could cause harm. In a study by Schiavone et al.[23], patients' overall perception of safety was found to be satisfactory, and only 24 patients rated safety as bad/very bad. Thirty-one incidents that could cause harm have been identified.[23] These results are similar to our study.

The Patient Measures of Safety Scale is the first tool developed to systematically and routinely collect information from patients about the safety of their care.[16] This scale allows the healthcare service to proactively identify its strengths and weaknesses when it is used at the clinical level. In addition, it may be a guide for planning necessary initiatives to prevent errors from occurring. More knowledgeable patients with ongoing treatments, especially those who become familiar with the details of their treatment, may be more aware of errors or delays.[25] PMOS is a tool that guides how patients can fulfill this role and can reveal valuable data about improving patients' safety.[4] In terms of developing new methods to improve safety by evaluating patient safety and contributing factors in hospital settings from the perspective of patients, the current study is of vital importance. Current information on quality and safety comes mainly from the reports of healthcare professionals, but incident reporting systems suffer from under-reporting.[4,17] PMOS-30 or 10 might be used in addition to such other patient safety tools as incident reporting systems. By providing a mechanism for the systematic collection of this information, it might be helpful for healthcare organizations in their organizational learning.

Study Limitations

Being conducted with a patient population in only two hospitals is the most significant limitation of the study. Therefore, the tool needs to be used with larger patient populations. Besides, since this questionnaire administered to inpatients may be known to the staff, patients may hesitate to identify undesirable conditions. In this case, there might be a deficiency in incident reports/notifications.

CONCLUSION

According to the results of this study, PMOS-30 and 10 scales showed acceptable reliability and validity. PMOS might help to systematize the process of obtaining safety feedback from patients as part of patient safety practices. Using PMOS questionnaires, healthcare administrators can identify initiatives to improve safety and healthcare quality in hospital settings. For future research, it is recommended to investigate differences between clinics in different hospitals, to identify missing and erroneous situations, and to conduct interventional studies.

MAIN POINTS

- Measuring patients' perception of safety can contribute to the development of a safety culture.
- Patients' perceptions of safety can improve service quality and providing cost-effective care.
- Involving patients in reporting adverse events can help identify safety culture gaps and reduce medical errors.

ETHICS

Ethics Committee Approval: Ethics board permission was received from the Ethics Committee of the Akdeniz University Faculty of Medicine (approval number: KAEK-871, date: 01.12.2021) and permission of the institutions where the study was to be conducted was obtained.

Informed Consent: In addition, informed consent was obtained from patients who were to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ü., A.S., Design: A.Ü., A.S., Data Collection and/or Processing: A.Ü., A.S., Analysis and/or Interpretation: A.Ü., A.S., Literature Search: A.Ü., A.S., Writing: A.Ü., A.S.

DISCLOSURES

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RESEARCH ARTICLE

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The Effects of Propofol and Ketofol on Hemodynamics, End-Tidal Carbon Dioxide, Integrated Pulmonary Index and Recovery in Patients Undergoing Endoscopy and Colonoscopy

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Abstract

BACKGROUND/AIMS: In this study, we aimed to compare the effects of propofol and ketofol on hemodynamics, end-tidal carbon dioxide ($EtCO_2$), integrated pulmonary index (IPI), peripheral oxygen saturation (SpO_2) and sedation quality during endoscopy and colonoscopy performed under anesthesia.

MATERIALS AND METHODS: One hundred patients aged 18-79 years with American Society of Anesthesiology class I-III were randomly divided into two groups: the propofol group (1%) and the ketofol mixture group (group P and group K, respectively). Sedation was achieved with 0.15 mL/kg doses of both drugs, followed by additional 0.05 mL/kg doses based on the patients' Ramsey Sedation Scores. Before the procedure, the basal values of heart rate (HR), $EtCO_2$, IPI, and SpO_2 were obtained, as well as instantaneous trend data. systolic blood pressure, diastolic blood pressure, and mean blood pressure values were recorded prior to the procedure (baseline values), at the 1st, 5th, 10th, 15th, 25th, 30th minutes, and at the conclusion of the procedure. The duration of anesthesia and the procedure, the amount of propofol administered, the rate of spontaneous eye opening, and recovery parameters were also recorded.

RESULTS: The mean blood pressure values at the 1st, 5th, 10th, 15th, 20th minutes, at the end of the intervention, and at the 5th minute after the procedure were found to be higher in group K compared to group P. HR, SpO_2, $EtCO_2$ and IPI values were higher in group K than in group P. Time to spontaneous eye opening was significantly lower in group K compared to group P. In addition, the recovery period during which the modified Aldrete score was >9 did not differ between groups. Additional doses and total propofol consumed during the procedure were significantly lower in group K than in group P.

CONCLUSION: Ketofol appears superior to propofol in endoscopic procedures due to its superior hemodynamic and respiratory stability, without affecting recovery time. Incorporating non-invasive $EtCO_2$ and IPI measurements into standard respiratory monitoring equipment improves monitoring quality and facilitates its execution.

Keywords: Colonoscopy, endoscopy, ketamine, propofol, pulmonary, sedation

INTRODUCTION

One of the most common non-operating room anesthesia applications involves endoscopic procedures of the gastrointestinal system (GIS). Short-acting anesthetic medications without side effects should be preferred, as these procedures are performed daily.[1,2] Propofol is one of the most frequently administered intravenous anesthetics currently available. It is utilized extensively both inside and outside

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the operating room. It is superior to other anesthetic agents such as thiopental, benzodiazepines, and opioids due to its rapid recovery, minimal residual effects on the central nervous system, and antiemetic properties. In recent years, it has been favored for use as the sole anesthetic agent during endoscopic procedures.[3] When propofol is used as the sole anesthetic agent, high doses may be necessary in order to achieve the level and quality of sedation necessary for this procedure. However, high doses of propofol may increase the likelihood of anesthesia-related adverse effects. Therefore, various drugs, such as ketamine, lidocaine, and dexmedetomidine, are used in order to reduce the required dose of propofol.[4,5]

Ketamine, on the other hand differs from other anesthetic agents because it does not have a depressant effect on the cardiovascular and respiratory systems, and yet it has analgesic properties.[6] When propofol and ketamine are combined, the deficiencies in the efficacy of propofol are compensated for by the sympathomimetic and analgesic effects of ketamine, and the side effects of ketamine, such as nausea, vomiting, and psychomimetic effects, are mitigated by the antiemetic and potent hypnotic effects of propofol. Previous research has demonstrated that the combination of ketamine and propofol in the same syringe (ketofol) leads to more stable hemodynamics and reduces the likelihood of side effects.[7]

Ensuring patient safety during anesthesia applications outside of the operating room remains an important concern, and there is a need for new monitoring methods which will contribute to standard monitoring during such procedures. The integrated pulmonary index (IPI) is a numerical value which combines four important parameters measured by noninvasive end-tidal carbon dioxide ($EtCO_2$) monitoring in order to provide a straightforward indication of the patient's ventilation status. $EtCO_2$, respiratory rate, oxygen saturation (SpO_2), and heart rate (HR) are these integrated parameters.[8] Consequently, IPI combines the advantages of ventilation monitoring and oxygenation monitoring and may be used as a simple and portable device for monitoring patients during sedation, as it may enable the earlier detection of problems in comparison to conventional monitoring. Additional ventilation status monitoring with capnography decreases the incidence of respiratory depression and hypoxemia.[9,10]

The primary aim of this study was to compare the effects of propofol and ketofol on hemodynamics during endoscopy and colonoscopy under anesthesia. The secondary objective was to compare their effects on respiratory parameters using the new monitoring techniques of $EtCO_2$ and IPI. In addition, the quantity and quality of sedation were also recorded. Our hypothesis is that ketofol will produce superior hemodynamic, respiratory, and sedative outcomes compared to propofol alone.

MATERIALS AND METHODS

Study Design

This double-blind, randomized, prospective study was conducted in the Anesthesiology and Reanimation and Gastroenterology Clinics of the University of Health Sciences Türkiye, Samsun Training and Research Hospital (approval number: 2019/4/32, date: 01.01.2020-01.07.2020), after approval by the Local Ethics Committee (Clinical Research Ethics Committee of University of Health Sciences Türkiye, Samsun Training and Research Hospital) and the Medicines and Medical Devices Agency (19-AKD-123). This study adhered to the Declaration of Helsinki and written informed consent was obtained from each participant.

Study Population

After obtaining informed consent, one hundred American Society of Anesthesiology (ASA) I, II, and III patients aged 18 to 70 who underwent elective upper GIS endoscopy and colonoscopy were included in this study. The following patients were excluded: those who did not consent to inclusion in this study, patients with a history of allergy to any medications used in this study, those with uncontrolled hypertension, severe renal, hepatic, cardiovascular, and respiratory system disease, those patients with a history of epilepsy, those with intracranial space-occupying lesions, patients who were pregnant, patients with severe neuropsychiatric disorders, and those with a body mass index >30.

Setting

The closed envelope method was used to randomly assign patients into two groups consisting of 50 patients each: group P (propofol) and group K (ketofol). The same gastroenterologist performed all endoscopy and colonoscopy procedures, and the same anesthesiologist administered sedoanalgesia to all patients. Our study was designed to be double-blinded and accordingly the patient, the anesthetist, and the gastroenterologist were unaware of which anesthetic medication would be administered.

Preparation of Ketofol and Propofol

100 mg of ketamine (2 mL of 50 mg/mL Ketalar; Pfizer, Zentiva, Türkiye) and 200 mg of propofol (10 mL of 2% propofol Lipuro; Fresenius Kabi GmbH, Austria) were withdrawn into a 20 mL syringe to complete the total volume to 20 mL. Thus, a mixture of 10 mg/mL propofol + 5 mg/mL ketamine was obtained (mixture with 2:1 ratio).

The preparation of propofol; 10 mg/mL propofol was prepared by withdrawing 1% propofol-Lipuro (10 mL of 2% propofol Lipuro; Fresenius Kabi GmbH, Austria) from the ampoule into a 20 mL syringe.

Preparation Before Endoscopy

Patients fasted for 8 hours before the procedure. Their demographic information such as their age, gender, body weight, and height were recorded upon admission. Oxygen (2-4 L/min) was administered via nasal cannula. After the patients were taken to the endoscopy room, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP), respectively, SpO_2 and $EtCO_2$ monitoring was initiated. The mixture of medications in the syringe, prepared by the anesthesiologist in charge of this study, was administered to the patient as a 0.15 mL/kg IV push by the anesthetist following the patient. After the response to verbal stimuli decreased and the corneal reflex disappeared, the gastroenterologist was allowed to begin the procedure. During the procedure, the degree of the patients' sedation was targeted to be >4 according to the Ramsay Sedation Scale (RSS). In cases of RSS <4, an additional dose of 0.05 mL/kg of the anesthetic medication was administered as an intermittent bolus.

Follow-Up Assessments

The basal values of HR, $EtCO_2$, IPI, and SpO_2 were obtained before the procedure, and the instantaneous trend data were recorded. SBP, DBP, and MBP values before the procedure (the baseline value), at the 1st, 5th, 10th, 15th, 20th, 25th, 30th minutes of the procedure and at the end of the procedure were recorded. Other parameters including $EtCO_2$, IPI, SpO_2 and HR were obtained as instant data output from the Capnostream 6™ Portable Respiratory Monitor and recorded.

Hypertension was defined as MBP higher than 20% of the initial value during or after the procedure. If the patient developed hypertension, signs of superficial anesthesia (eye-opening, movement) were initially evaluated. If the anesthesia was found to be superficial (RSS <4), an additional dose of 0.05 mL/kg IV of the anesthetic medication was administered. If hypertension persisted for more than one minute despite an additional dose, it was concluded that the anesthesia was not superficial and perlinganit 50-100 µg IV was administered. The perlinganit dose was repeated when necessary. A 20% lower MBP value than the initial value was accepted as hypotension. When the patient developed hypotension, ephedrine 5 mg IV was administered, and the dose of ephedrine was repeated when necessary. A HR of <45 beats/min was considered as bradycardia, and bradycardia was treated with atropine 0.5 mg IV. In cases of HR >100 beats/min, superficial anesthesia findings were re-evaluated. In cases of superficial anesthesia (RSS <4), an additional dose of 0.05 mL/kg IV of anesthetic medication was given. When it was concluded that the anesthesia was not superficial, 5-10 mg esmolol was administered IV. The dose of esmolol was repeated when necessary.

The duration of anesthesia was measured from the time of the first dose of propofol or ketofol until the patient's eyes opened. The duration of the procedure was determined by recording the time from the beginning to the end of the process. Induction, additional doses, and total medication doses were recorded. In addition, the time of spontaneous eye opening following the procedure and the time of Modified Aldrete Score (MAS) >9 were recorded.

At the conclusion of the procedure, the patients were given oxygen through a mask and monitored in the observation room with the emergency equipment at hand. HR, MBP, and SpO_2 were recorded at the 5th, 10th, 20th, and 30th minutes after the procedure. Complications (hypertension, hypotension, bradycardia, bronchospasm, allergic rash, nausea, vomiting, cough, dizziness, diplopia, agitation, desaturation, apnea, airway obstruction, laryngospasm, aspiration) during and after the procedure were recorded.

Statistical Analysis

Sample size calculation was based on the primary outcome variable. Mean arterial pressure (82.1±15.1 mmHg) measured 5 minutes after the start of sedation in a pilot study of 10 patients receiving propofol was used for the sample size calculation. This frame was chosen because hemodynamic stability was achieved and endoscopy was initiated. Since a 10% change in mean arterial pressure was considered significant, 44 participants were calculated as required for each group in this study with an alpha level of 0.05, a beta level of 0.10 and power level of 0.95. To account for potential drop-outs, a decision was made to include a minimum of 50 patients per group.

Statistical analysis was performed using IBM SPSS v23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). The Student's t-test was used to compare the means between the two groups. Conformity to normal distribution was examined using the Kolmogorov-Smirnov test. A two-way analysis of variance was used to compare parameters according to their group and time. The results of the analysis are presented as mean ± standard deviation for quantitative data, and a p-value of <0.05 was considered statistically significant.

RESULTS

There was no difference between the groups in terms of their age, gender, height, weight, ASA classification, duration of anesthesia, and duration of procedure (endoscopy + colonoscopy) (p>0.05) (Table 1).

The MBP values of group P and group K during the procedure and in the observation room are shown in Table 2. The mean values of MBP at 1st, 5th, 10th, 15th, 20th minutes, at end of procedure and post-procedure 5th min differed between the groups (p<0.05).

The RSS values of group P and group K are shown in Table 3. The RSS mean values at 1st, 5th, 10th, 15th, 20th, and 25th minutes differed between the groups (p<0.001).

Table 1. Demographic characteristics of the groups

	Group K, (n=50), Mean ± SD/n (%)	Group P, (n=50), Mean ± SD/n (%)	p
Age (years)	50.2±13.9	51.2±10.2	0.700
Gender			
Male	20 (40)	20 (40)	1.000
Female	30 (60)	30 (60)	
Height (cm)	164.4±9.4	164.7±9.3	0.848
Weight (kg)	76.4±12.6	76.8±14.1	0.893
ASA I/II/III	12 (24)/32 (64)/6 (12)	12 (24)/32 (64)/6 (12)	1.000
Comorbidities			
- Hypertension	34 (89.5)	32 (84.2)	0.978
- Diabetes mellitus	9 (23.7)	8 (21.1)	
- Coronary artery disease	6 (15.8)	6 (15.8)	
- Bronchial asthma	4 (10.5)	3 (7.9)	
- COPD	3 (7.9)	5 (13.2)	
Duration of anesthesia (min)	24.6±3.6	24.8±4.2	0.859
Duration of procedure (min)	22.6±3.6	22.8±4.2	0.820

ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, min: Minimum.

Table 2. Mean blood pressure values of the groups

Time	Group K, (mmHg), Mean ± SD	Group P, (mmHg), Mean ± SD	p
Beginning of the procedure	100.8±12.8	99.8±13.2	0.707
1st min	92.7±10.3	82.2±15	**<0.001**
5th min	94.2±12.2	80.2±15.2	**<0.001**
10th min	90.6±11.3	78.4±16.4	**<0.001**
15th min	91.7±10.7	84.3±13.4	**0.003**
20th min	93.6±10.5	83.7±13.8	**<0.001**
25th min	94.0±7.5	85.2±17.3	0.083
30th min	99.5±0.7	76.5±15.2	0.100
End of the procedure	93.5±8.5	89.3±11.4	0.035
After the procedure 5th min	94.7±7.2	90.3±11.0	**0.021**
After the procedure10th min	94.9±7.2	92.5±8.9	0.136
After the procedure 20th min	95.6±6.8	94.7±8.8	0.548
After the procedure 30th min	97.3±7.4	95.9±11.5	0.470

SD: Standard deviation, min: Minute.

Table 3. Ramsey Sedation Scale of the groups

Time	Group K, Mean ± SD	Group P, Mean ± SD	p
Beginning of the procedure	1.2±0.4	1.3±0.4	0.339
1st min	4.9±0.3	4.4±0.6	**<0.001**
5th min	4.8±0.5	3.9±0.7	**<0.001**
10th min	4.4±0.6	3.7±0.8	**<0.001**
15th min	4.6±0.6	4.1±0.6	**<0.001**
20th min	4.8±0.5	4.3±0.5	**<0.001**
25th min	4.7±0.5	4.3±0.7	**<0.001**
30th min	4.5±0.7	4.6±0.5	0.846
End of the procedure	4.6±0.6	4.7±0.5	0.348

SD: Standard deviation, min: Minute.

HR was found to be statistically significant between the groups at the beginning, 0-5 minutes, 5-10 minutes, 10-15 minutes, 15-20 minutes, 20-25 minutes, 25-30 minutes and >30 minutes ($p<0.05$) (Table 4).

The mean SpO_2 value was 98.1±2% in group K and 96.8±3.4% in group P. A statistically significant difference was found in the mean SpO_2 values ($p<0.05$) (Table 5). The mean $EtCO_2$ level in our study was 34.4±5.6 mmHg in group K and 29.6±9.3 mmHg in group P, and this difference was statistically significant ($p<0.05$).

The mean IPI value was 9.4 in group K and 7.3 in group P, which was statistically significant ($p<0.05$). When the interaction between group and time was analyzed, the mean IPI of the ketofol group at baseline was 9.6, and it was 9.2 for the propofol group. The highest mean onset time was observed in the ketofol group (Table 6).

The mean time to reach MAS >9 in the recovery period was 242.4±54.6 sec in group K, while it was 250.4±50.1 sec in group P ($p=0.447$). Spontaneous eye opening was observed at an average of 171.6±17.8

Table 4. Multiple comparison results of heart rate by group and time

	Beginning	0-5 minute	5-10 minute	10-15 minute	15-20 minute	20-25 minute	25-30 minute	>30 minute	Total
Group K, (beat/min.)	$88.9±18.4^{A,K,I,F}$	$91.3±13.7^{I}$	$88.7±11.8^{H}$	$83.8±12.7^{E}$	$83.8±12.8^{E}$	$83.7±13.7^{E}$	$81.8±12.2^{C}$	$86.4±9.6^{A}$	86.2±13.2
Group P, (beat/min.)	$92.6±16.7^{K,I,H}$	$89.4±16^{K}$	$86.7±14.9^{A}$	$83.3±14.4^{G}$	$82.3±14.7^{C}$	$81.3±16.4^{F}$	$79.2±16.6^{D}$	$73.7±8.9^{B}$	84.4±15.6
Total, (beat/min.)	$90.7±17.6^{f}$	$90.4±14.9^{f}$	$87.7±13.5^{e}$	$83.5±13.6^{d}$	$83±13.8^{c}$	$82.5±15.1^{b}$	$80.6±14.6^{a}$	$82±11.1^{a}$	85.3±14.5

$^{A-K}$: There is no significant difference between values with the same letter, $^{a-f}$: There is no significant difference between main effects with the same letter.

Table 5. Multiple comparison results of peripheral oxygen saturation by group and time

	Beginning	0-5 minute	5-10 minute	10-15 minute	15-20 minute	20-25 minute	25-30 minute	>30 minute	Total
Group K, (%)	$99.2±1.2^{L}$	$98±2.4^{K}$	$97.8±2.1^{H}$	$98.2±1.7^{EF}$	$98.3±1.9^{C}$	$98.4±1.7^{C}$	$98.3±1.9^{C,F}$	$96.5±2.2^{A}$	98.1±2
Group P, (%)	$98.6±2^{K,E,F,C}$	$96.8±3.7^{I}$	$96.1±4.3^{G}$	$96.9±3.2^{B}$	$97.2±2.8^{E}$	$97.1±2.9^{D}$	$96.9±3.3^{B,I}$	$96.3±3.1^{A,G}$	96.8±3.4
Total, (%)	$98.9±1.7^{f}$	$97.4±3.2^{e}$	$96.9±3.5^{d}$	$97.6±2.7^{a}$	$97.7±2.4^{c}$	$97.7±2.5^{c}$	$97.5±2.8^{b}$	$96.3±2.9^{a}$	97.5±2.9

$^{A-L}$: There is no significant difference between values with the same letter, $^{a-f}$: There is no significant difference between main effects with the same letter.

Table 6. Comparison of integrated pulmonary index values according to group and time

	Beginning	0-5 minute	5-10 minute	10-15 minute	15-20 minute	20-25 minute	25-30 minute	>30 minute	Total
Group K	$9.6\pm0.7^{B,F,I}$	9.3 ± 1^{F}	9.5 ± 0.8^{I}	9.4 ± 1^{B}	9.3 ± 1^{F}	9.4 ± 0.9^{B}	$9.5\pm0.9^{B,J}$	$9.5\pm0.7^{B,J}$	9.4 ± 1
Group P	$9.2\pm1^{B,F,I}$	7.6 ± 2.7^{K}	7.3 ± 2.8^{H}	7.1 ± 2.7^{G}	7.1 ± 2.6^{E}	7.5 ± 2.2^{D}	7.2 ± 2.2^{C}	6.1 ± 2.4^{A}	7.3 ± 2.6
Total	9.4 ± 0.9^{f}	8.4 ± 2.2^{c}	8.4 ± 2.3^{a}	8.3 ± 2.4^{e}	8.2 ± 2.3^{d}	8.5 ± 1.9^{c}	8.3 ± 2.1^{b}	7.3 ± 2.5^{a}	8.3 ± 2.2

$^{A-K}$: There is no significant difference between values with the same letter, $^{a-f}$: There is no significant difference between main effects with the same letter.

sec in group K and 213.4±48.8 sec in group P, and this difference was statistically significant (p<0.001). For anesthesia onset, the procedure start time was 71.5±9.2 sec in group K and 76.6±13.6 sec in group P, and this difference was statistically significant (p=0.031).

The mean values of propofol used in induction did not differ between the groups (group K: 113.8±15.8 mg vs. group P: 121.2±24.2; p=0.089). The additional dose of propofol was 39.4±18.4 mg in group K and 163.1±55.3 mg in group P, this difference was statistically significant (p<0.001). The average total amount of propofol used per patient was 140.2±26.9 mg in group K and 284.1±60.8 mg in group P, which was statistically significant (p<0.001).

An additional dose was administered in 68% (n=34) of the patients in the group K, an additional dose was given to all patients (n=50) in the group P. There was a statistically significant difference between the groups in terms of additional doses in maintenance (p<0.001). While no complications developed in group K during the procedure, hypotension requiring intervention was observed in 2 patients, bradycardia in 1 patient, and respiratory depression in 12 patients in group P.

DISCUSSION

This study demonstrated that ketofol has better effects on hemodynamics and respiratory parameters when compared to propofol use alone and also ketofol did not cause delayed recovery time. Ketofol can be prepared in a single injector by combining ketamine and propofol in the desired proportions. It is frequently used in clinics because it is convenient to use these two medications in the same injector, it is safe in terms of dose titration, and it provides high-quality sedation. Concomitant use reduces the side effects of each medication compared to their use separately and enables the use of lower doses of these medications. Due to its short recovery time, absence of respiratory suppression, and ability to provide effective analgesia, ketofol can be used safely, particularly in the elderly and in those patients with co-morbidities.[6,7,11]

To minimize the risk of complications in endoscopic procedures performed under sedoanalgesia, the patient's level of sedation is vital. In patients undergoing colonoscopy, Türk et al.[12] compared the combination of propofol and ketamine to the combination of propofol and alfentanil and found that RSS was higher in the ketamine group. David and Shipp[13] administered sedation to patients in the emergency department, and reported that ketofol provided better sedation quality and depth when compared to propofol. In our study, the depth of sedation was also evaluated with RSS. Accordingly, while there was no statistically significant difference between the groups in terms of their baseline RSS values before the procedure, it was found that the mean RSS values at the 1st, 5th, 10th, 15th, 20th, and 25th minutes were significantly higher in the ketofol group. A more statistically significantly profound sedation was achieved in those patients in the ketofol group. This was attributed to the hypnotic and sedative effects of ketamine administered with propofol and its analgesic properties. In addition, the rapid onset and short duration of the effect of propofol alone necessitated the need for more than one additional dose for maintenance during the procedure in group P. In our study, additional doses were given to 34 patients in the ketofol group during the procedure, while more than one additional dose was required in all patients in the propofol group.

In their study, Smischney et al.[14] examined the effect of propofol and ketofol as induction agents on hemodynamics. They reported that ketofol provided better hemodynamic stability in the first 10 minutes after induction. Aberra et al.[15] investigated the effects of propofol and ketofol on laryngeal mask placement conditions and hemodynamic stability in pediatric patients and observed that mean blood pressure and HR were higher in the ketofol group. At the same time, there was a significant decrease in mean blood pressure and HR in the propofol group. As a result, they reported that ketofol could be used as an alternative to propofol in pediatric anesthesia. Tosun et al.[16] compared the effects of propofol-ketamine and propofol-fentanyl combinations in 90 pediatric patients who underwent upper GIS endoscopy. The authors observed that the patients in the propofol-ketamine group tolerated endoscopy better, and the HR and mean blood pressure values of the patients in this group were more stable.

Regarding hemodynamic data, our study yielded similar outcomes to those of the aforementioned studies. A crucial finding from this study was that, despite being under control, hypertensive patients were present in both groups. Antihypertensive agents with a variety of mechanisms of action can be used to treat hypertension. Consequently, the hemodynamic responses of these patients to anesthetics were not uniform. Even though the number of hypertensive patients in our study was comparable between groups, this may be considered a limitation of this study.

In a meta-analysis involving five studies and 1,250 patients in which propofol and ketofol were used in the procedural sedation of adults in the emergency department, the incidence of respiratory side effects was found to be lower in the ketofol group when compared to the propofol group, and the peripheral oxygen saturation values of those patients in the propofol group were found to be lower than those in the ketofol group.[17] In a prospective study by Elkalla and El Mourad[18] comparing the sedation efficiency and safety of propofol, dexmedetomidine and ketofol for drug-induced sleep endoscopy in patients with sleep apnea, dexmedetomidine and ketofol were found to provide a safe respiratory profile without significant hemodynamic side effects. During the procedure, our study recorded peripheral oxygen saturation values as instantaneous trend data. The difference between the mean SpO_2 values of 98.1% in the ketofol group and 96.8% in the propofol group was statistically significant. There was no significant decrease in SpO_2 values in the ketofol group compared to the baseline value. In terms of peripheral oxygen saturation, our study's findings were comparable to those of the studies discussed previously.

In a study by Turan et al.[19] in which capnography monitoring was added to oxygen saturation monitoring for better monitoring of the respiratory parameters, 30 patients who were sedated for a gastroscopy/colonoscopy procedure with an IPI monitor were evaluated, and a decrease in the SpO_2 value was detected in only two patients, despite the fact that five patients required ventilation with a mask (IPI score of 1-3). The authors reported that IPI monitoring could detect respiratory problems which may develop in patients earlier than pulse oximetry could and this may provide benefits for the patient and the anesthesiologist. Gozal and Gozal[20] used IPI monitoring in children who underwent deep sedation and observed that the IPI monitor could detect all respiratory problems with 98% specificity. In addition, the authors stated that for less experienced healthcare professionals, an IPI monitor might be helpful in the follow-up of pediatric patients undergoing sedation.

In our study, we found the mean IPI values for group K and group P to be 9.4 and 7.3 respectively, with the difference being statistically significant. In the ketofol group, the IPI values were similar to the baseline. In contrast, the IPI values of the propofol group decreased significantly relative to the baseline value and were statistically significantly lower than those of the ketofol group at all times. Although SpO_2 was normal in 12 patients in group P, respiratory depression requiring intervention occurred and IPI values remained low during apnea episodes in these patients. Respiratory depression and apnea episodes requiring intervention were not observed in any patient in group K. In our study, we found that the IPI monitor was a superior early indicator to pulse oximetry for patient intervention in emergency situations, consistent with the findings of the aforementioned studies.

Anderson et al.[21] evaluated the role of capnography in the detection of respiratory involvement in pediatric patients who received propofol prior to orthopedic procedures. They found that while all of the patients who developed apnea were detected by capnography, none of them were detected by clinical follow-up and pulse oximetry. The authors reported that continuous measurement with capnography during the procedure is superior to clinical observation and pulse oximetry for detecting adverse respiratory and airway events. Hypopneic hypoventilation is a type of hypoventilation that is difficult to detect except through capnography in the follow-up of sedated patients. Remarkably, Langhan et al.[22] reported that all hypoventilation episodes, or hypopneas, have an $EtCO_2$ of 30 mmHg or less. Hypopnea's low $EtCO_2$ levels are caused by an increase in dead space as tidal volume decreases. Numerous studies have focused on the definitions of apnea and bradypnea, but their commentary on this type of breathing is limited. Changes in respiratory rate allow for the detection of bradypnea and apnea. Hypopnea, on the other hand, cannot be detected through physical examination or the conventional monitoring of the respiratory tract.

In our study, the mean $EtCO_2$ value was 34.4 mmHg in group K and 29.6 mmHg in group P, and a statistically significant difference was observed between the two groups. While mean $EtCO_2$ values in the propofol group were significantly lower than the baseline value, the mean $EtCO_2$ value in the ketofol group was statistically insignificantly higher and more stable than the baseline value. We believe the low $EtCO_2$ values in the propofol group were due to $EtCO_2$ being ≤30 mmHg in almost all of the hypoventilation attacks, that is, hypopneic hypoventilation. Although peripheral oxygen saturation was normal in 12 patients in this group, respiratory depression occurred and $EtCO_2$ could not be measured during the apnea episodes in these patients, which caused the average $EtCO_2$ values to be low. Respiratory depression and apnea episodes requiring intervention were not observed in any patient in the ketofol group.

In a study evaluating side effects, Willman and Andolfatto[23] reported that no patients administered propofol and ketamine experienced hypotension, bradycardia, vomiting, laryngospasm, or any side effects at discharge. In the study conducted by Amornyotin et al.[24] in which colonoscopy was performed under anesthesia, hypotension was observed in 16 (32%) patients and bradycardia was observed in one patient in the propofol group. In comparison, hypotension was observed in 7 (14%) patients in the ketofol group. The authors reported the ketofol combination as having fewer cardiovascular side effects. In a meta-analysis by Jalili et al.[25], the authors reported that ketofol may cause less respiratory depression requiring intervention and less bradycardia and hypotension than propofol alone, and the authors suggested ketofol as an alternative to propofol. In our study, none of the patients in the ketofol group developed complications during the procedure. However, in the propofol group, we observed two patients with hypotension which required intervention, one patient with bradycardia, and twelve patients with respiratory depression.

Study Limitations

This study had a number of limitations. This study did not utilize BIS monitoring in conjunction with the Ramsey sedation score for sedation monitoring. With the application of BIS, more objective sedation values could be predicted. Secondly, the study population included patients with controlled hypertension. Although the number of hypertensive patients in both groups was comparable, the different mechanisms of action of the drugs used by these patients may have altered the effects of the anesthesia. Thirdly, in the concomitant use of propofol and ketamine, the literature-recommended ratio of 1:2 was used, and no other ratios were employed.

CONCLUSION

In comparison to the propofol group, the hemodynamic and respiratory parameters were more stable in the ketofol group, the side effects were less frequent, and ketofol use did not result in prolonged recovery. However, it would be appropriate to support this study with more extensive randomized, controlled series and comparative studies of ketofol administered at different rates. In addition, we believe that making IPI and non-invasive end-tidal carbon dioxide monitoring routine among the standard infrastructure and equipment in non-operating room anesthesia applications can be advantageous for both the patient and the anesthesiologist, as respiratory problems and other potential complications can be detected more accurately than when pulse oximetry is used alone.

MAIN POINTS

- It is preferred that the anesthetic agent used in endoscopic procedures be efficient, not interfere with hemodynamic and respiratory data, and not prolong the recovery time.
- Ketofol was more reliable in terms of hemodynamic and respiratory data when compared to propofol, and its side effects were less common.

- In non-operating room anesthesia, IPI and non-invasive $EtCO_2$ monitoring are reliable in detecting respiratory problems and potential complications in patients.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Samsun Training and Research Hospital Institution Ethics Evaluation Board (approval number: 2019/4/32).

Informed Consent: This for study written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., H.K.Ç., Concept: A.A., H.K.Ç., Design: A.A., H.K.Ç., Z.D., Data Collection or Processing: A.A., Analysis or Interpretation: A.A., H.K.Ç., Z.D., Literature Search: A.A., H.K.Ç., Writing: A.A., H.K.Ç.

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RESEARCH ARTICLE

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The Effects of Manikin-Based and Standardized-Patient Simulation on Clinical Outcomes: A Randomized Prospective Study

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Abstract

BACKGROUND/AIMS: Simulation-based learning improves performance in the clinical learning environment. The aim of this study was to determine the effects of manikin-based and standardized-patient (SP) simulation modalities on clinical outcomes applied in stoma care in nursing students.

MATERIAL AND METHODS: A prospective randomized study was conducted consisting of two phases. In the first phase, simulation modalities on the knowledge and skill levels of 64 nursing students were investigated. In the second phase, the skill levels were observed in a clinical learning environment. Data were collected by using the Stoma Skill Form, Stoma Knowledge Form and Simulation-based Learning Evaluation Scale.

RESULTS: The students' knowledge levels were significantly higher after the SP modality than after the manikin-based modality (p=0.012). However, no significant differences were observed between the skill levels of the groups except in regards to communication, which was higher after the SP modality.

CONCLUSION: The findings of this study indicate that both of the simulation modalities helped the students gain competencies and prepare for clinical environments, and both led to equal skill levels in such environments.

Keywords: Clinical outcome, clinical skill, simulation modality, stoma care, nursing education

INTRODUCTION

Simulation is a learning method in which real experiences are recreated in completely interactive ways.[1,2] There are different types of simulation as part of simulation activities, such as task-trainer, manikin-based, standardized-patient (SP), and computer-based simulation modalities. An SP modality uses a person who has been carefully coached to simulate an actual patient in a real health care situation. The SP interacts with students in experiential education and assessment contexts.[3,4] In contrast, a manikin-based modality uses a manikin which represents a patient using heart and lung sounds, palpable pulses, voice interactions, and other human capabilities which can be controlled by a simulationist using computers and software.[4]

Simulation-based experience is considered one of the best methods for teaching nursing skills.[5] However, while the development of psychomotor skills is a core learning goal in nursing education, there is limited empirical evidence in the extant nursing literature which supports simulation's efficacy at teaching such skills.[6] Furthermore, there have been limited studies on the different simulation modalities used in nursing education, including their specific efficacies in regards

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to the development of skills and the results of clinical practice outcomes.[6,7] Specifically, it is recommended that the knowledge and psychomotor skills gained in simulation environments be evaluated in clinical environments and in relation to clinical practice outcomes.[8,9]

This study aimed to address these research gaps by investigating the effects of manikin-based and SP simulation modalities on the knowledge and psychomotor skills of nursing students. The main aim of this study was to determine which of the two simulation modalities was more effective in helping the students develop their clinical stoma care skills.

MATERIAL AND METHODS

Study Design

This study was carried out as a randomized prospective study. Data were collected between October, 2016 and February, 2017 in İstanbul, Türkiye. This study was approved by Acıbadem University and Acıbadem Healthcare Organizations Medical Research Ethics Committee (ATADEK) (approval number: 2016-14/13, date: 25/08/2016). All students and patients participating in the study were informed and written informed consent was obtained.

Setting and Participants

The initial study population was 67 second-year undergraduate students. Students who had previous experience with stoma care were excluded. After this criterion was applied, the sample size for this research was 64 students. The data was collected simultaneously during surgical practice.

The students were divided into two groups using the simple random method and the program Random Allocation Software (version 2.0.0). One group learned using a manikin-based simulation modality and the other group learned using an SP simulation modality.

Procedure

The study then consisted of two stages. The study flow chart is given in Figure 1.

Scenario Procedures

The two different modalities were used to study the students' stoma knowledge and skill levels; this step was carried out in the university's simulation laboratory.

An artificial stoma and a defecation moulage were applied to each modality to increase the simulations' levels of fidelity. The scenarios were designed to last for ten minutes for each student.

The participants' levels of knowledge were measured before the scenario was implemented (with a pre-test) and shortly after the scenario debriefing (with a post-test). The scenario content included caring for a patient who had a stoma due to colon cancer.

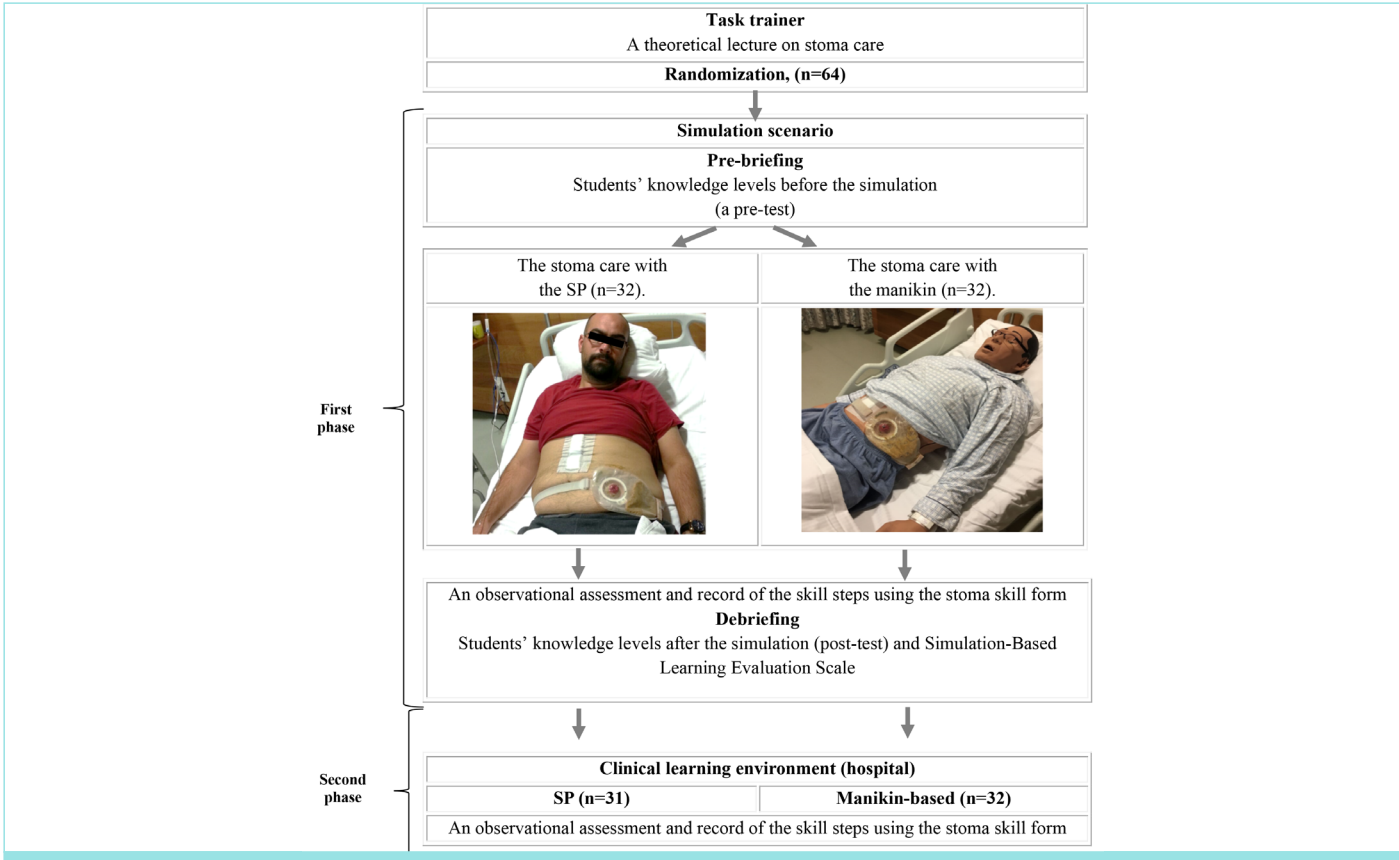

Figure 1. Study flow chart.

SP: Standardized-patient.

One independent observer (nursing instructor in the simulation and ostomy nurse in the hospital) and one investigator evaluated each student's skills in performing the stoma care steps. Each student was evaluated from an observation room, which provided the ability to view the student from all angles with a One-Way mirror and cameras.

Clinical Procedures

The subjects' skill levels in regards to caring for patients with stomas were investigated in clinical-learning environments at four university hospitals. The students were divided randomly among the hospitals, then each stoma care skill was examined in the patient room. This was carried out by the academic researcher and ostomy nurses at the hospitals.

The care was performed on patients who had received postoperative colostomies and had no complications which prevented the care procedures from being carried out. In total, each student performed stoma care 63 times across the 61 patients. The first stoma care application by each student was observed.

Measures

Stoma Knowledge Form

This evaluation was developed in accordance with the extant literature on stoma care; it consisted of 30 items related to stoma care. There were 17 correct statements and 13 incorrect statements regarding this topic. The students select "true," "false," or "no idea" for each item. Correct answers were given one point and incorrect answers were given zero points; the possible total scores ranged from 0 to 30.

Stoma Skill Form

This form was used to examine 26 items and was developed based on the extant literature; it assessed the steps necessary for proper stoma care. For each student, the steps involved in stoma skills were assessed as insufficient (zero), i.e., incorrect or skipped; partially sufficient (one), i.e., applied correctly and on time but ineffective for easily passing between skill steps; and sufficient (two), i.e., applied correctly and on time and effective for easily passing between skill steps. A final score was obtained by summing up the scores for the 26 skill steps; the possible total scores ranged from 0 to 52.

Simulation-Based Learning Evaluation Scale

This scale was developed by Hung et al.[10], and the validity and reliability of a Turkish version of the test were evaluated by Uslu and Yavuz van Giersbergen[11]. This scale has five subscales and 37 items. Responses are scored using a five-point Likert scale ranging from one (*strongly disagree*) to five (*strongly agree*), and the total scores can range between 37 and 185 points. The basic competencies which a nurse should have are examined: namely, *the nursing process*, *patient safety*, *professional knowledge*, *communication*, and *attitude of reflection*.

Statistical Analysis

The software Number Cruncher Statistical Systems (NCSS) was used for statistical analyses (the 2007 version by NCSS, LLC in Kaysville, Utah, the United States of America). Student's t-test was used for two-group comparisons of variables with normal distributions, and the paired sample *t*-test was used for intragroup comparisons. Statistical significance was accepted as $p<0.05$.

RESULTS

The first phase included 64 nursing students; 86% (n=55) were female and their mean age was 20.18±1.43 years. The second phase included 63 students as one student left the study.

As mentioned earlier, 61 patients were treated by the students during phase two. The patients mean age was 56.7 years and 61% (n=37) were male. Colon cancer was the underlying reason for the stoma placement in 93.4% (n=57) of the patients.

It was determined that the knowledge levels of both groups increased after the simulation scenarios (p=0.267). The knowledge levels were significantly higher for the SP group after the training in the first phase, as shown in Table 1 (p=0.012).

The stoma skill form scores are shown in Table 1. No significant differences were found between the overall scores of the groups for scenario implementations (p>0.05) and clinical practice (p>0.05). However, for both groups, there was a significant increase in the students' stoma skill scores during clinical practice (p≤0.001 for both groups).

Table 1. The stoma knowledge and skill levels of the students

Stoma knowledge level (min.: 0, max.: 30)	**Simulation modality**		
	SP, (n=32)	**Manikin-based, (n=32)**	**p[a]**
	Mean ± SD	**Mean ± SD**	
Pre-test	24.81±2.22	24.06±2.80	0.240
Post-test	26.34±1.41	25.13±2.25	0.012*
Difference	1.53±1.74	1.06±1.61	0.267
p[b]	<0.001**	0.001**	
Stoma skill level (min.: 0, max.: 52)	**SP, (n=31)**	**Manikin-based, (n=32)**	
	Mean ± SD	**Mean ± SD**	
During scenario implementation	24.06±5.05	22.00±5.91	0.136
During clinical practice	32.13±6.07	31.23±6.14	0.563
Difference	8.06±6.78	9.23±7.34	0.513
p[b]	<0.001**	<0.001**	

[a]: Independent samples t-test; [b]: Paired t-test; *p<0.05; **p<0.01, min.: Minimum, max.: Maximum, SD: Standard deviation, SP: Standardized-patient.

The scores obtained by both groups using the Simulation-Based Learning Evaluation Scale were not statistically significantly different for the categories of *nursing process*, *patient safety*, *professional knowledge*, or *attitude* (p>0.05). However, the scores obtained by the SP students were significantly higher for the category of *communication* (p=0.048) (Table 2).

Table 2. The students' simulation-based learning evaluation scale scores by subscale

		Simulation modality		
		SP, (n=32)	Manikin-based, (n=32)	p
Nursing process	Min.-max.	31-45 (36)	27-45 (36.5)	t=0.313
	Mean ± SD	36.91±4.32	36.56±4.47	0.756[c]
Patient safety	Min.-max.	32-40 (38,5)	29-40 (39)	Z=-0.082
	Mean ± SD	37.34±2.70	37.00±3.43	0.935[d]
Professional knowledge	Min.-max.	22-33 (26)	17-35 (26)	t=1.117
	Mean ± SD	26.63±3.01	25.63±4.07	0.268[c]
Communication	Min.-max.	21-35 (30.5)	21-35 (28)	t=2.022
	Mean ± SD	30.06±3.68	28.34±3.10	0.048*[,c]
Attitude of reflection	Min.-max.	20-30 (26,5)	20-30 (26)	t=-0.043
	Mean ± SD	26.28±2.79	26.31±3.01	0.966[c]

[c]: Student's t-test; [d]: Mann-Whitney U test, *p<0.05, min.: Minimum, max.: Maximum, SD: Standard deviation, SP: Standardized-patient.

DISCUSSION

In this study, the knowledge and skills of the students were evaluated separately and objectively using two simulation modalities: manikin-based and SP-based. Some studies have reported that simulation-based learning can increase the knowledge capacities of students,[12,13] whereas others have indicated that it cannot.[14] Hegland et al.[15] noted a need for highly standardized random controlled studies to address this issue. This study provided research to address this gap and suggested that such simulations do indeed improve the knowledge of students.

However, it was found that the post-training knowledge scores were significantly higher for the SP group than for the manikin-based group; therefore, the training which used the SP simulation modality was more effective. This finding is supported by research conducted by Tuzer et al.[16]. This study's results indicated that the more realistic the simulations are, the more effective they are in facilitating the acquisition and reinforcement of knowledge.

Moreover, the SP group had higher *communication* scores on the Simulation-Based Learning Evaluation Scale than the other group. SP modality increases the communication skills of students and contributes to patient safety, both during patient care and during patient discharge.[17] It is recommended to help students develop not only their psychomotor skills but also their communication skills.[18]

However, no significant differences were found between the two modalities with regards to the stoma skill scores of the students, and this finding is supported by research conducted by Tuzer et al.[16]. Some studies have reported that manikin-based simulations lead to better skill outcomes than SP simulations as the use of real people in simulations can increase stress and thus affect the performance of students.[19]

Realistic simulations can lead to improved skills and clinical performance.[20] The experience students gain in simulation-based training promotes the achievement of learning outcomes throughout clinical practice.[21]

Indeed, the present study found that the skill scores of all the students increased significantly after they had received training, regardless of the simulation method they used, although their communications skills increased more with SP training than with manikin-based training.

Study Limitations

Our study had some limitations. Firstly, its sample size was small and it recruited from only one nursing school, which limits the generalizability of our results. Secondly, the stoma skills and knowledge forms were prepared by the researcher and so are not valid reliable tools. Although there are limitations of this study, this research provides a basis for future research. It is an important preliminary step in proving clinical outcomes of simulation-based learning.

CONCLUSION

While SP and manikin-based modalities can increase post-training knowledge and stoma care skill levels equally, the SP method can lead to significantly higher communication skills than the manikin-based method. The recreation of a near-actual environment during ssimulation experiences can prepare students for clinical environments and help them gain competencies.

MAIN POINTS

- Simulation-based learning methods aid the development of cognitive and psychomotor skills.
- Simulation-based learning improves performance in the clinical learning environment.
- The SP method can lead to significantly higher communication skills than the manikin-based method.
- The modality appropriate to the learning objectives should be selected during simulations.

ETHICS

Ethics Committee Approval: This study was approved by by Acıbadem University and Acıbadem Healthcare Organizations Medical Research Ethics Committee (ATADEK) (approval number: 2016-14/13, date: 25/08/2016).

Informed Consent: All students and patients participating in the study were informed and written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.U., M.Y.V.G., Concept: Y.U., M.Y.V.G., Design: Y.U., M.Y.V.G., Supervision: Y.U., M.Y.V.G., Data Collection and/or Processing: Y.U., M.Y.V.G., Analysis and/or Interpretation: Y.U., M.Y.V.G., Literature Search Y.U., M.Y.V.G., Writing: Y.U., M.Y.V.G., Critical Review: Y.U., M.Y.V.G.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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New Lymph Node Parameters and a Comparison with the American Joint Committee on Cancer N-Stages in Breast Cancer

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Abstract

BACKGROUND/AIMS: The N-stage of TNM systems considers only the number of metastatic lymph nodes (NMLN) in breast cancer (BC). However, new lymph node parameters refer to the number of harvested lymph nodes (NHLN) and negative lymph nodes (NNLN), which have had an increasing significance in the current literature. This study aimed to compare NHLN, NNLN, lymph node ratio (LNR), modified lymph node ratio (mLNR), and log odds of positive lymph nodes (LODDS) against the standard American Joint Committee on Cancer (AJCC) N-stage for the prognosis of BC patients.

MATERIALS AND METHODS: This study was designed retrospectively. The socio-demographic data, clinical features, histopathological factors, treatment modalities, receptor status of BC, and lymph node related parameters (AJCC N, LNR, mLNR, LODDS) were identified. Then, lymph node related parameters were compared for cancer-related mortality (CRM), cancer recurrence, disease-free survival (DFS), and overall survival (OS).

RESULTS: Eight hundred seven women who underwent surgery for BC were included in this study according to its eligibility criteria. The mean follow-up period was 113.34±74.85 (range: 6-378) months. The NHLN was 21.24±9.22, the NMLN was 4.85±7.38, the NNLN was 16.39±9.48, the LNR was 0.23±0.29, the mLNR was 5.38±7.38 and the LODDS was -0.74±0.80 on average. During the follow-up period, 42 (5.2%) patients had local recurrence, 188 (23.3%) had distant metastases, and 252 (31.2%) patients died due to BC. NMLN, LNR, mLNR, and LODDS were found to be significantly higher, and NNLN was significantly lower in those patients with cancer recurrence and CRM ($p<0.001$). AJCC N-stages, and also LNR, mLNR, and LODDS groups according to the calculated cut-off values, were significant for DFS and OS according to survival analysis. In Cox regression analysis, only LODDS was a significant independent risk factor for OS [$p=0.014$, heart rate (HR)=3.78, 95% confidence interval (CI) for HR: 1.30-10.94)].

CONCLUSION: The results indicated that LODDS was more successful compared to other lymph node staging systems, especially for OS. However, randomized prospective controlled studies with larger samples and homogeneous study groups are needed to create standard classification systems as alternatives to AJCC N.

Keywords: Modified lymph node ratio, breast cancer, log odds of positive lymph nodes, lymph node ratio, lymph node staging

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INTRODUCTION

Breast cancer (BC) is the second most common malignancy after lung cancer worldwide. Moreover, BC is the most common cause of death due to cancer in women in a certain age group (40-49 years old), so this feature makes BC highly significant among other malignancies. Since most women with BC are non-metastatic at their time of diagnosis, very promising results have been reported with multidisciplinary management.[1] The management of BC depends on many different factors. The age, pathological stage of the BC, the biological characteristics of the BC [such as hormone receptor status, human epidermal growth factor receptor-2 (HER-2) status], and lymphatic or vascular invasion are just some prior determinants for treatment strategy. Axillary lymph node involvement and the number of metastatic lymph nodes (NMLN) were assumed to be the most important prognostic factors in the decision of adjuvant radiotherapy.[2] Under current clinical guidelines, pathological examination of at least 10 harvested lymph nodes with level 1-2 axillary dissection is accepted for the correct staging of the axillary lymph node stage.[3] However, axillary dissection cannot be surgically performed with the same intensity in every patient due to reasons such as the experience of the surgeon or the pathologist, the patient's age, the patient's anatomical structure, and/or concomitant diseases. The count of metastatic lymph nodes in the axillary dissection material is divided into three groups according to the N-stage of the American Joint Committee on Cancer (AJCC) 8th edition staging system. Under this classification, the total count of the harvested lymph nodes or the number of negative lymph nodes (NNLN) is not taken into account. As patients are classified by the number of "positive lymph nodes only", a heterogeneous group is actually formed. Thus, axillary lymph node staging with the current N classification may change, result in inadequate treatment, and/or may be insufficient in predicting the prognosis.[4] Therefore, it may be appropriate to consider not only the number of positive lymph nodes, but also the total number of lymph nodes and the number of NNLN in order to determine a more reliable prognosis for BC patients. There are new studies showing that the total lymph node count is a better prognostic parameter than the metastatic lymph node count.[5-7] Also, it has been supported by various studies that the pN classification, which evaluates the ratio lymph node ratio (LNR) of the NMLN to the number of harvested lymph nodes (NHLN), is more successful in determining the prognosis of BC.[4,5,8,9] However, as a limitation of LNR, the prognostic power of this value decreases in those patients with LNR values of "0 or 1".[10,11] Therefore, the "modified lymph node ratio (mLNR)" was calculated by modifying the LNR classification (by adding 0.5 to both the numerator and the denominator) thus eliminating the possibility of a mLNR value of 0.[11]

Another more complicated lymph node classification is the "log odds of positive lymph nodes (LODDS)", calculated as the logarithm of the odds ratio (OR) between positive and NNLN. There are studies in the literature reporting that LNR, mLNR, and LODDS for BC patients have better prognostic value than the pN classification made with only the number of lymph nodes with metastasis.[10-13] There have been different studies investigating the importance of one or more of the NHLN, the number of NNLN, LNR, mLNR and LODDS values in the prognosis of BC. However, the existing literature did not include studies with all these values as covariates in determining the prognosis of operated BC in a large series including different molecular subtypes, and long-term follow-up in our country. Therefore, this study aimed to compare NHLN, NNLN, LNR, mLNR, and LODDS against the standard AJCC N stage for the prognosis of BC patients.

MATERIALS AND METHODS

Design

The study was designed retrospectively. Our study population consisted of patients treated and followed up for breast carcinoma between the years of 1989-2021 in University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital. Permission was obtained from the necessary places for data sharing.

Eligibility Criteria

Patients with bilateral BC, male BC cases, those who received neoadjuvant therapy, those cases without follow-up, or those with missing data were excluded. During the examination of the records, 1,873 patients were investigated. The final number of patients according to the eligibility criteria was determined to be 807 patients. All patients, in the final analysis, underwent breast-conserving surgery or mastectomy with axillary dissection. After surgery, all patients were administered adjuvant chemotherapy and/or radiotherapy and/or endocrine therapy according to NCCN guidelines.

Outcome Parameters

The patient's demographics, clinical and pathological factors, and treatment modalities (types of surgery, adjuvant therapy, or hormone therapy) were identified. The tumor characteristics including the histologic type of tumor (invasive ductal carcinoma, invasive lobular carcinoma, mixed carcinoma, and special types), the histologic grade, the tumor size, the histologic features, and the presence of lymphovascular (LVI) were determined. Estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative, or unknown), and HER-2 status (positive, negative, or unknown) were determined. Finally, tumor molecular subtypes were classified as luminal A (ER-positive and/or PR positive/HER-2 negative), luminal B (ER-positive and/or PR positive/HER-2 positive), HER-2 overexpressing (ER-negative/PR negative/HER-2 positive) or triple negative (ER-negative/PR negative/HER-2 negative). The pT stages and pN stages were determined according to the TNM classification of the relevant diagnostic pathology report of the AJCC 8th edition. The NHLN and the number of NNLN were also recorded in detail. The LNR was defined as the ratio of NMLN to NHLN. mLDR was calculated with the formula [LD (+) + 0.5]/[LDT + 0.5]. LODDS was determined by taking the logarithm of the ratio as follows: Log [LD (+) + 0.5]/[LD (-) + 0.5]. Optimal cut-off points were analyzed for all these pN staging parameters, and their sensitivity and specificity were determined. Cancer-related mortalities (CRM) and cancer recurrences during follow-up were determined. Lymph node parameters were compared for disease-free survival (DFS) and overall survival (OS).

Statistical Analysis

Statistical analysis was performed by the SPSS 22.0 program (IBM Corp., Armonk, NY, USA). Nominal variables were compared with the chi-squared test. Scale variables were tested for normality distribution by the Kolmogorov-Smirnov test. Scale variables between two groups were compared using the t-test or the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was used to determine the significant cut-off value for mLNR. Kaplan-Meier survival analysis with log-rank comparisons was performed in groups consisting of lymph node-related parameters. Also, significant variables for recurrence and cancer-related deaths according to univariate analysis underwent a Cox regression model for DFS and OS.

RESULTS

Eight hundred seven women who underwent surgery for BC were included in this study according to the eligibility criteria. Their mean age was 53.98±13.14 (range: 23-99) years. While the most common BC histological type was invasive carcinoma-NOS (n=554, 69.2%), according to the molecular classification, the patients were mainly in the Luminal A group (n=338, 54.3%). The mean follow-up period was 113.34±74.85 (range: 6-378) months. The histopathological findings of the tumors are given in Table 1. The NHLN was 21.24±9.22, the NMLN was 4.85±7.38, the NNLN was 16.39±9.48, the LNR was 0.23±0.29, the mLNR was 5.38±7.38 and the LODDS was -0.74±0.80 on average (Table 2).

During the follow-up period, 42 (5.2%) patients experienced local recurrence and 188 (23.3%) had distant metastases, resulting in 252 (31.2%) deaths due to BC. The one-year overall survival (OS) rate was 0.984, the 3-year rate was 0.926, the 5-year rate was 0.849, and the 10-year rate was 0.708 for all patients. The one-year DFS rate was 0.981, the 3-year rate was 0.911, the 5-year rate was 0.842, and the 10-year rate was 0.741 for all patients. While the NHLNs in patients with CRM and cancer recurrence were similar, conversely, in those patients who did not develop recurrence and survived, NMLN, LNR, mLNR, and LODDS were found to be significantly lower compared to those with cancer recurrence or CRM (Table 3). In contrast to this, the number of NNLN was found to be significantly lower in those patients with cancer recurrence and CRM ($p<0.001$). The rate of cancer recurrence and CRM were significantly higher in those patients with mLNR >2.52 [Table 1, OR: 2.55, 95% confidence interval (CI) for OR: 1.84-3.55 and OR: 2.12, 95% CI for OR: 1.55-2.91]. Conversely, cancer recurrence (NNLN >13.0) and CRM (NNLN >15.5) were significantly lower in those patients with NNLN 14 and above (Table 1, OR: 2.40, 95% CI for OR: 1.74-3.32 and OR: 1.81, 95% CI for OR: 1.33-2.48). According to Cox regression analysis, increased NNLN was significantly related to a lower risk of cancer recurrence in non-metastatic patients (TNM N0) ($p<0.001$, HR: 15.87, 95% CI: 3.78-66.67). Also, in N0 patients, increased NNLN was significantly related to a lower risk of CRM ($p<0.017$, HR: 3.58, 95% CI: 1.26-10.21). However, in N0 patients, no significant cut-off value was found for cancer recurrence and CRM in the ROC analysis of the NNLN (log-rank: 0.963 and 0.609).

Mastectomy ($p<0.001$), positive HER-2 (0.028), LVI invasion ($p<0.001$), advanced T-stage ($p<0.001$), advanced N-stage ($p<0.001$), LNR >0.140 ($p<0.001$), mLNR >2.52 ($p<0.001$) and LODDS >-0.728 ($p<0.001$) were significantly related with cancer recurrence. Also, mastectomy ($p<0.001$), positive PR (0.032), LVI invasion (0.048), advanced T-stage ($p<0.001$), advanced N-stage ($p<0.001$), LNR >0.117 ($p<0.001$), mLNR >2.52 ($p<0.001$) and LODDS >-0.805 ($p<0.001$) were significantly related with CRM (Table 4).

According to ROC analysis, LNR, mLNR, and LODDS were found to be significant variables for both cancer recurrence and CRM, but the sensitivity and specificity for the calculated cut-off values were low (Table 5, Figure 1, 2). According to Kaplan-Meier survival analysis, both DFS and OS differed significantly in LNR groups determined according to the cut-off value and four LNRs ($p<0.001$, Figure 3-6). Also, the LODDS and mLNR groups determined according to the cut-off value were significant for DFS and OS according to survival analysis ($p<0.001$, Figure 7-10). Similarly, AJCC N staging was found to be significant for DFS and OS according to the survey analysis (Figure 11, 12). According to Cox regression analysis, among the lymph node parameters, only LODDS were found to be significant independent risk factors for OS [$p=0.014$, HR: 3.78, 95% CI for HR: 1.30-10.94, (Table 6)].

Table 1. An overall summary of findings

		n	%
Side	Right	406	50%
	Left	401	50%
Surgery	Mastectomy	664	82%
	Breast conserving surgery	143	18%
Histological type	Invasive ductal carcinoma	554	69%
	Invasive lobular carcinoma	66	8%
	Mixed carcinoma	72	9%
	Special types	109	14%
Grade	Grade 1	27	5%
	Grade 2	333	61%
	Grade 3	189	34%
Nuclear grade	Grade 1	14	4%
	Grade 2	207	66%
	Grade 3	91	29%
Lymphovascular Invasion	Negative	280	59%
	Positive	197	41%
Perinodal involvement	Negative	197	51%
	Positive	190	49%
ER	Negative	289	38%
	Positive	470	62%
PR	Negative	291	39%
	Positive	462	61%
HER-2	Negative	448	73%
	Positive	164	27%
Ki67	Negative	188	30%
	Positive	430	70%
Molecular classification	Luminal A	338	54%
	Luminal B	118	19%
	Triple negative	115	18%
	HER-2-positive	52	8%
T-stage	T1	204	25%
	T2	469	58%
	T3	85	11%
	T4A	6	1%
	T4B	29	4%
	T4C	1	0%
	T4D	3	0%
N-stage	N0	237	29%
	Isolated tumor cell	2	0%
	Micro-metastasis	4	0%
	N1	258	32%
	N2	174	22%
	N3	132	16%
M-stage	None	787	98%
	Distant metastasis	20	2%

Table 1. Continued

		n	%
TNM-stage	1A	83	10%
	1B	3	0%
	2A	194	24%
	2B	181	22%
	3A	174	22%
	3B	20	2%
	3C	122	15%
	4	22	3%
Local recurrence	None	765	95%
	Yes	42	5%
Survival	Survived	454	56%
	Died	252	31%
	Missed	101	13%
LNR groups (literature)	LNR=0	237	29%
	0< LNR ≤0.2	290	36%
	0.2< LNR ≤0.65	173	21%
	LNR >0.65	107	13%
LODDS groups (literature)	LODDS ≤-1.5	169	21%
	-1.5< LODDS ≤-1.0	176	22%
	-1.0< LODDS ≤-0.5	198	25%
	-0.5< LODDS ≤0	106	13%
	LODDS >0	158	20%
mLNR risk groups recurrence/ survival	mLNR ≤2.52	415	51%
	mLNR >2.52	392	48.%
NHLN risk groups recurrence/ survival	NHLN ≤19.50	389	48%
	NHLN >19.50	418	52%
NMLN risk groups for recurrence/ survival	NMLN ≤2.50 (low risk)	448	56%
	NMLN >2.50 (high risk)	359	44%
NNLN risk groups for recurrence	NNLN ≤13.00 (low risk)	320	40%
	NNLN >13.00 (high risk)	487	60%
NNLN risk groups for survival	NNLN ≤15.50 (low risk)	387	48%
	NNLN >15.50 (high risk)	420	52%
LNR risk groups for recurrence	LNR ≤0.140 (low risk)	456	57%
	LNR >0.140 (high risk)	351	43%
LNR risk groups for survival	LNR ≤0.117 (low risk)	425	53%
	LNR >0.117 (high risk)	382	47%
LODDS risk groups for recurrence	LODDS ≤-0.728 (low risk)	456	57%
	LODDS >-0.728 (high risk)	351	43%
LODDS risk groups for survival	LODDS ≤-0.805 (low risk)	419	52%
	LODDS >-0.805 (high risk)	388	48%

Distribution of patients in risk groups according to calculated cut-off values of lymph node parameters is also given. NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes, ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor-2.

Table 2. The mean, standard deviation, minimum and maximum values of the dissected lymph node parameters

	m	SD	Minimum	Maximum
NHLN	21,242	9,221	1,000	71,000
NMLN	4,850	7,381	0.001	53,000
NNLN	16,392	9.486	0.001	70,000
LNR	0.229	0.285	0.001	1,000
mLNR	5,380	7.378	0.509	53,509
LODDS	-0.739	0.796	-2.061	1,949

NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes, m: Mean, SD: Standard deviation.

DISCUSSION

The AJCC pN staging classification is based only on the absolute number of positive lymph nodes. This classification does not take into account the density of axillary lymph node dissection in surgical dissection, and it is instead dependent on the number of lymph nodes detected in the postoperative axillary dissection material. This is particularly relevant when the number of lymph nodes detected in axillary dissection is very low and thus not able to be accurately evaluated pathologically. However, the lower limit of the number of lymph nodes to be evaluated in axillary lymph node dissection materials is not clearly defined. As a guideline, it is recommended to assess at least 10 dissected lymph nodes for pN staging.[14] A mathematical model of axillary lymph node involvement was tested in a large series of 1,446 patients with invasive BC, and it was shown that pN staging can be achieved with 90% accuracy by evaluating at least 10 lymph nodes which have been dissected.[15] The mean NHLN found in our study was much higher than the number suggested by the literature. NHLN was not a significant factor for cancer recurrence, CRM, DFS, or OS in this study, but as the number of NNLNs increased, recurrence and CRM decreased, and DFS and OS increased. NHLN was more than double the number recommended in the literature, which is sufficient for NMLN and NNLN-dependent staging. For this reason, a classification which includes or combines NMLN and NNLN variables may provide more information.

Additionally, there are also studies investigating the predictive values of the NNLN number in the survival of BC. The predictive value of the intact lymph node count in BC patients remains uncertain.[16,17] In our study, 239 patients did not have lymph node metastases. A significant cut-off value for NNLN could not be determined in these patients, but it was shown that both DFS and OS increased significantly with increasing NNLN. Among all patients, an NNLN of 13 or more for cancer recurrence and 15.5 or more for CRM was determined as a good prognostic factor. Similarly, Kuru[18] indicated that an NNLN number over 15 was significantly associated with a better prognosis. In another study, NNLN was found to affect survival in BC with 4 or more metastatic lymph nodes.[19] In another case series of 455 cases in which the NNLN cut-off value was determined as 5, it was shown that DFS and OS were better in those with NNLN numbers of 5 and above. However, when multivariate analysis was performed in that same study, no difference was found in DFS and OS.[20] In our study, only the LODDS variable for OS was found to be significant among the lymph node parameters in multivariate analysis. However, the ACOSOG Z0011 randomized trial demonstrated that the extension of axillary lymph node dissection did

Table 3. Distribution of lymph node parameters according to recurrence and mortality groups with t-test statistics

	Recurrence					Survival				
	None		Recurrence		p	Survive		Ex		p
	m	SD	m	SD		m	SD	m	SD	
NHLN	21,122	8,865	21,584	10,186	0.819	21,051	8,605	22,147	10,603	0.495
NMLN	3,629	5,699	8,344	10,067	<0.001	3,456	5,199	7,214	9,776	<0.001
NNLN	17,493	9,288	13,239	9,361	<0.001	17,595	9,194	14,933	10,107	<0.001
LNR	0.179	0.246	0.373	0.337	<0.001	0.176	0.246	0.315	0.324	<0.001
mLNR	4,158	5,696	8,875	10,060	<0.001	3,985	5,196	7,743	9,770	<0.001
LODDS	-0.873	0.717	-0.355	0.881	<0.001	-0.884	0.707	-0.498	0.884	<0.001

NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes, m: Mean, SD: Standard deviation.

Table 4. Distribution of nominal variables according to recurrence and mortality groups with chi-square statistics

		Recurrence					Survival				
		None		Recurrence		p	Ex		Survive		p
		n	%	n	%		n	%	n	%	
Surgery	Mastectomy	470	79%	194	93%	**<0.001**	238	94%	331	73%	**<0.001**
	Breast conserving surgery	128	21%	15	7%		14	6%	123	27%	
ER status	Negative	203	36%	86	44%	0.061	99	42%	146	34%	**0.038**
	Positive	359	64%	111	56%		139	58%	289	66%	
PR	Negative	211	38%	80	41%	0.428	99	42%	143	33%	**0.032**
	Positive	347	62%	115	59%		139	58%	287	67%	
HER-2	Negative	340	76%	108	67%	**0.028**	131	70%	270	76%	0.121
	Positive	110	24%	54	33%		57	30%	86	24%	
Lymphovascular Invasion	Negative	228	64%	52	42%	**<0.001**	76	52%	182	62%	**0.048**
	Positive	126	36%	71	58%		70	48%	112	38%	
Molecular classification	Luminal A	263	57%	75	46%	<0.075	94	49%	216	60%	0.084
	Luminal B	82	18%	36	22%		41	21%	65	18%	
	Triple negative	80	17%	35	21%		40	21%	56	16%	
	HER-2 overexpressed	34	7%	18	11%		18	9%	24	7%	
T-stage	T1	178	30%	26	13%	**<0.001**	47	19%	142	32%	**<0.001**
	T2	352	60%	117	57%		143	58%	255	57%	
	T3	46	8%	39	19%		33	13%	41	9%	
	T4	15	3%	24	12%		24	10%	11	2%	
N-stage	N0	200	33%	39	19%	**<0.001**	56	22%	153	34%	**<0.001**
	N1	216	36%	46	22%		68	27%	164	36%	
	N2	117	20%	57	27%		61	24%	90	20%	
	N3	65	11%	67	32%		67	27%	47	10%	
M-stage	None	598	100%	189	90%	**<0.001**	242	96%	444	98%	0.176
	Distant metastasis	0	0%	20	10%		10	4%	10	2%	
LNR groups (literature)	LNR=0	199	25%	38	5%	**<0.001**	55	7%	152	19%	**<0.001**
	0< LNR ≤0.2	232	29%	58	7%		77	10%	183	23%	
	0.2< LNR ≤0.65	116	14%	57	7%		67	8%	81	10%	
	LNR >0.65	51	6%	56	7%		53	7%	38	5%	
LODDS groups (literature)	LODDS ≤-1.5	144	24%	25	12%	**<0.001**	40	16%	110	24%	**<0.001**
	-1.5< LODDS ≤-1.0	148	25%	28	13%		38	15%	117	26%	
	-1.0< LODDS ≤-0.5	150	25%	48	23%		62	25%	114	25%	
	-0.5< LODDS ≤0	78	13%	28	13%		37	15%	52	11%	
	LODDS >0	78	13%	80	38%		75	30%	61	13%	

Table 4. Continued

		Recurrence					Survival				
		None		Recurrence		p	Ex		Survive		p
		n	%	n	%		n	%	n	%	
mLNR cut-off groups	mLNR ≤2.5257	343	57%	72	34%	**<0.001**	99	39%	263	58%	**<0.001**
	mLNR >2.5257	255	43%	137	66%		153	61%	191	42%	
NHLN risk groups recurrence/ survival	NHLN ≤19.50	291	36%	98	12%	0.659	119	15%	218	27%	0.839
	NHLN >19.50	307	38%	111	14%		133	16%	236	29%	
NMLN risk groups for recurrence/ survival	NMLN ≤2.5	371	46%	77	10%	**<0.001**	109	14%	283	35%	**<0.001**
	NMLN >2.5	227	28%	132	16%		143	18%	171	21%	
NNLN risk groups for recurrence	NNLN ≤13.0	204	25%	116	14%	**<0.001**	117	14%	152	19%	
	NNLN >13.0	394	49%	93	12%		135	17%	302	37%	
NNLN risk groups for survival	NNLN ≤15.5	254	31%	133	16%		140	17%	185	23%	**<0.001**
	NNLN >15.5	344	43%	76	9%		112	14%	269	33%	
LNR risk groups for recurrence	LNR ≤0.140	379	47%	77	10%	**<0.001**	111	14%	290	36%	
	LNR >0.140	219	27%	132	16%		141	17%	164	20%	
LNR risk groups for survival	LNR ≤0.117	353	44%	72	9%		104	13%	269	33%	**<0.001**
	LNR >0.117	245	30%	137	17%		148	18%	185	23%	
LODDS risk groups for recurrence	LODDS ≤-0.728	377	47%	79	10%	**<0.001**	114	14%	289	36%	
	LODDS >-0.728	221	27%	130	16%		138	17%	165	20%	
LODDS risk groups for survival	LODDS ≤-0.805	348	43%	71	9%		100	12%	268	33%	
	LODDS >-0.805	250	31%	138	17%		152	19%	186	23%	**<0.001**

ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor-2, LNR: Lymph node ratio, LODDS: Log odds of positive lymph nodes, mLNR: Modified lymph node ratio, NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes.

Table 5. Cut-off values of lymph node parameters calculated by ROC analysis for cancer recurrence and cancer-related mortality with their sensitivity and specificity

Variable(s)	Area	p	Cut-off value	Sensitivity	Specificity		
			Lower	Upper			
Recurrence							
NHLN	0.505	0.819	0.458	0.552	**19,500**	**0.531**	**0.487**
NMLN	0.666	0	0.621	0.710	**2,500**	**0.632**	**0.620**
NNLN	0.362	0	0.317	0.407	**13**	**0.445**	**0.341**
LNR	0.673	0	0.629	0.717	0.140	0.632	0.634
mLNR	0.670	0	0.625	0.714	2,524	0.675	0.676
LODDS	0.674	0	0.630	0.718	-0.728	0.622	0.630
Survival							
NHLN	0.521	0.340	0.477	0.565	**19,500**	**0.528**	**0.586**
NMLN	0.617	0	0.574	0.660	**2,500**	**0.567**	**0.506**
NNLN	0.426	0.001	0.382	0.470	**15,500**	**0.444**	**0.445**
LNR	0.388	0	0.348	0.427	0.117	0.407	0.442
mLNR	0.391	0	0.352	0.431	2,526	0.421	0.431
LODDS	0.448	0.448	0.448	0.448	0.448	0.448	0.448

ROC: Receiver operating characteristic, NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes.

not improve the survival of BC patients compared to negative or less than three positive sentinel lymph nodes after surgery. Also, expanded axillary lymph node dissection was recommended to be avoided. They showed that radical axillary lymph node dissection followed by axillary radiotherapy was associated with higher morbidity.[21]

LNR staging is recommended as another lymph node staging in BC patients. There are different reasons for this. Firstly, LNR has been shown to be more advantageous over pN stage, especially in those patients with low NHLN counts.[5] Another factor is that LNR makes the staging system more comparable between different oncological managements.[22]

Finally, it partially prevents pN deviations.[23,24] The importance of LNR in BC is increasing currently, but the cut-off values recommended for LNR varies widely in the literature.[25,26] Although LNR is generally divided into groups according to different threshold values in studies, there is no general agreement. The most accepted classification was proposed by Vinh-Hung et al.[12] This recommended classification was based on 1,829 patient results. In that study, LNR rates were divided into three risk groups (low, ≤0.20; intermediate, 0.21-0.65; and high, >0.65). There have been studies using this classification[27]. In our study, we tested this classification and analyzed a cut-off value in our own population. Both the classification reported in the literature and the dual classification according to the cut-off values determined in this study were significant for DFS and OS. However, the cut-off values in this study were in the low-risk group according to the classification in the literature and were partially compatible (0.140 for recurrence and 0.117 for CRM). A sufficient number of original studies and meta-analysis studies are needed for a universally used LNR classification.

In order to increase the prognostic power of the LNR value over time, especially for those patients with LNRs of "0 or 1", mLNR has been suggested and it is thought to be more powerful. However, there are limited studies in the literature on this subject. Wen et al.[11] recommended groupings as 0.5 and below vs. above 0.5 for the mLNR ratio in a large series (n=3,339). In their study, it was shown

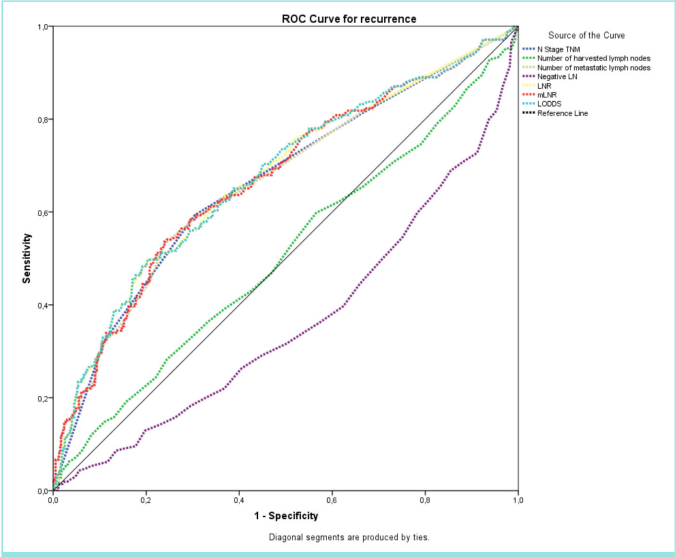

Figure 1. ROC curves of lymph node parameters for cancer recurrence.

ROC: Receiver operating characteristic.

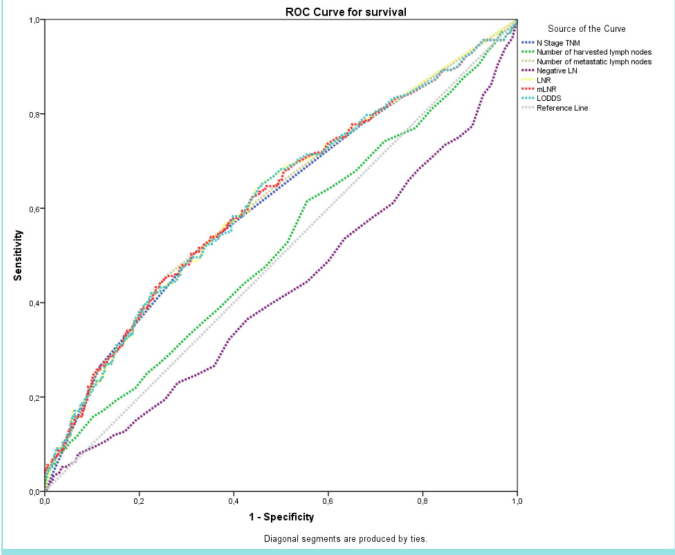

Figure 2. ROC curves of lymph node parameters for cancer related mortality.

ROC: Receiver operating characteristic.

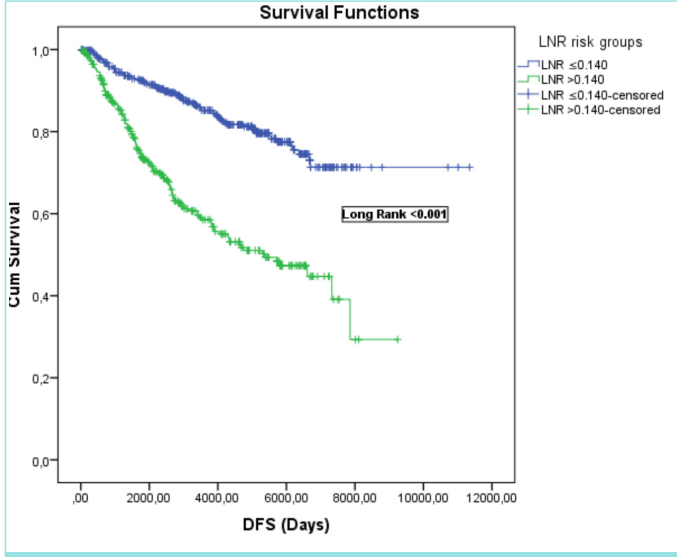

Figure 3. Kaplan-Meier DFS graph of LNR groups by cut-off values.

DFS: Disease-free survival, LNR: Lymph node ratio.

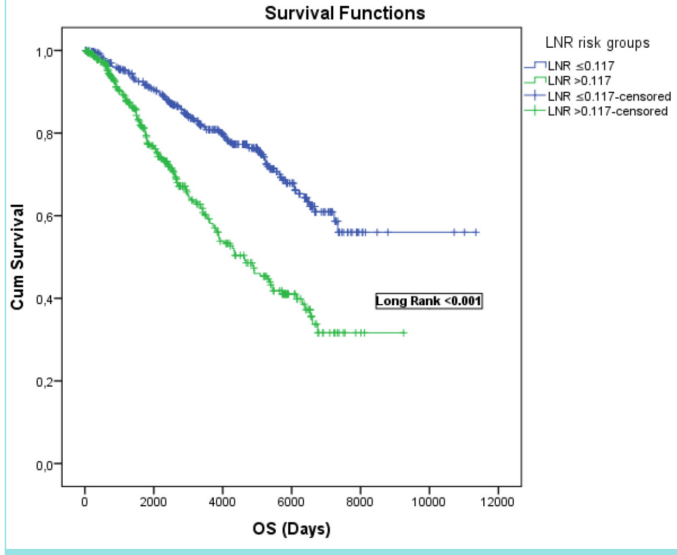

Figure 4. Kaplan-Meier OS graph of LNR groups by cut-off values.

OS: Overall survival, LNR: Lymph node ratio.

that mLNR is an independent parameter in cancer-specific survival and is a much stronger prognostic factor than classical pN staging, especially in those patients with limited lymph node counts. Similarly, the importance of mLNR was supported by a much larger number of BC patients (n=264,096) and two cut-off values for mLNR were recommended in that study; 0.20 and 0.50 were suggested.[10] In the present study, the cut-off value of mLNR was found to be 2.52, with this value being higher than the previously recommended values. Despite the high number of NHLNs in our study, this finding may be due to large number of axillary dissections or heterogeneity in the patient groups.

The LODDS is a similar parameter derived from NMLN and NNLN and it is discussed in the literature with different cut-off values. In the literature, the LODDS classification has been shown to be a convenient prognostic factor in determining survival in different cancers.[28,29] It was also an independent prognostic factor in BC and it was superior to pN staging.[12] In some studies, similar LODDS classifications were used, but their effects on survival were found to be different. This may be due to the small number of BC cases in these studies.[30] The cut-off values of LODDS for cancer recurrence (-0.728) and CRM (-0.805) in our study provided a useful distinction for DFS and OS. Also, according to multivariate analysis, LODDS was reported to be an independent risk factor for OS among all lymph node staging systems.

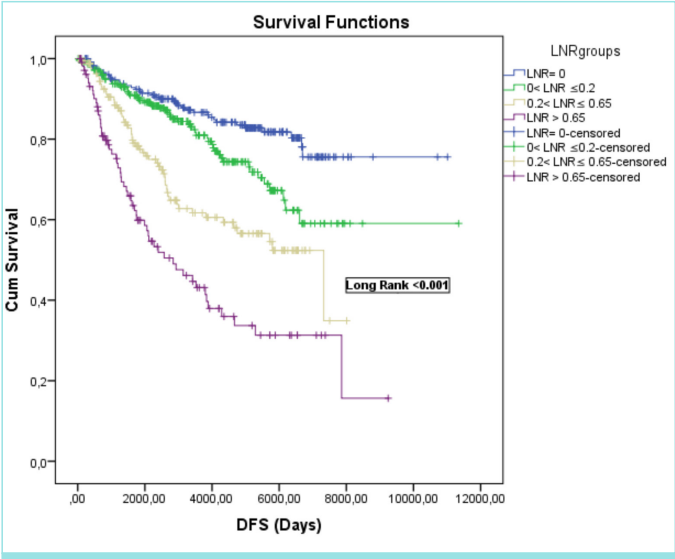

Figure 5. Kaplan-Meier DFS graph of LNR groups cited in the literature.

DFS: Disease-free survival, LNR: Lymph node ratio.

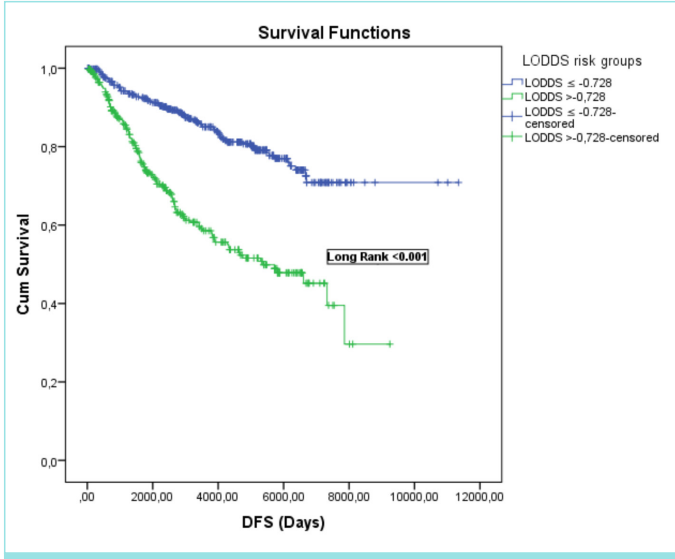

Figure 7. Kaplan-Meier DFS graph of LODDS groups by cut-off values.

DFS: Disease-free survival, LODDS: Log odds of positive lymph nodes.

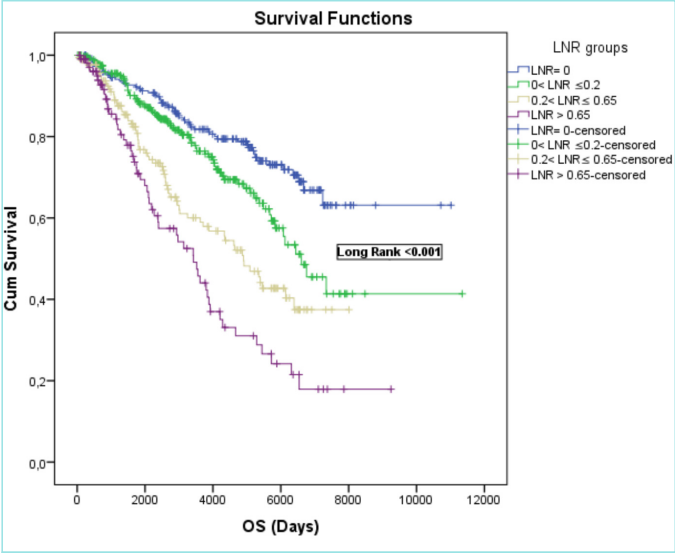

Figure 6. Kaplan-Meier OS graph of LNR groups cited in the literature.

OS: Overall survival, LNR: Lymph node ratio.

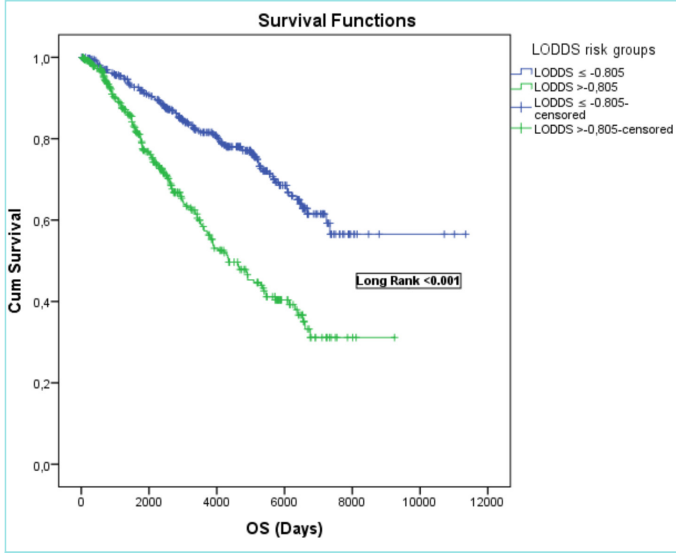

Figure 8. Kaplan-Meier OS graph of LODDS groups by cut-off values.

OS: Overall survival, LODDS: Log odds of positive lymph nodes.

Study Limitations

The present study has a list of limitations which should be considered. Firstly, the retrospective design of this study may have caused data to be lacking. Additionally, the sampling of this study was from a single center which may have caused selection bias despite the large sample size. Also, the time of initial diagnosis of some cases goes back to 1989, so HER-2 status could not be accurately identified in some patients. However, this situation was not an obstacle to our primary purpose in this study. Thirdly, the changes in treatment options over time may have affected outcomes. Therefore, we cannot apply detailed therapy categories to the prognostic models.

CONCLUSION

In the present study, we assessed the survival of BC patients in Türkiye in order to determine different parameters of lymph node status (NHLN, NNLN) and the prognostic value of some different lymph node staging methods (AJCC N-stage, LNR, mLNR, LODDS). Until now, there had been no study comparing the different parameters of lymph node status and the N-stage for predicting BC outcomes with surgery in the Turkish population. The results showed that LODDS seems to be a better option compared to pN classification for OS, which is consistent with previous studies. The present study demonstrated that LODDS has greater usefulness in determining BC patients with distant metastasis compared with the AJCC pN classification.

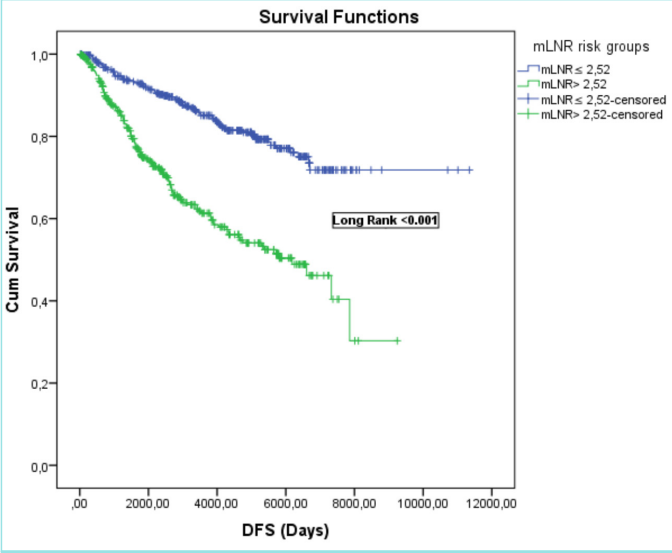

Figure 9. Kaplan-Meier DFS graph of mLNR groups by cut-off values.

DFS: Disease-free survival, mLNR: Modified lymph node ratio.

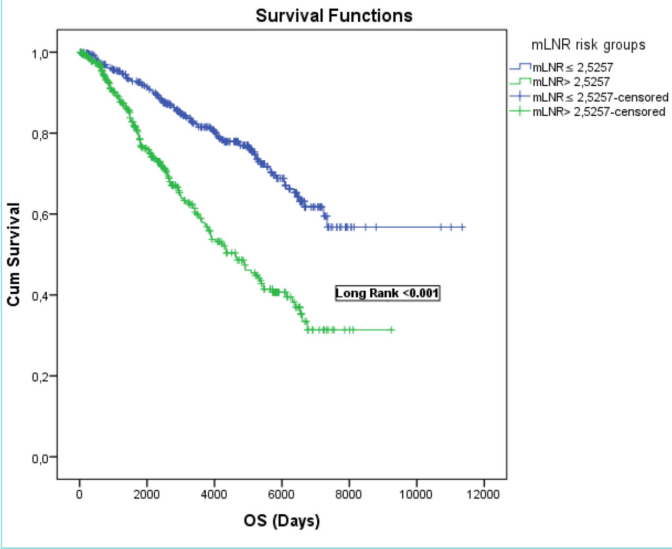

Figure 10. Kaplan-Meier OS graph of mLNR groups by cut-off values.

OS: Overall survival, mLNR: Modified lymph node ratio.

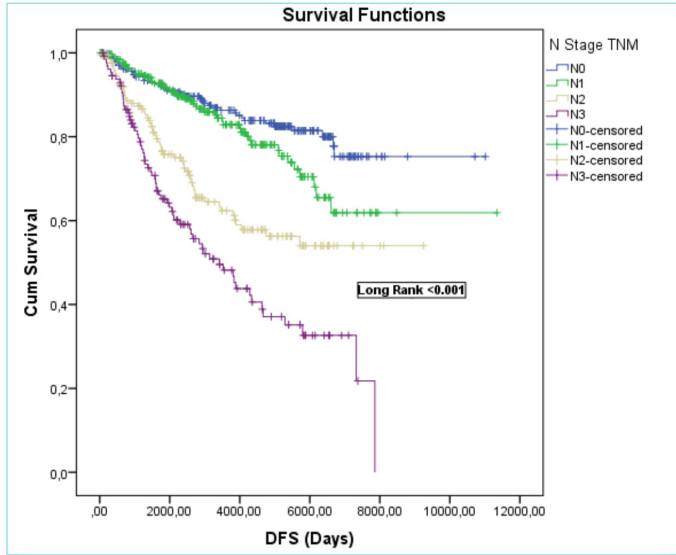

Figure 11. Kaplan-Meier DFS graph of AJCC N-stages.

DFS: Disease-free survival, AJCC: American Joint Committee on Cancer.

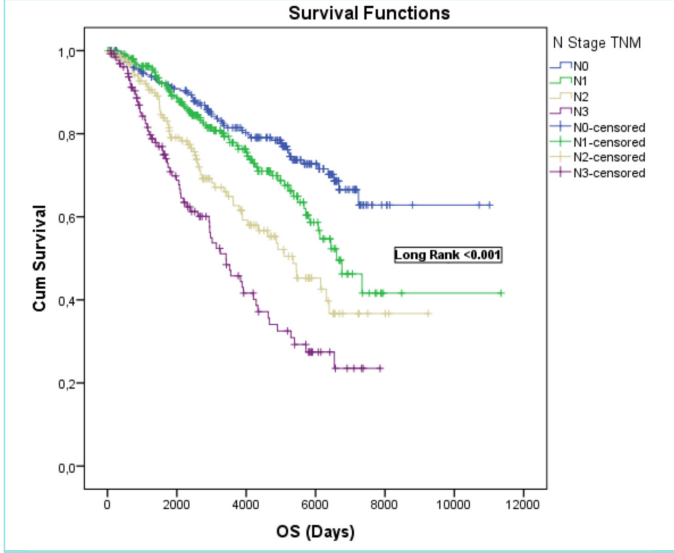

Figure 12. Kaplan-Meier OS graph of AJCC N-stages.

OS: Overall survival, AJCC: American Joint Committee on Cancer.

Table 6. Cox regression analysis of lymph node parameters for disease-free survival and overall survival

Disease-free survival					
	B	p	HR	95% CI for HR	
				Lower	Upper
N-stage (N0)	-	0.617	-	-	-
N-stage (N1)	0.016	0.962	1,016	0.521	1,981
N-stage (N2)	0.336	0.263	1,399	0.777	2,519
N-stage (N3)	0.155	0.627	1,167	0.626	2,175
LNR	-0.050	0.968	0.951	0.083	10,957
mLNR	0.027	0.084	1,027	0.996	1,058
LODDS	0.425	0.481	1,529	0.470	4,980
NNLN	-0.007	0.656	0.993	0.964	1,023
Overall survival					
	B	p	HR	95% CI for HR	
				Lower	Upper
N-stage (N0)	-	0.766	-	-	-
N-stage (N1)	-0.303	0.311	0.739	0.411	1,327
N-stage (N2)	-0.216	0.428	0.805	0.472	1,376
N-stage (N3)	-0.175	0.571	0.839	0.458	1,538
LNR	-1,534	0.174	0.216	0.024	1,970
mLNR	0.025	0.112	1,026	0.994	1,058
LODDS	1,331	0.014	3,784	1,308	10,947
NNLN	0.023	0.068	1,023	0.998	1,049

CI: Confidence interval, HR: Heart rate, LODDS: Log odds of positive lymph nodes, NHLN: Number of harvested lymph nodes, NNLH: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio.

MAIN POINTS

- In this article study, we assessed the survival of Turkish patients with breast cancer to determine different parameters of lymph node status (NHLN, NNLN) and the prognostic value of different lymph node staging methods (AJCC N-stage, LNR, mLNR, LODDS.
- Until now, no study comparing different parameters of lymph node status and the lymph node staging methods for predicting outcome in BC patients with mastectomy has been reported in Turkish population.
- The results indicated that LODDS is superior to pN classification for OS.
- We can say that the LODDS has obvious advantages in discriminating patients in non-distant metastatic BC compared with the AJCC pN classification.

ETHICS

Ethics Committee Approval: The study was designed retrospectively. Permission was obtained from the necessary places for data sharing.

Informed Consent: Informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ö.E., A.İ., B.Z., Concept: N.Ö.E., İ.B., B.Z., Design: N.Ö.E., A.İ., B.Z., Data Collection or Processing: N.Ö.E., A.İ., Analysis or Interpretation: N.Ö.E., İ.B., A.İ., Literature Search: N.Ö.E., İ.B., Writing: N.Ö.E., İ.B.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

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The Effect of the COVID-19 Pandemic on Dermocosmetic Application Demand in North Cyprus

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Abstract

BACKGROUND/AIMS: In the literature, it has been reported that during the pandemic period, people's interest in dermocosmetic applications for facial rejuvenation increased and there was a greater demand for minimally invasive procedures. According to our literature search, we could not find any data on how the pandemic affected the dermocosmetic practices and personal care habits of the people living in North Cyprus. In our study, we aimed to evaluate the demand for dermocosmetic application methods during the coronavirus disease 2019 pandemic period and to compare any changes with the cosmetic application habits of people during the pre-pandemic and the pandemic periods.

MATERIAL AND METHODS: A questionnaire was administered to 153 patients who applied to our outpatient clinic for dermocosmetic applications between March, 2020 and December, 2021. Questions were asked about changes in the usage of anti-aging products, hair changes, nail applications and make-up habits between the pre-pandemic period and the pandemic period. In addition, the frequency of dermocosmetic applications was also investigated. The type of protective face mask used, the duration of daily mask usage, and dermatological complaints related to the mask were all reported on.

RESULTS: The dermocosmetic procedures requested during the pandemic period were mainly botulinum toxin (55%) and medical skin care (54.2%), as well as filler (11.1%), platelet-rich plasma injection (6.5%) and mesotherapy (4%). Of the 153 people who applied for dermocosmetic application during the pandemic period, 84 in our study (54.9%) reported that they were having this application for the first time in their lives.

CONCLUSION: During the pandemic period, the demand for dermocosmetic applications continued, and it was noteworthy that even those who had not had this habit prior to the pandemic started having these applications.

Keywords: Cosmetic procedures, COVID-19, pandemics, skincare products

INTRODUCTION

The coronavirus disease-2019 (COVID-19), which first emerged in December, 2019, was declared a global pandemic by the World Health Organization on March 11th, 2020. As a result, many countries were forced to take extensive quarantine measures in order to contain this epidemic. The first case in North Cyprus was identified on the 10th of March, 2020 and various measures were taken by the government in North Cyprus, such as the closure of schools and a partial or full lockdown.[1]

It is known that interest in cosmetic procedures and the use of skin care products decreased due to the effects of the many restrictive factors such as the limited availability of information about the disease and lockdown, particularly at the beginning of the COVID-19 pandemic. In the subsequent period, with the clarification of more information about the diagnosis, prevention methods and treatment of the disease, the process of adapting to the new situation started and an increase in the tendency for skincare and practices related to personal appearance was observed.[2,3] To the best of our knowledge, no other study was conducted on how the pandemic affected people's dermocosmetic practices and

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personal care habits in our country, and there are also very few studies on this subject in the literature in general. In this study, we aimed to evaluate the demands for dermocosmetic applications during the pandemic period and to make comparisons with the current literature.

MATERIALS AND METHODS

Patients who applied to our outpatient clinic between March, 2020 and December, 2021 for dermocosmetic applications were included in our study. This study was approved by Near East University's Local Ethics Committee (approval number: 2022/99-1471). Verbal informed consent was obtained from the patients included in this study, and the questions in the questionnaire which were created by reviewing the relevant literature were asked. The questionnaires were administered to those patients who gave verbal consent by contacting them via the phone numbers or e-mail addresses listed in the contact information registered in our clinic. Demographic questions were asked about their age, gender, daily working hours during the pandemic period, and the possibility of working from home during the pandemic. In addition, respondents were asked about their own history of quarantines as well as their first-degree relatives and friends during the pandemic process, and if a first-degree relative or friend had died due to COVID-19. In addition, changes in anti-aging products, hair changes, nail applications, changes in make-up habits, continuity of laser epilation applications, oral collagen and/or oral vitamin use for hair and skin health were investigated in terms of the pre-pandemic and pandemic periods. The patients participating in this survey were also questioned about their frequency of medical skin care, botulinum toxin, dermal filling, mesotherapy and PRP applications, sunscreen usage habits, exercise and weight change. The type of protective face mask used during the pandemic period, the duration of daily protective face mask usage, and dermatological complaints related to the use of protective face masks were reported on.

Statistical Analysis

The study data were analysed by 25.0 version of SPSS for Windows (IBM Corporation, Armonk, New York). In terms of descriptive statistics, the calculation of frequencies, mean ± standard deviation (SD), ratios and percentages was undertaken using the sociodemographic data collected and other measurements performed in this study. The independent t-test was used to examine the relationships between the responses of the patients before and during the pandemic. Qualitative variables were categorized and they are presented as frequencies and percentages. Quantitative variables are presented as means and SDs. A p-value <0.05 was considered significant.

RESULTS

A total of 153 patients, 14 (9.2%) men and 139 (90.8%) women, aged between 18-73 (36.6±10.9) years were included in this study. The daily working hours of the patients participating in this study, the ratio of patients included in this study who worked from home during the pandemic period, the rate of those who had received the COVID-19 vaccine, those who had been quarantined due to contact with a person diagnosed with COVID-19, those who had been diagnosed with COVID-19, and any death history due to COVID-19 are shown in Table 1.

The data on changes in cosmetic habits such as topical anti-aging products, hairstyle or colour, make-up habits and nail applications during the pandemic of the patients included in this study are shown in Table 2.

Forty-seven (30.7%) of the patients included in this study reported that they continued laser epilation applications at the clinic. Twenty-two (14.4%) of the participants stated that they started using oral collagen for skin health, while 21 (13.7%) started using oral vitamins for hair and skin health during the pandemic period.

The types of protective face masks used by the patients included in this study, the daily protective face mask usage hours and the distribution of dermatological complaints related to protective face masks are shown in Table 3.

The dermocosmetic application demands of the participants in the 2 years preceding the pandemic and during the pandemic are compared in Table 4. It can be observed that the demands for medical skin care, botulinum toxin and dermal filler applications increased statistically significantly during pandemic. Of the 153 people who applied for dermocosmetic applications during the pandemic, 84 (54.9%) reported

Table 1. Demographic features of the participants

Variable	n (%)*
Gender	
Female	139 (90.8%)
Male	14 (9.2%)
Age (years) (mean ± SD; range)	36.6±10.9; 18-73
Daily working hours (hours/day) (mean ± SD; range)	6.5±3.03; 0-10
Working from home	51 (33.3)
COVID-19 vaccine	81 (52.9)
Quarantined	
Him/herself	25 (16.3)
First degree relative	32 (20.9)
Friend	55 (35.9)
Diagnosed with COVID-19	
Him/herself	5 (3.3)
First degree relative	25 (16.3)
Friend	31 (20.3)
Died due to COVID-19	
First degree relative	4 (2.6)
Friend	1 (0.7)

SD: Standard deviation, COVID-19: Coronavirus disease-2019.

Table 2. Changes in women's cosmetic habits

Variable		n	%*
Make-up habits	Stopped wearing make-up	49	32
	Started wearing make-up	4	2.6
Hair applications	Change in hairstyle or colour	72	47.1
	Started to do hair colouring at home	36	23.5
Nail applications	Stopped nail applications	60	39.2
	Started to do nail applications at home	39	25.5
	Continued going to a centre for nail applications	30	19.6
Anti-aging products usage	Made changes in anti-aging products	13	8.5

that they were having a dermocosmetic application for the first time in their lives.

The exercise habits and weight change data of the participants during the pandemic period are shown in Table 5.

The changes in the sunscreen product usage habits of the participants during the pandemic period are shown in Table 6. Sunscreen product usage was 79.8% before the pandemic and it decreased to 64.1% during the pandemic.

DISCUSSION

In our study, the most requested dermocosmetic procedure during the pandemic period was found to be botulinum toxin application (55%). This may be due to the fact that people focused more on the upper face due to the use of protective face masks, the application of botulinum toxin especially creates positive results in this area, and it is preferred because it maintains its effectiveness for an average of 6 months with a single-session application. Chugh et al.[4] reported that patients treated with botulinum toxin showed significantly reduced negative moods. This situation may have caused an increase in demand among people who have the habit of applying botulinum toxin regularly, with the effect of inducing a negative mood during the pandemic period. In our study, 35 (41.6%) of 84 people to whom botulinum toxin was applied reported that they had had botulinum toxin at least once before. In the study of Aslan Kayıran et al.[2], it was reported that those patients who had botulinum toxin and dermal fillers before the pandemic continued these procedures during the pandemic period.

It was reported that patient willingness to have aesthetic procedures and the frequency of surgery increased significantly, especially when compared with other areas of facial plastic and reconstructive surgery during the COVID-19 pandemic. It is thought that the quarantine, the obligation to stay at home and the necessity to use protective face masks may have created an extra opportunity for patients who want to have privacy during their process of recovering after cosmetic surgery.[5]

It was reported that there was a greater demand for minimally invasive procedures such as botulinum toxin, dermal filler, PRP, dermaroller and chemical peeling for facial rejuvenation during the pandemic period.[6,7] According to a study conducted in Türkiye, the most frequently performed cosmetic procedures during the pandemic were botulinum toxin (25.4%), medical skincare treatment (31%), chemical peeling (24.5%) and dermal filler (12.5%).[2] In our study, when the frequency of dermocosmetic procedures applied during the pandemic period was evaluated, it was found to be botulinum toxin (55%), medical skincare (54.2%), dermal filler (11.1%), PRP (6.5%) and mesotherapy (4%) respectively. Gao et al.[8] reported on the distribution cosmetic procedures during the pandemic period and found that 55.9% were laser and light treatments, 22.6% were botulinum toxin and dermal filler injections, and 14.6% were chemical peeling.

Pikoos et al.[9] reported an increase in appearance-oriented behaviours such as mirror checking and appearance comparisons in people with higher dysmorphic anxiety during the COVID-19 pandemic. Also, another study reported an association between COVID-19-related stress and negative body image in adults.[10] It has been argued that spending too much time at home during the pandemic period, the increase in the use of social media, the longing for innovation and change due to the stress brought on by the pandemic conditions, as well as the increase in the use of video conferencing platforms caused an increase in concerns about facial appearance and this accelerated the demand for cosmetic applications.[5,11]

Of the 153 people who applied for dermocosmetic applications during the pandemic period, 84 people in our study (54.9%) reported that

Table 3. Features of the protective face masks used by the participants

Variable	n (%)*
Types of protective face masks	
Three ply masks	120 (78.4)
Cloth mask	33 (21.6)
Daily mask usage hours	
Less than 4 hours/day	59 (38.6)
4-8 hours/day	66 (43.1)
More than 8 hours/day	28 (18.3)
Dermatological complaints related to protective face mask usage	78 (51)
New onset acne after using mask	34 (22.2)
Increase in acne	12 (7.8)
Facial itching, redness and dandruff	32 (20.9)

Table 4. Dermocosmetic applications before and during the pandemic

Cosmetic procedure	Before pandemic	During pandemic	p[a]	
	n (%)*	n (%)*		
Medical skincare	36 (23.5)	83 (54.2)	0.001	
Botulinum toxin	35 (22.9)	84 (55)	0.001	
Dermal filler	8 (5.2)	17 (11.1)	0.001	
Face PRP	7 (4.6)	1 (0.6)	0.790	
Hair PRP	4 (2.6)	10 (6.5)	0.906	
Face mesotherapy	3 (2)	6 (4)	0.749	

PRP: Platelet-rich plasma injection.

Table 5. Exercise habits and weight change

Variable	n (%)*
Exercise habits	
Stopped exercising during the pandemic	70 (45.8)
No exercising before or during	50 (32.7)
Started to exercise during the pandemic	25 (16.3)
Continued to exercise	8 (5.2)
Weight change	
No change in their weight	61 (39.9)
Gained weight	59 (38.6)
Lost weight	33 (21.6)

Table 6. Participants' use of sunscreen

Variable	n (%)
Use of sunscreen	
Continued to use	91 (59.5)
Discontinued during the pandemic	31 (20.3)
Not using	24 (15.7)
Started to use	7 (4.6)

they were having this application for the first time in their lives. In another study conducted in Türkiye, it was reported that 56.8% of the participants had never had a cosmetic procedure before.[2]

In studies conducted in Nepal and Poland, it was reported that the rate of hair dyeing decreased during the pandemic period.[12,13] In our study, 47.1% of the participants reported changes in their hair style or colour and 23.5% of the participants stated that they started to dye their hair at home during the pandemic period.

Aslan Kayıran et al.[2] reported that while 29.7% of people regularly wore make-up before the pandemic, this rate was reduced to 9.9% during the pandemic period. In studies conducted in Nepal and Poland, it was reported that make-up materials application rates decreased during the pandemic period.[12,13] In our study, 34.6% of the participants reported a change in make-up habits, 32% reported that they stopped wearing make-up during the pandemic period, and 2.6% started using make-up when they had not had this habit before.

In our study, 47 (30.7%) of the participants reported that they continued laser epilation applications in a centre. In the study of Aslan Kayıran et al.[2], it was found that 31.6% of the participants continued laser epilation. Bakhati and Agrawal[13] revealed a decrease in hair removal practices during the pandemic. In a study among Polish women, hair removal rates did not change significantly.[12]

We also evaluated anti-aging product usage in our study. One hundred and forty (91.5%) of the participants reported that they continued using the topical antiaging product which they had been using during the pre-pandemic period, while 13 (8.5%) made a change. In the study of Aslan Kayıran et al.[2], it was reported that there was no change in the rate of anti-aging product use before and during the pandemic.

Giacalone et al.[14] reported that protective masks used during the pandemic period had an inducing effect on acne, rosacea and seborrheic dermatitis. Techasatian et al.[15] reported that 54.5% of participants had adverse skin reactions related to the use of protective face masks, which were acne (39.9%), facial rash (18.4%) and itching (15.6%), respectively. In our study, 78 people (51%) reported dermatological complaints related to protective face masks, 22.2% had new-onset acne, 20.9% had facial itching, redness and dandruff, and 7.8% had existing acne on the face. In our study, no statistically significant relationship was found between mask type and skin reaction (p=0.09).

Study Limitations

Regarding the daily use of protective face masks, it was reported that wearing a protective face mask for more than 4 hours a day increased the risk of adverse skin reactions.[15] In our study, a statistically significant relationship was found between mask wearing time and skin reactions, and more reactions were reported in those who wore a mask for more than 8 hours a day (p=0.009).

CONCLUSION

In our study, the most requested dermocosmetic procedures during the pandemic period were found to be botulinum toxin and medical skin care applications. The reason why botulinum toxin application was preferred could be that people focused more on the upper face due to the use of protective face masks. On the other hand, medical skin care applications may have been preferred more because it is a non-invasive and painless procedure, more financially affordable, and the person feels special during the application. As a result, during the pandemic period, the demand for dermocosmetic applications continued, and it was noteworthy that even those who did not have this habit previously started having these applications.

MAIN POINTS

- To the best of our knowledge, no other study was previously conducted on how the pandemic affected people's dermocosmetic practices and personal care habits in North Cyprus.
- During the pandemic period, the demand for dermocosmetic applications continued, and it was noteworthy that even those who did not have the habit prior to the pandemic began using these applications.
- In our study, the most requested dermocosmetic procedures during the pandemic period were found to be botulinum toxin and medical skin care applications.

ETHICS

Ethics Committee Approval: This study was approved by Near East University's Local Ethics Committee (approval number: 2022/99-1471).

Informed Consent: Verbal informed consent was obtained from the patients included in this study.

Peer-review: Externally peer-reviewed.

DISCLOSURES

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RESEARCH ARTICLE

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Assessment of the Push-Out Bond Strength of Three Different Root-End Filling Materials in Retrograde Cavities Using Three Different Retro Preparation Techniques

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Abstract

BACKGROUND/AIMS: The aim of this study was to evaluate the push-out bond strength of root-end cavities filled with different retrograde filling materials.

MATERIALS AND METHODS: Straight and single root canals of 180 maxillary incisor teeth were prepared, obturated, and randomly divided into nine groups (n=20 per group). In each group, one of the root-end cavity preparation techniques (drill, erbium:yttrium, aluminum-garnet laser, or ultrasonic retrotip) was applied and matched with a retrograde filling [ProRoot mineral trioxide aggregate (MTA), Tech Biosealer Root End, or Biodentine]. Three slices were sectioned from the root apex, and the middle ones were selected. They were placed in a universal testing machine, applying push-out force until bond failure occurred. The push-out bond strength values at bond failure were analyzed using Kruskal-Wallis H test and post-hoc multiple comparison test ($p<0.05$).

RESULTS: The bond strengths between the root-end cavities prepared with a bur, laser, and ultrasonic retrotip and the filling materials (MTA, Tech Biosealer Root End, and Biodentine) were determined to be statistically significantly different ($p<0.05$). The highest mean value occurred in the ultrasonic + Biodentine group, whereas the lowest mean value was seen in the bur + Tech Biosealer group. There were no statistical differences between the cavities prepared with laser and ultrasonic retrotip and filled with MTA and Biodentine ($p>0.05$). However, the mean bonding strength of Biodentine placed in cavities prepared with the drill was significantly higher than MTA and Tech Biosealer ($p<0.05$).

CONCLUSION: In laser-prepared cavities, Tech Biosealer showed lower bonding strength compared to the other materials. Similarly, in ultrasonic retrotip prepared cavities, Biodentine and MTA showed better bonding, while Tech Biosealer showed a weaker bonding.

Keywords: Retrograde cavity, laser, ultrasonic, Tech Biosealer Root End, Biodentine

INTRODUCTION

To have a successful outcome from endodontic treatment, the endodontist should seal the root canal to provide a fluid-tight seal in all three dimensions.[1] In some cases, pathological formations might occur at the periapical area, and applying a non-surgical process to remove them might not work effectively. For these cases, surgical action becomes necessary.[2] The rationale of endodontic surgery is the regeneration of the periapical tissues to a healthy state. It is a procedure which involves apical resection, root-end cavity preparation, and root-end filling. Surgical intervention is preferred when periapical pathology is resistant or one of the following is present: overfilled canals, a barrier in the canal, ridges, apical transportations, broken instruments, or perforations.[2,3]

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To achieve successful results by endodontic surgery, one has to select a high-profile root-end filling material. In an ideal situation, it has to be biocompatible, to promote healing, to have good strength and excellent sealing ability, to be radiopaque, to not be affected by moisture, and to be easy to manipulate.[4] Numerous different materials have been used for root-end filling from the past to the present. The most common ones are amalgam, composite resins, glass ionomers, zinc oxide eugenol cement, mineral trioxide aggregate (MTA), and super ethoxy-benzoic acid.[5] Despite the distinct properties of these materials, none of them covered all of the above-mentioned properties of an ideal root-end filling material.[6] Nevertheless, calcium-silicate types of cement yielded improved clinical results compared to the other materials, owing to their hydraulic material properties.[7] Therefore, MTA, a calcium silicate cement, was proposed as an alternative material to overcome the shortcomings of the filling materials used in the past. While it had superior properties, the disadvantages of MTA were its longer setting time and being challenging to handle. For this reason, the search for a better material continued.[6,8] Subsequently, another calcium silicate-based material was introduced, named Biodentine (Septodont). It had beneficial properties such as good sealing ability, biocompatibility, easy manipulation, and a short setting time.[3] One of the latest materials put forward with calcium content was Tech Biosealer Root End. According to its manufacturers, it was biocompatible, and it had applications such as perforation repairing, root-end filling, and vital pulp therapy.[9,10]

The clinical success of endodontic surgery depends on another procedure, the method chosen for the root-end cavity preparation.[11] Traditionally, dentists use a bur to prepare root-end cavities. Still, this technique has several limitations such as causing microleakages, smear layer formation on the surface of the cavity, inadequate depth of the cavities, having limited access to the cavities causing an imperfect alignment to the long axis of the root and off-centered root-end preparation. These deficiencies increase the risk of lateral perforation.[2] To overcome these problems, ultrasonic retrotips were developed. Due to the shape of the ultrasonic tip, it has several advantages, such as producing a conservative, deep and centralized cavity with a refined shape. In addition, it helps to identify additional canals and unexpected isthmuses and it reduces the number of dentinal tubules exposed at the resected surfaces.[2,12] Despite its advantageous properties, its most typical drawback is the occurrence of dentin cracks observed after using ultrasonic retrotips, thuse affecting the apical seal.[13] Therefore, new methods are necessary. In recent years, in addition to ultrasonic tips, lasers have also been used as an alternative for retrograde cavity preparation. One example of hard-tissue lasers is erbium:yttrium, aluminum garnet (Er:YAG).[14] Practicing apicoectomy using Er:YAG has various benefits. It prevents dentine cracks because it does not contact the dentine and does not vibrate. In addition, it decreases the contamination probability at the operating field. It also reduces the possibility of traumatization in the surrounding tissues.[14] On the other hand, there is also a contrary opinion about the non-contact operation, seeing it as a disadvantage since there is no tactile feedback.[14,15]

Our study aimed to examine the push-out bond strength of three different root-end filling materials (ProRoot MTA, Tech Biosealer Root End, Biodentine) in cavities prepared using three different techniques (burs, ultrasonic retrotips, Er:YAG lasers). We expected to obtain statistically significant differences in bond strength values when different root-end filling materials and cavity preparation techniques were applied. The null hypothesis was to have no statistically significant difference in bond strength values when the inspected materials and techniques were combined.

MATERIALS AND METHODS

The study was performed at the Ankara University Faculty of Dentistry, and the Ethics Board approved the study protocol (approval number: 36290600/25). Informed consent was obtained.

In our study, 180 maxillary incisor extracted human teeth with a single and straight root canal and completely formed apices were used. Preoperative radiographs were taken to check the root canal anatomy. According to Schneider classification,[16] the radiographs were analyzed to select those teeth which had 5 degree or less root curvature, to verify that the canals were straight. Teeth with calcifications and broken tools were omitted from this study. The teeth were placed in 5% sodium hypochlorite (Werax, Spot Dental San., İzmir, Türkiye) for 60 minutes. The hard and soft tissue on the surface of the teeth was debrided with the help of a periodontal curette, and the teeth were stored in 0.9% physiological saline solution.

The preparation of access cavities was performed using a diamond-coated fissure bur. A number 10-K File (Dentsply, Maillefer, Ballaigues, Switzerland) was inserted 1 mm above the apical foramen to confirm canal patency. The working length was standardized at 22 mm for all teeth. Each diameter of the foramen apical was compatible with a number 15K-File (Dentsply, Maillefer, Ballaigues, Switzerland). For each tooth, root canals were prepared by ProTaper rotary files (Dentsply, Maillefer, Ballaigues, Switzerland) up to size F3. Between each file size, 2 mL of 5% sodium hypochlorite (Werax, Spot Dental San., İzmir, Türkiye) was applied. Then, the process was continued by flushing with 5 mL of EDTA (Werax, Spot Dental San., İzmir, Türkiye). Finally, the specimens were subjected to irrigation using 10 mL of distilled water, and dried using absorbent paper points. A master cone of size #30 was selected and confirmed via radiographs. The canals were filled with gutta-percha (Dentsply, Maillefer, Ballaigues, Switzerland) and AH Plus root canal sealer (Dentsply DeTrey, Konstanz, Germany) by the lateral compaction technique. Excess gutta-percha was removed with a hot instrument. To establish the quality of obturation, radiographs were taken along the directions of mesiodistal and buccolingual. Cavit (Cavit G ESPE, Seefeld, Germany) was used to seal the access cavities. The specimens were kept in an environment with a temperature of 37 °C and 100% humidity until the sealer was set.

Apical resection of all groups was performed at 90° to the long axis of the root and 3 mm from the apices by conventional fissure diamond bur. The selected teeth were randomly assigned to 9 groups (n=20 per group) which would be used to prepare root-end cavities and insert the retrograde filling materials (Table 1). In all groups, all retrograde cavities were prepared 3 mm deep using the selected technique of the group.

Groups 1 to 3 were prepared with a diamond-coated round bur (REF 806314, 010, Meisinger, Germany). Group 4, group 5, and group 6 were prepared with the Er:YAG laser system (Kavo Key 3+, KaVo, Biberach, Germany) with the following settings: the wavelength was 1.8 m, the energy was set at 450 mJ/pulse, the repetition rate was 4 Hz., and it was on contact mode with water cooling. Group 7, group 8, and group 9 were performed with a diamond-coated ultrasonic retrotip having an angle of 90° with a working length of 3 mm. (E30LD, NSK, Nakanishi Inc., Tokyo, Japan). The ultrasonic device was used at medium power.

Each specimen's cavity was measured to have 3 mm depth using a periodontal probe. After aligning the probe perpendicular to the long axis of the tooth, the width of the cavity was measured to be 1.5 mm.

All cavities were flushed with 5 mL physiological saline solution. The retrograde filling materials were inserted, and the samples were wrapped in wet gauze soaked with normal saline. Next, cement was prepared through mixing, following the instructions of the manufacturers. Retrograde fillings were carried out using ProRoot MTA (Dentsply Tulsa, Johnson City, TN, USA) for Groups 1, 4, and 7; Tech Biosealer Root End (Isasan, Rovello Porro, Co, Italy) for groups 2, 5, and 8; and Biodentine (Septodont, Saint-Maur-des-fosses, France) for groups 3, 6, and 9. The cavities were dried with a piece of cotton pellet. In each section, cement was inserted into the root canal cavity with an MTA gun (Dentsply Maillefer, Ballaigues, Switzerland). In this process, a hand plugger was used to compact the cement.

All of the samples were stored for a week in an environment of 37 °C and 100% humidity. All samples were embedded in self-curing acrylic blocks along their long axis so that the apex of the root-end could be seen from the acrylic.

Each embedded specimen's apical part was incised into 1 mm thick slices perpendicular to the long axis using a 0.3 mm thick diamond blade (Mikrotom, Stuers, Copenhagen, Denmark) and a low-speed saw (Metkon, Micracut precision cutter, Bursa, Türkiye). The incision was applied under constant water irrigation. Three slices of 1 mm thickness were dissected from each specimen, and only the middle-sliced disk was selected for testing.

The chosen dentine disks were placed in a universal testing machine (Lloyd LRX; Lloyd Instruments Ltd, West Sussex, UK). The samples were placed on an acrylic slab with a central hole of 1.5 mm diameter to allow the free motion of the plunger, which had a diameter of 0.6 mm. Since the disks had an ascending angle from apical to coronal, they were placed into the testing machine in order to receive force applied from the apical surface to eliminate any friction between the filling material and the dentin.

A compressive load was applied on the surface of materials at a 1 mm/min constant speed until failure occurred. At the time of dislodgement, computer software recorded the maximum load in Newtons (N). Then, the force values were converted to MPa to calculate the push-out bond strength (Figure 1).

Table 1. Experimental groups of the study

Group number	Root tip cavity method	Number of samples (n)	Retrograde filling material
1	Bur (conventional method)	20	ProRoot MTA
2		20	Tech Biosealer Root End
3		20	Biodentine
4	Laser system (Er:YAG)	20	ProRoot MTA
5		20	Tech Biosealer Root End
6		20	Biodentine
7	Ultrasonic retrotip	20	ProRoot MTA
8		20	Tech Biosealer Root End
9		20	Biodentine

Er:YAG: Erbium:yttrium, aluminum garnet, MTA: Mineral trioxide aggregate.

Statistical Analysis

Statistical analysis was performed using the non-parametric Kruskal-Wallis H test because the data was not normally disturbed according to Shapiro Wilk's test ($p<0.05$ for all variables). After the Kruskal-Wallis H test, the post-hoc Dunn's multiple comparison test was employed to determine which groups differed from each other (PASW Statistics 20; SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $p<0.05$.

RESULTS

In our study, the bond strength between the root-end cavities prepared with the bur, laser, and ultrasonic retrotip and the filling materials, MTA, Tech Biosealer Root End, and Biodentine were statistically significant ($p<0.05$), as shown in Table 2, 3.

The highest mean value was observed in the ultrasonic retrotip prepared and Biodentine filled group ($p>0.05$). In contrast, the lowest mean value was obtained in the bur prepared and Tech Biosealer filled group ($p<0.05$). Among the preparation techniques, there were no statistical differences between the cavities prepared with the laser and ultrasonic retrotip and filled with MTA and Biodentine ($p>0.05$). However, bur prepared cavities showed statistically significant and lower values than the other preparation techniques ($p<0.05$). In bur prepared cavities, the highest bond strength was seen in the Biodentine filled cavities ($p<0.05$). Tech Biosealer showed lower bonding strength than the other materials in the laser and ultrasonic retrotip prepared cavities ($p<0.05$). The statistical difference between MTA and Biodentine was not significant in those cavities prepared with the laser or the ultrasonic retrotip ($p>0.05$). Tables 2, 3 display the mean values, standard deviations, and the statistical analysis results of the Kruskal-Wallis H test along with post-hoc tests for all the groups.

DISCUSSION

The prognosis of apical surgery depends on how well the canal is obturated and sealed after performing cavity preparation. Therefore,

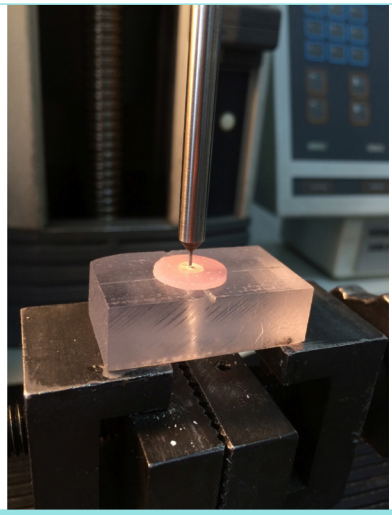

Figure 1. Universal test machine.

it is essential to prepare the cavity optimally to implement root-end filling adequately after apicoectomy.[13,17]

The selection of tooth specimens is essential for the study. Wu et al.[18] reported that they chose the same teeth groups with similar teeth length, similar root canal diameter, and similar root canal anatomies in order to eliminate variations. In addition, caries can degrade the mineral and organic composition of the samples.[19] Therefore, in this study, in order to standardize root canals and eliminate variations, we selected newly extracted, single, and straight rooted human maxillary incisors which had no caries or restorations.

One component of endodontic surgery is root-end resection. It promotes the elimination of debridement, pathological periradicular tissue, and anatomical variations. Applying 3 mm resection on the root apex will eliminate apical ramifications, lateral canals, resorptions, perforation defects, canal obstructions, and separated endodontic instruments.[13,17]

The ideal depth of the root-end cavity should be a 3 mm class I cavity with parallel dentin walls. If the cavity has less depth, apical ramifications and lateral canals cannot be removed, leading to unsuccessful treatment.[11] Hence, in this study, we performed the resection 3 mm above the root apex and prepared class I cavities with 3 mm of depth in order to deal with the difficulties mentioned above.

It is common to prepare root-end cavities with burs in a micro handpiece. However, this process results in various difficulties. Since the bur does not have an angle, it becomes difficult to prepare the cavity walls parallel to each other, it is not always possible to access to the root-end, and there is a heightened risk of lingual perforation of the root.[2] With the development of ultrasonic instruments, many of these problems have been solved. Ultrasonic retrotips are manufactured with various shapes and angles, so improving surgical treatment phases. They improve the surgical area entrance and produce a better centralized, conservative, and cleaner cavity;[11] thus, decreasing the number of dentinal tubules exposed and reducing apical leakage.[2] Unfortunately, ultrasonic retrotips have the critical disadvantage of generating a high number of fractures during the preparation of dentine walls.[20] Peters et al.[12] demonstrated in their study that diamond-coated retrotips produced a better-quality surface with fewer cracks than cavities prepared with

Table 2. Mean values of groups, standard deviations (SD), and Kruskal-Wallis H and post-hoc multiple comparison test results

Groups							Kruskal-Wallis H test		
		n	Mean ± SD (MPa)	Median (MPa)	Min (MPa)	Max (MPa)	Average	H	p
1	Bur + MTA	20	5.04±0.76	5.18	2.84	5.93	25.35	158.56	0.001
2	Bur + Tech Biosealer	20	4.5±1.27	4.36	2.02	7.99	19.15		
3	Bur + Biodentine	20	8.8±0.63	8.9	7.28	9.78	95.3		
4	Laser + MTA	20	9.74±0.67	9.65	8.37	10.83	124.05		
5	Laser + Tech Biosealer	20	6.43±0.55	6.51	4.99	7.3	48.1		
6	Laser + Biodentine	20	10.15±0.79	10.2	8.55	11.67	138.25		
7	Ultrasonic + MTA	20	10.01±0.6	10.07	8.6	10.9	133.65		
8	Ultrasonic + Tech Biosealer	20	7.74±0.37	7.77	7.06	8.43	71.35		
9	Ultrasonic + Biodentine	20	10.83±0.62	10.82	9.92	11.85	159.3		
Total		180	8.14±2.32	8.61	2.02	11.85	2-3 2-4 2-7 2-6 2-9 1-3 1-4 1-7 1-6 1-9 5-4 5-7 5-6 5-9 8-4 8-7 8-6 8-9 3-9		

SD: Standard deviation, MTA: Mineral trioxide aggregate.

Table 3. Comparisons between groups using post-hoc multiple comparison tests

1	Bur + MTA									
2	Bur + Tech Biosealer	-								
3	Bur + Biodentine	+	+							
4	Laser + MTA	+	+	-						
5	Laser + Tech Biosealer	-	-	-	+					
6	Laser + Biodentine	+	+	-	-	+				
7	Ultrasonic + MTA	+	+	-	-	+	-			
8	Ultrasonic + Tech Biosealer	-	-	-	+	-	+	+		
9	Ultrasonic + Biodentine	+	+	+	-	+	-	-	+	
Groups		Bur + MTA	Bur + Tech Biosealer	Bur + Biodentine	Laser + MTA	Laser + Tech Biosealer	Laser + Biodentine	Ultrsnc + MTA	Ultrsnc + Tech Biosealer	Ultrsnc + Biodentine
		1	2	3	4	5	6	7	8	9

(+): A statistically significant difference between the groups, (-): no statistically significant difference between the groups. MTA: Mineral trioxide aggregate.

stainless steel ultrasonic retrotips. Vivan et al.[21] stated in their study that diamond-coated ultrasonic tips demonstrated cutting effectiveness and regular root-end preparation. However, more cracks were observed when they were used at high-power settings.[22] Bernardes et al.[23] found in their *in vitro* study that there were no cracks after using an ultrasonic retrotip at a medium-power setting. In light of this information, we used diamond-coated ultrasonic retrotips with an angle of 90° at a medium-power setting.

Another preparation technique used for root-end cavity preparation is the laser. There are many published laser types used in apical surgery. When laser irradiation is applied to dentin, water interfered ablation occurs, vaporizing the water content of the dental hard tissues following expansion and micro-explosions. It results in debris and the removal of the smear layer and micro-retentive irregularities by leaving a rough surface which allows for better mechanical bonding to form between the root-end filling and the dentinal walls.[24-26] Samad-Zadeh et al.[27] described in their study that the Er:YAG laser technique results in an irregular surface without a smear layer and the exposure of dentinal tubules, which leads to better penetration for the retrograde filling material on the wall of the cavity. However, this procedure can produce side effects. Melting, fissures or carbonization might occur, surrounding tissues might have cracks or pulpal temperature could increase. To overcome these drawbacks, Er:YAG and Er,Cr:YSG lasers were introduced.[24-26] In another study, the Er:YAG laser was used with an output power of 1W, and it was reported that no smear layer or debris were left.[28] In another study, lasers were used at a 1.8 W power output, and the irradiated dentin surfaces showed irregularities and roughness. They had no smear layer, and the tubules were open, which provided micro-retentive patterns.[29] Considering the above results, in our study, we chose the Er:YAG laser and used it in contact mode with the following parameters: 1.8 W 450 mj 4 Hz.

Apical microleakage is one of the reasons for the failure of endodontic treatment. Considering the success of endodontic surgery, selecting a retrograde filling material is a significant choice.[30] Below, we examine the properties of the filling materials which were part of this study.

The first filling material we used was MTA. It has various notable root-end filling characteristics: biocompatibility, a good sealing capability, high strength under compression, radiopacity, insolubility in fluids, and antibacterial effects. Inducing hard tissue formation is another advantage.[11] However, MTA has drawbacks such as having a long setting duration (2 hours 45 min) and being burdensome to manipulate.[11]

To overcome the drawbacks of MTA, new materials based on calcium silicate were introduced.[31] Biodentine and Tech Biosealer Root End are two of them. Biologically, Biodentine can seal well, it is biocompatible, and it can induce odontoblast differentiation and apposition of reparative dentin.[32] Its setting time is about 12 min.[11] It has a wide range of applications, and it is also used as a retrograde filling material in endodontic surgery.[31]

The other mentioned calcium silicate-based material is Tech Biosealer. As stated by the manufacturers, it has perfect biocompatibility, and forms a thin layer rich in calcium and phosphate on its surface, and then connects to the bone tissue through this biologically active apatite layer without a distinct boundary.[33] Therefore, Tech Biosealer is suitable for repairing perforations, it can be used for vital pulp therapy, and it is a root-end filling substance.[32]

The present study showed that the filling materials' bond strength was affected by the root-end preparation method. Independent of the cavity preparation technique, Tech Biosealer Root End showed lower bond strength, while Biodentine showed the best bond strength. When the cavity preparation techniques were considered, minimum bond strength values were seen in those cavities prepared with a bur compared to those prepared with a laser or ultrasonic tips. Mean push-out bond strength outcomes were higher in those groups prepared with the laser than in groups prepared by the bur, and the highest bond strength values in all groups were seen in the root-end samples prepared with ultrasonic tips. Bur prepared cavities might show weak bond strength values due to the cavity surface's poor condition caused by the preparation method. Compared with lasers and ultrasonic tips, rotary burs produce more debris and smear layer leftover,[24,34] weakening the contact between the filling material and cavity walls. Overall, the larger smear layer leftover produced by burs helps to explain why burs show the weakest bond strength compared to lasers and ultrasonic tips with all retrograde filling materials. In comparison, lasers and ultrasonic retrotips can remove debris and the smear layer so that retrograde cavity materials can penetrate the cavity walls.[22,24,25,33-36] This capability could explain why the bond strength values of MTA and Biodentine did not show a statistically significant difference during the comparison of Er:YAG laser and ultrasonic tips, but the bond strengths of both materials were weaker for samples prepared with the Er:YAG laser.

Open dentinal tubules and uneven surfaces lead to the increased micro-retention of the lasered dentin surface; this, in turn, increases adhesion.[26] Furthermore, sub-superficial changes occurring on the irradiated dentin have effects on adhesion. During ablation, water evaporates and causes mechanical shock. It might cause sub-superficial cracking in the dentin and might lead to dental materials adhering less to the irradiated surfaces.[37]

In our study, Biodentine showed higher bond strength values than MTA and Tech Biosealer Root End. A statistically significant difference between Biodentine and Tech Biosealer Root End was obtained. This outcome could be a result of the materials' physical and chemical properties. Biodentine's smaller particle size might cause the cement to penetrate deeper inside the dentinal tubules, improving bond strength. This feature could explain the higher values for Biodentine.[38]

The porosity of Biodentine is lower than that of MTA,[39] and the one having the most porosity is Tech Biosealer Root End.[5] This result could explain the increased bond strength of Biodentine as well. In one study, GIC, MTA, and Biodentine materials were compared concerning their marginal adaptations. The lowest marginal gaps are observed with Biodentine, which also showed good marginal adaptation. MTA followed second to Biodentine, while a very high marginal gap was observed with GIC.[39] This study shows that Biodentine and MTA have satisfactory marginal adaptation to the cavity wall, explaining the outcome of the improved bond strength of Biodentine in our study.

Study Limitations

The main limitation of this study was that, since it was performed with *in vitro* conditions, further long-term *in vivo* studies are necessary to evaluate the sealing ability of root-end material to dentine interfaces, considering the effects of blood contamination. Another clinical limitation to overcome is the large size of the handpiece of the Er:YAG

laser, which makes it challenging to handle. However, in our case, the preparation procedure on extracted human teeth simplified its handling and application.

CONCLUSION

In the scope of this *in vitro* study, we can conclude that the highest bond strength values were seen in ultrasonic tip prepared cavities filled with Biodentine, and the weakest bond strength values were seen in bur prepared cavities filled with Tech Biosealer Root End. Irrespective of the root-end filling materials, bur prepared cavities showed statistically significant weaker values than the other preparation techniques ($p<0.05$). In cavities prepared with the laser and ultrasonic techniques, no statistical difference was observed between their bonding strengths ($p<0.05$). Regardless of the preparation techniques used, Tech Biosealer Root End showed the weakest bond strength. In cavities prepared with a bur, the mean bond strength value was significantly higher in Biodentine than the other materials ($p<0.05$). In the laser prepared cavities, ProRoot MTA and Biodentine's mean bond strength values were statistically higher than Tech Biosealer Root End ($p<0.05$), and in ultrasonic retrotip prepared cavities, ProRoot MTA and Biodentine's mean bond strength values were statistically significantly higher than Tech Biosealer Root End ($p<0.05$). According to these results of this study, the null hypothesis was rejected, since we found statistically significant differences in bond strength values between the different material and technique combinations.

MAIN POINTS

- The stability of the retrograde filling is essential to prevent micro-leakage. In this context, adaptations of different retrograde filling materials to dentine were compared by applying different cavity methods.
- The highest mean value occurred in the ultrasonic + Biodentine group, whereas the lowest mean value was obtained in the bur + Tech Biosealer group.
- There were no statistical differences between the cavities prepared with laser or ultrasonic retrotips and filled with MTA or Biodentine ($p>0.05$).
- As a retrograde cavity preparing technique, diamond-coated ultrasonic retrotips at medium power and Er:YAG lasers with 1.8 W power output can be used.
- Biodentine and ProRoot MTA, which are calcium silicate types of cement, can be used as a root-end cavity filling material.

ETHICS

Ethics Committee Approval: The study was performed at the Ankara University Faculty of Dentistry, and the Ethics Board approved the study protocol (approval number: 36290600/25).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.C.E., Design: F.S.S., İ.Ö., Supervision: F.S.S., Fundings: B.Ç., Materials: F.C.E., Data Collection and/or Processing: F.C.E., Analysis and/or Interpretation: F.C.E., Literature Search: B.Ç., Writing: F.C.E., Critical Review: F.S.S.

DISCLOSURES

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RESEARCH ARTICLE

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Does Preoperative Anemia Affect Complications after Thoracic Surgery? A Tertiary Center Experiences

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Abstract

BACKGROUND/AIMS: Preoperative anemia has been associated with an increased risk of postoperative complications after major surgeries. The incidence of anemia is not low according to the literature. We designed this study to find out our incidence of preoperative anemia and the relationship between preoperative anemia and postoperative complications in thoracic surgical patients.

MATERIAL AND METHODS: This study was designed as retrospectively study. The demographic features, including age, sex, the American Society of Anaesthesiologists scores, preoperative hemoglobin (Hb) levels, transferrin saturations, comorbidities, blood types and blood product transfusions, complications, mortality, types of surgery, lengths of intensive care unit (ICU) stay, chest tube removal times and lengths of hospital stay were recorded. The relationships between anemia and complications were evaluated.

RESULTS: A total of 225 patients were initially included in this study, with 2 patients later being excluded. The preoperative Hb value of 40.4% of the patients was below 13 mg/dL. Complications were seen in 58 (26.0%) patients in total. Complications were observed in 22 (24.4%) patients with preoperative Hb levels below 13 mg/dL and in 36 (27.1%) patients with preoperative Hb levels above 13 mg/dL. Postoperative erythrocyte suspension (ES) was used in 9.7% of patients without complications, while this rate was 24.1% in those patients with complications.

CONCLUSION: This study did not find a correlation between preoperative anemia and postoperative complications after thoracotomy, but anemic patients required more ES transfusion and ES is related with prolonged ICU and hospital stay. We can conclude that preoperative anemia indirectly affects postoperative complications in thoracic surgery.

Keywords: Anemia, postoperative complications, thoracotomy

INTRODUCTION

Preoperative anemia has been associated with an increased risk of postoperative complications, extended lengths of hospital stay, and increased risk of death.[1] The anemia incidence in patients with lung cancer was found to be 37.6% in the European Cancer Anemia survey.[2] In the study by Chamogeorgakis et al.[3], preoperative anemia was 28% in male and 8% in female patients undergoing thoracic surgery.

As anemia is related to many complications, it is important to receive anemia treatment before surgery. However, the time needed for correction means postponing the surgery, which is generally unacceptable to surgeons. Therefore, many anemic patients undergo surgery without sufficient treatment.

This study was designed to evaluate the incidence of anemia in our hospital as its primary endpoint. The secondary endpoint was to determine the relationship between anemia, postoperative

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complications and the effects of blood transfusions on postoperative complications in anemic patients.

MATERIALS AND METHODS

The patients included in this study underwent thoracic surgery between May, 2020 and April, 2022. We retrospectively reached the data of 225 patients in total who underwent thoracotomy between these dates and were eligible for this study. This study was designed as a retrospective one; permission was taken from the hospital to use the patients' data. Ethical approval was obtained from the Ankara University Hospital Ethical Committee (approval number: 2022/613, date: 30.11.2022), and the clinical trial was registered under the reference number NCT05673161. Those patients aged under 18 years, who had urgent surgery, had known bleeding disorders, renal insufficiency, hepatic insufficiency, or congestive heart failure were excluded from this study.

We recorded demographic features including age, sex, the American Society of Anaesthesiologists (ASA) scores, preoperative hemoglobin (Hb) levels, transferrin saturations, comorbidities, blood product transfusions, complications, mortality, types of surgery, lengths of intensive care unit (ICU) stay, chest tube removal times and lengths of hospital stay. The patients were divided into two groups according to their preoperative anemia presence. Anemia was defined as a Hb level <13 g/dL in both males and females.[4] Complications were determined as cardiac, respiratory, infectious or other complications after surgery.

Statistical Analysis

The SPSS 11.5 program was used to analyze the study data. Mean ± standard deviation and median were used as descriptors for quantitative variables, and the percentage of patients for qualitative variables. The Mann-Whitney U test was used to determine whether there was a difference between each category of the qualitative and quantitative variables, since the assumptions of normal distribution were not provided. The chi-squared and Fisher's exact tests were used to examine the relationship between two qualitative variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 225 patients were included in this study; two patients were subsequently excluded from this study because of missing data, and ultimately, the data on a total of 223 patients were analyzed within the scope of this study.

Fifty-five (24.7%) of the patients included in this study were female, 168 (75.3%) were male, and the mean age of the patients was 60.75±10.22 years. There were 75 (33.6%) patients with an ASA score of 1, 141 (63.2%) patients with a score of 2, and 7 (3.1%) patients with a score of 3. The preoperative Hb value of 40.4% of the patients was below 13 mg/dL, and the preoperative Hb value for 59.6% of the patients was equal to or greater than 13 mg/dL. In addition, 48.4% of the patients had a postoperative Hb value below 13 mg/dL, while 51.4% had a postoperative HB value greater than 13 mg/dL (Table 1).

There were 20 (30.1%) patients with a preoperative Hb value above 13 mg/dL and a transferrin saturation below 20%. Complications were seen in 6 (27.3%) patients with transferrin saturation ≤20% and in 11 (21.6%) patients with transferrin saturation >20%, but there was no significant difference in complication rates between these two groups (p=0.597).

Intravenous (i.v.) Fe was given to 7 (7.8%) of the patients with a preoperative Hb value below 13 mg/dL. Complications were seen in 2 (28.6%) of these patients who were given i.v. Fe and in 20 (24.1%) of the

Table 1. Demographics

Variables		
Gender, n (%)	Female	55 (24.7)
	Male	168 (75.3)
Age (n=223)	Mean ± SD	60.75±10.22
	Median (minimum-maximum)	62.00 (20.00-81.00)
Surgery type, n (%)	Lung resection and mediastinal lymph node dissection	191 (85.8)
	Video-thoracoscopy, wedge resection	8 (3.6)
	Wedge resection, (single or multiple)	6 (2.7)
	Thoracotomy, major exploration	6 (2.7)
	Lung resections after neoadjuvant chemoradiotherapy	4 (1.8)
	Lung resection, chest wall resection + reconstruction	3 (1.3)
	Lobectomy/segmentectomy	3 (1.3)
	Pneumonectomy and major vascular surgery	1 (0.4)
	Lobectomy with concomitant decortication	1 (0.4)
ASA, n (%)	1	75 (33.6)
	2	141 (63.2)
	3	7 (3.1)
Preop Hb, n (%)	<13 mg/dL	90 (40.4)
	≥13 mg/dL	133 (59.6)
Postop Hb, n (%)	<13 mg/dL	108 (48.4)
	≥13 mg/dL	115 (51.6)

Hb: hemoglobin, SD: Standard deviation, ASA: American Society of Anaesthesiologists.

patients who were not given i.v. Fe. However, there was no significant difference between these two groups in terms of complication rates (p=1.000).

The transfusion of blood product was only seen in the postoperative period. Postoperative erythrocyte suspension (ES) was used in 20 (22.2%) patients with preoperative Hb levels of 13 mg/dL or below. Postoperative ES was used in 10 (7.5%) patients with preoperative HB levels above 13 mg/dL, and there was a statistically significant difference between these two groups (p=0.002) (Table 2).

Complications were seen in 58 (26.0%) patients in total. Complications were observed in 22 (24.4%) patients with preoperative Hb levels below 13 mg/dL and in 36 (27.1%) patients with preoperative Hb levels above 13 mg/dL. However, no significant difference was found between these two groups in terms of complication rates (p=0.661) (Table 3).

While the mean postoperative ES was 1.06±0.25 units in patients without complications, it was 1.50±0.76 in those patients with complications. There was a significant difference between these two groups in terms of their mean postoperative ES (p=0.043).

When evaluated as a ratio, postoperative ES was used in 9.7% of patients without complications, while this rate was 24.1% in those patients with complications. There was a significant difference between these two groups in terms of postoperative ES use (p=0.006).

There was no significant difference between those patients with preoperative Hb values below and those above 13 mg/dL in terms of tube removal time, length of stay in the ICU or hospital stay (p=0.440, p=0.912 and p=0.653, respectively) (Table 4).

A significant difference was found between those patients with and those without postoperative ES in terms of length of stay in the ICU and hospital stay (p=0.038 and p<0.001, respectively). While the mean length of stay in the ICU was 2.62±2.06 days in those patients who did not need postoperative ES, this period was 3.47±2.57 days in those patients who needed postoperative ES. The mean hospital stay was significantly higher in those patients who received postoperative ES (Table 5). However, the length of ICU stay and hospital stay did not differ statistically between anemic and nonanemic patients (p=0.912 and 0.653, respectively).

Table 2. Postoperative ES use according to Hb level

Variables		Preop Hb		p-value
		<13 mg/dL	≥13 mg/dL	
		n (%)	n (%)	
Postop ES	(-)	70 (77.8)	123 (92.5)	0.002
	(+)	20 (22.2)	10 (7.5)	

Hb: Hemoglobin, ES: Erythrocyte suspension.

Table 3. Complications according to Hb level

Variables		Preop Hb			p-value
		<13 mg/dL	≥13 mg/dL	Total	
		n (%)	n (%)	n (%)	
Complications	(-)	68 (75.6)	97 (72.9)	165 (74.0)	0.661
	(+)	22 (24.4)	36 (27.1)	58 (26.0)	

Hb: Hemoglobin.

DISCUSSION

The results of this retrospective study did not conclude a correlation between preoperative anemia and postoperative complications after thoracotomy. However, an important result of this study was that ES transfusion is related to prolonged ICU and hospital stays. Anemic patients required more ES transfusion, so preoperative anemia is related to postoperative ES transfusion, which is related to prolonged ICU and hospital stays.

Anemia is one of the most common and modifiable risk factors for major surgeries. The most common etiology of preoperative anemia is iron deficiency. The major causes of anemia in lung cancers include impaired intestinal iron absorption and reduced bone marrow response to erythropoietin.

Table 4. Chest tube removal time, ICU stay and hospital stay according to Hb level

Variables	Preop Hb				p-value
	<13 mg/dL		≥13 mg/dL		
	Mean ± SD	Median (min.-max.)	Mean ± SD	Median (min.-max.)	
Chest tube removal time (days)	4.99±5.29	4.00 (1.00-47.00)	5.47±5.15	4.00 (1.00-46.00)	0.440
ICU stay (days)	2.73±2.00	2.00 (1.00-9.00)	2.74±2.26	2.00 (1.00-16.00)	0.912
Hospital stay (days)	7.62±4.31	6.00 (3.00-22.00)	7.81±4.20	7.00 (2.00-21.00)	0.653

Hb: Hemoglobin, ICU: Intensive care unit, SD: Standard deviation, min.: Minimum, max.: Maximum.

Table 5. ICU stay and hospital stay in means of ES use

Variables	Postop ES				p-value
	(-)		(+)		
	Mean ± SD	Median (min.-max.)	Mean ± SD	Median (min.-max.)	
ICU stay (days)	2.62±2.06	2.00 (1.00-16.00)	3.47±2.57	3.00 (1.00-11.00)	0.038[a]
Hospital stay (days)	7.31±3.92	6.00 (2.00-21.00)	10.47±5.15	9.00 (4.00-22.00)	<0.001[a]

ICU: Intensive care unit, ES: Erythrocyte suspension, SD: Standard deviation, min.: Minimum, max.: Maximum.

One of the main causes of the increase in mortality is the elevation in the frequency of blood and blood product transfusions.[5] The results of a previous study concluded that more than 1/3 of patients who underwent thoracotomy were anemic. Thoracotomies are challenging cases in terms of oxygen transport and bleeding. This means that anemia becomes increasingly important for these patients.

As anemia is an important risk factor, treatment of anemia becomes especially crucial for these patients. Implementing patient blood management principles improves outcomes after surgery and anemia treatment is one of these.[6] Another important issue is not only to give Fe, but also to wait enough time for its efficaciousness. Unfortunately, only a small portion of the patients received Fe before surgery, and treatment was performed within one week prior to the surgery. In two of the 7 patients who were treated with Fe, complications were observed. Hence, it is difficult to draw any conclusions from this result.

Fernandes et al.[7] concluded that anemic patients undergoing pulmonary resection demonstrated an increased incidence of respiratory and infectious complications. This previous study concluded that there was no significant difference between anemic and nonanemic patients in terms of complications. Taylor et al.[8] conducted a large-volume multicenter retrospective study and found that anemia did not emerge as an independent predictor of postoperative complications or perioperative mortality, but anemia was independently associated with a significantly reduced overall survival for patients undergoing lung resection.

Preoperative Hb level is the major risk factor for perioperative blood transfusion practices in oncologic thoracic surgery.[9] It has been reported that blood transfusion increases the chance of recurrence in patients undergoing surgery for lung cancer.[10] This previous study showed that ES transfusion was statistically related to complications, where all transfusions were applied during the postoperative period. This can be explained by following "patient blood management" rules during the intraoperative period.

Patient blood management has changed our clinic practice regarding transfusions. The approach includes the optimization of hematopoiesis, minimizing blood loss, and evaluating anemia tolerance. Optimization of hematopoiesis consists of anemia treatment, which is an important element in reducing transfusions. Another important issue is to use restrictive transfusion thresholds when deciding on transfusion. Although there are many scientific studies supporting the patient blood management approach, some surgeons still decide on transfusion by just looking at declines in Hb levels.

Preoperative anemia is one of the strong risk factors for the need for perioperative red blood cell transfusions in lung surgery patients.[9] Although we could not find a relationship between anemia and postoperative complications, we found that ES transfusion was related to postoperative complications. Performing surgery in anemic patients may lead to ES transfusion, which may result in complications after thoracic surgery.

The length of ICU stay and hospital stay were also affected by ES transfusion. ES transfusion resulted in longer ICU and hospital stays according to previous results. Saraçoğlu et al.[5] found that preoperative anemia was associated with an extended length of stay in the hospital and in the ICU.

The results of this study conclude that anemia is not associated with postoperative complications after thoracic surgery, but ES transfusion is. The anemic patients included in this study generally had mild anemia, which did not result in complications. However, complication rates increased with ES transfusions.

CONCLUSION

Even though our results did not find a relationship between preoperative anemia and complications, we can say that preoperative anemia has an indirect effect on postoperative complications in thoracic surgery.

MAIN POINTS

- Erythrocyte suspension transfusion is related to prolonged ICU and hospital stays in patients undergoing thoracic surgery.
- Anemic patients undergoing thoracic surgery required more erythrocyte suspension transfusions.
- Preoperative anemia indirectly affects postoperative complications in thoracic surgery.
- Preoperative anemia should be treated in those patients undergoing thoracotomy.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Ankara University Hospital Ethical Committee (approval number: 2022/613, date: 30.11.2022), and the clinical trial was registered under the reference number NCT05673161.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.Y.G., B.M.Y., B.C.M., Concept: Ç.Y.G., B.C.M., Design: Ç.Y.G., B.M.Y., F.K., A.K., B.C.M., Data Collection and/or Processing: Ç.Y.G., F.K., A.K., Analysis and/or Interpretation: Ç.Y.G., B.M.Y., Literature Search: Ç.Y.G., B.M.Y., F.K., A.K., Writing: Ç.Y.G., B.C.M.,

DISCLOSURES

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RESEARCH ARTICLE

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Psychometric Properties of the Turkish Version of the Adolescent Health Promotion Scale: Short Form

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Abstract

BACKGROUND/AIMS: This study was conducted with the aim of testing the psychometric properties of the Adolescent Health Development Scale-Short Form in Türkiye as a methodological study.

MATERIALS AND METHODS: This study included 814 students attending grades 7 to 11 in three different secondary schools and two different high schools selected out of secondary and high schools located in Western Türkiye which were attached to the Directorate of Education of İzmir Province and it used simple random sampling method. The data from this study were evaluated using percentage, mean analysis, and validity-reliability analysis.

RESULTS: The total Cronbach's alpha coefficient of the Turkish scale was 0.85. Strong correlations were found between test and re-test ($r=0.85$, $p<0.001$). The results of Confirmatory Factor Analysis revealed that the model fit index of the scale had a goodness-of-fit index of 0.95 and a comparative fit index of 0.97.

CONCLUSION: Validity and reliability analyses demonstrated that the scale was a valid and reliable means of measurement which can be used to determine the health promotion behaviors of adolescents in a Turkish sample.

Keywords: Health promotion, adolescents, psychometrics

INTRODUCTION

The World Health Organization (WHO) defines the age group 10 to 19 as the "adolescent period" and reported that adolescents make up 20% of the world population.[1] According to WHO data, there are approximately 1.2 billion adolescents in the world. In particular, in some countries, one-fourth of the population is made up of adolescents, and this number is expected to increase gradually until 2050. According to data from the Türkiye Demographic and Health Survey,[2] the number of children under 15 years of age makes up 15% of the total population, and the proportion of adolescents aged 10 to 19 constitutes 16% of the population in Türkiye.

The adolescent period is one of rapid development in terms of physical, psychological, and social aspects; however, it is also a period of opportunity in which positive behaviors become habits.[3] The ability of adolescents, who are regarded as the future of societies, to maintain their health in this development period is an important determinant of their individual and social development. Therefore, determining the health promotion behaviors of adolescents is crucial.[4]

Health promotion is defined as the increasing control over an individual's health and improving their health.[5] It focuses on promoting individual abilities and skills, as well as changing social, environmental, and economic conditions affecting the health of individuals and society. Health promotion in adolescents seeks to improve their control over their health, thereby reducing diseases and improving their quality of life in all health-related aspects.[4] During the transition from childhood to adulthood, adolescents form behavioral patterns and make lifestyle choices which affect their health in the future.[6] In particular, health

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problems and risky health behaviors (such as smoking and alcohol use) which emerge during adolescence affect the physical and cognitive development of adolescents.[4] Adolescents may exhibit some risky health behaviors. For example, normally preventable risk behaviors such as tobacco use, unhealthy food or snack consumption, alcohol consumption and other drug use, and inadequate physical activity occur frequently during adolescence and continue to prevail in adulthood and thus cause health problems. These risky health behaviors may adversely affect the health of both adolescents and young adults, and they may develop serious health problems (such as violence, substance abuse etc.).[7] Furthermore, studies have shown that these health problems also lead to serious financial burdens.[8,9]

According to a previous Youth Risk Behavior Surveillance System (2017) report, 14.8% of adolescents aged 10 to 24 were obese, 29.8% were alcohol users, 19.8% were substance users, 8.8% smoked, and 13.2% were electronic cigarette users; furthermore, 19% experienced bullying and 7.4% had attempted suicide in the previous year.[7] In addition, according to the WHO (2016)[10] report, more than 80% of adolescents did not perform any physical activity, and the obesity rate among adolescents had increased 10-fold over the last 40 years. Additionally, adolescents mostly skipped their breakfast meals. A study conducted in the USA found that one out of every 10 adults using cigarettes started smoking before the age of 18, and every day, 2,000 children under the age of 18 have their first cigarette experience, and more than 300 of these children became active smokers. Studies have also found that one in four children had a chronic disease (diabetes, epilepsy, etc.), with an obesity rate of 20.6%, particularly in adolescents.[11]

Studies have revealed that these behaviors seen in adolescence constitute a risk in adulthood. For example, the literature demonstrates that children with high body mass indices may have increased risk of cardiovascular disease in their adulthood and that individuals who consume alcohol during adolescence are at greater risk of experiencing chronic illness and mental health problems in adulthood.[12] Developing healthy behavior in childhood is easier and more effective than trying to change unhealthy behaviors in adulthood.[6] Evidence-based studies have shown that in adolescents, in particular, bad health habits can be prevented in adulthood, and this situation will not only promote the health of adolescents, but also the health of the society and will encourage lifestyle changes. For all these stated reasons, the state of health promotion in adolescents warrants examination.

The school environment is an important area where adolescent behavior and routines are shaped, helping adolescents to become aware of their health and adopt health-related attitudes and behaviors as a lifelong habit.[13] Adolescents spend about 6 hours a day at school; therefore, the school is a unique environment in which the health of adolescents can be promoted and risky health behaviors can be determined. The National Health Education Standards also emphasize that secondary and high school students should have course content aimed at promoting and improving health in their curriculum.[7] Therefore, evaluating the health improvement behaviors of adolescence, which is a risky period, is crucial.[11]

The reliability and validity for the development of health in adolescents in Türkiye were made using a scale.[14] This scale consists of 40 items, and the Cronbach's alpha coefficient of the social support, nutrition behaviors, exercise, and stress management subdimensions of this scale is less than 0.70; item load values of the scale are between 0.13 and 0.51, and the explanatory variance ratio is 38.48%. Furthermore, it is assumed that adolescents can safely fill in the items in the scale due to the high number of items in the scale. The Adolescent Health Promotion Scale: Short Form (AHPS-SF) is a 21-item scale which was developed by Chen et al.[15]. This scale is the only one with proven validity and reliability to determine the health promotion behaviors of all adolescents aged 13 to 19. The lack of Turkish validity and reliability for this scale which evaluates the health promotion behaviors of adolescents is a major deficiency in the field. In this context, the aim of this study titled "Adolescent Health Development Scale: Short Form" was to test the psychometric properties of this scale in Türkiye.

Research Questions

- Is the Adolescent Health Development Scale: Short Form valid in Türkiye?

- Is Adolescent Health Development Scale: Short Form reliable in Türkiye?

MATERIALS AND METHODS

Participants and Procedures

This study was conducted with the aim of testing the psychometric properties of the Adolescent Health Development Scale: Short Form in Türkiye as a methodological study. The data for this study were obtained from students attending grades 7 to 11 in three different secondary schools and two different high schools between September-December 2019. Students were selected from secondary and high schools which were attached to the Directorate of Education of İzmir Province located in Western Türkiye.

In this study, a total of 900 students from 11 schools affiliated to the Narlıdere District National Education Directorate were included in three different secondary schools and two different high schools determined by a simple random sampling method. However, only 814 children who agreed to participate in this study, had parental consent, and completed the scales properly were included. During the process, there were no students without parental consent, but 76 students were not included in this study due to missing items in the scale forms. The scales were applied by the researchers at the hours permitted by the school administration. Data was collected between September and December, 2019. The inclusion criteria were the following: a) aged 13 to 18 years, b) voluntarily agreeing to participate in this study, with signed parental consent forms. The exclusion criteria were as follows: a) adolescents with special learning difficulties, b) adolescents wishing to quit the study at any stage of the study, and c) adolescents without signed parental consent forms. There was a method which was suggested for the sample size and it included three rules, namely the 5s, 10s and 100s rule. It was emphasized that the researcher should include at least five individuals for each item in order to perform the factor analysis. There should also be 10 individuals for each item unless there was a problem about connecting with people.[16] Therefore, the scale was administered to those who met the inclusion criteria and submitted written consent for participation in this study.

Instruments

Data were collected using the Descriptive Information Form (four questions including age, gender, economic status, and education level) and the AHPS-SF.

Descriptive Information Form

The form prepared by the researchers was in line with the literature[12-15] and consisted of 13 questions relating to the following: age, gender, class, educational status of their mother and father, whether he or she has breakfast in the morning, has a computer, can connect to the internet via his or her computer, has a smart phone, and can connect to the internet with their phone.

Adolescent Health Promotion Scale: Short Form

The Adolescent Health Promotion Scale was developed by Chen et al.[17] in 2003 and it is used to assess the health promotion behavior of adolescents. This scale consists of 40 items and six subscales. The subscales can be listed as nutrition (six items), interpersonal support (seven items), health responsibility (eight items), self-realization (eight items), exercise (four items), and stress management (six items). The scale items are evaluated using a Likert-type scaling method; namely, "1: never, 2: sometimes, 3: usually, 4: frequently, 5: always". The scale score related to a specific area is obtained by adding the scores of the items in the subscale, and the total score of the scale is obtained by adding all the subscale scores. The scores which can be obtained from this scale range between 40 and 200. Higher scores suggest that adolescents possess good health promotion behaviors.[17]

The AHPS-SF was developed by Chen et al.[15] and it is based on the original form; its psychometric properties were examined. The scale consists of 21 items in total. The scale items are evaluated using the following Likert-type scaling method: "1: never, 2: sometimes, 3: usually, 4: frequently, 5: always". The factor load values of the original scale are between 0.51 and 0.76. The total Cronbach's alpha value of the scale is 0.90. The model fit indices of the scale are the following: goodness of fit index (GFI): 0.95, normed fit index (NFI): 0.93, non-normed fit index (NNFI): 0.98, comparative fit index (CFI): 0.98, and the Root Mean Square Error of Approximation (RMSEA) value was determined to be 0.028.[15]

Adaptation of the Short-Form Adolescent Health Promotion Scale

Three linguists independently translated the scale into Turkish. A separate linguist then translated the Turkish edition back into English. Seven nursing faculty members were canvassed for their expert opinions. The experts were shown the original and translated scale versions and asked to evaluate the compatibility of items on a scale from 1 (very compatible) to 4 (requires major modification). The instrument was tested by research team members on 20 adolescents after linguistic validity was confirmed. The remaining sample did not include those adolescents who participated in the pilot study. We concluded that the scale could be used with a large enough sample to test its reliability and validity as the adolescents had no negative feedback. For the test-retest reliability analysis, the scales were re-applied to the same 20 children eight weeks later.

Compliance with Ethical Standards

For validity and reliability, permission was obtained from the original scale owner through e-mail. Approval of the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2019/26-33, protocol number: 4884-GOA) and institutional approval were received before this research started. Following the approval of the ethics committee and institution, the purpose of this study was explained to the adolescents included in the sample and to their parents. A thorough explanation of the study aim was provided to the parents, and written permission of those who agreed to participate in the study was obtained.

Statistical Analysis

The Social Sciences Statistical System version 22.0 (SPSS Inc, Chicago, IL, USA) was used to test the data statistically. The adolescent sociodemographic data were analyzed by frequency, percentage, and mean. The Cronbach's alpha, test-retest and item-total correlations of Cronbach were used to assess reliability. For new measures, a Cronbach's alpha of 0.70 was acceptable.[18] In the item-total analysis, the appropriate coefficient had to be higher than 0.30.[19] The content validity index (CVI), confirmatory factor analysis (CFA) and exploratory factor analysis (EFA) were used to test the validity of the ratings. CVI was used to determine the accuracy of the views of the experts. The CVI for the total instrument, based on a 4-point scale, was the percentage of the total items assessed by the experts as being fair or very relevant.[20] The significance level was accepted as $p<0.05$.

RESULTS

Sample Characteristics

In this study, 52.6% of the adolescents involved were male, and their mean age was 14.46±1.57. Furthermore, 29.5% of the students (n=240) attended grade 8, and 33.7% (n=27) of the mothers of adolescents were high school graduates, whereas 34.2% (n=278) of the fathers were. When the income level of the children included in this study was examined; 6.2% (n=51) reported low income, 83.6% (n=684) middle income, and 9.7% (n=79) high income. It was determined that 23.3% (n=190) of the adolescents did not have breakfast in the morning. In addition, 64.9% of the adolescents (n=528) had their own computers and access to the internet. It was found that 56.6% (n=461) of adolescents were connected to the internet every day, 83.3% (n=719) had smart phones, and all of them could connect to the internet with their smart phones.

Validity Analysis

The scale was translated into Turkish by three linguists independently. Following this, the translation was reviewed and evaluated by the researchers. Then, the scale was revised by a Turkish language expert. The draft Turkish version of the AHPS-SF was translated back into English by two independent bilingual, bicultural translators whose native language was English and who had experience in health terminology and the linguistic and cultural aspects of the English language, producing two independent back-translated versions of the scale.[16,19,21]

Content Validity

For the content validity of the Turkish scale, seven experts were asked for their opinions. The item-level CVI and scale-level scale validity index (S-CVI) for the overall scale were determined to fall within the range of 0.90 to 1.00.

EFA revealed that the Kaiser-Meyer-Olkin (KMO) coefficient of the Turkish scale was 0.862 and the Bartlett test chi-squared (χ^2) test was 4,240,743 ($p<0.001$). EFA results demonstrated that the Turkish scale consisted of six subdimensions, and the total explanation variance of the scale was 56.197%. When the factor load values of the scale were examined, the range of the nutritional factor load values of the first subdimension was 0.54 to 0.75; the second subdimension (social support) was 0.44 to

0.83; the third subdimension (health responsibility) was 0.60 to 0.72; the fourth subdimension (life appreciation) was 0.47 to 0.72; the fifth sub-dimension (exercise) was 0.47 to 0.85; and the sixth subdimension factor load values (stress management) were 0.59 to 0.64 (Table 1).

Construct Validity

CFA noted that the sub-scale load values of the scale were the following: for the nutrition sub-scale, 0.50 to 0.53; for the social support sub-scale, 0.40 to 0.66; for the health responsibility sub-scale, 0.50 to 0.62; for the life appreciation sub-scale, 0.57 to 0.71; for the exercise sub-scale, 0.58 to 0.64; and for the stress management sub-scale, 0.51 to 0.56. From the results of the CFA, model fit indexes of the scale were the following: Model χ^2 was 449.58; df was 170 and RMSEA was equal to 0.045. Another model parameter was calculated by dividing the χ^2 value by the degree of freedom. If the outcome is less than 5, the model is deemed satisfactory.[19] This calculation was less than five (χ^2/df=2.64) (Table 2). As for the indices, the following values were determined: GFI: 95, adjusted GFI: 93, CFI: 97, incremental fit index: 97, relative fit index: 0.94, NFI: 95, and NNFI: 0.96 (Figure 1).

Reliability Analysis

Whereas the total Cronbach's alpha coefficient of the scale was 0.85, the Cronbach's alpha coefficient of the scale sub-scales were as follows: for the first sub-scale, 0.712; for the second sub-scale, 0.697; for the third sub-scale, 0.700; for the fourth sub-scale, 0.730; for the fifth sub-scale, 0.701; and for the sixth sub-scale, 0.702. Strong correlations were found between test and re-test (r=0.85, p<0.001). When analyzing item-total scale correlations, they ranged from 0.302 to 0.533 and they were statistically significant (p<0.001). The t-squared test of Hotelling was used to assess whether the measure had a bias in answer. The t-squared value of Hotelling was 1,842,675; F: 89.981 (p<0.001). Therefore, there was no bias in response in this scale.

Table 1. Factor Analysis and corrected item-total correlation of the Turkish Short-Form Adolescent Health Promotion Scale

Item description	Nutrition	Social support	Health responsibility	Life appreciation	Exercise	Stress management	Corrected item total correlations
1. I choose foods without too much oil	0.696						0.362
2. I include dietary fiber (e.g. fruits or vegetables)	0.753						0.310
3. Each meal includes the five food groups (e.g. bread, meat, milk, fruit, vegetable)	0.541						0.364
4. I speak up & share my feelings with others		0.828					0.302
5. I care about other people		0.525					0.354
6. I talk about my concerns with others		0.822					0.388
7. I make an effort to have good friendships		0.439					0.422
8. I read food labels when I shop			0.605				0.427
9. I watch my weight			0.667				0.469
10. I discuss my health concerns with a doctor or nurse			0.602				0.455
11. I check my body at least once a month			0.720				0.430
12. I usually think positively				0.466			0.473
13. I make an attempt to correct my defects				0.684			0.528
14. I make an effort to know what's important for me				0.721			0.533
15. I make an effort to feel interesting and challenged every day				0.542			0.499
16. I exercise rigorously for 30 minutes at least 3 times per week					0.817		0.438
17. I warm up before rigorous exercise					0.845		0.426
18. I make an effort to stand or sit up straight					0.474		0.453
19. I make an effort to determine the source of my stress						0.641	0.483
20. I make schedules and set priorities						0.632	0.466
21. I try not to lose control when things happen that are unfair						0.594	0.429
Explained variance (%)	56.197						

Table 2. Model fit indices for confirmatory factor analysis

χ^2	df	p	χ^2/df	GFI	AGFI	CFI	IFI	RFI	NFI	NNFI
449.58	170	<0.001	2.64	0.95	0.93	0.97	0.97	0.94	0.95	0.96

GFI: Goodness of fit index, AGFI: Adjusted goodness of fit index, CFI: Comparative fit index, IFI: Incremental fit index, RFI: Relative fit index, NFI: Normed fit index, NNFI: Non-normed fit index.

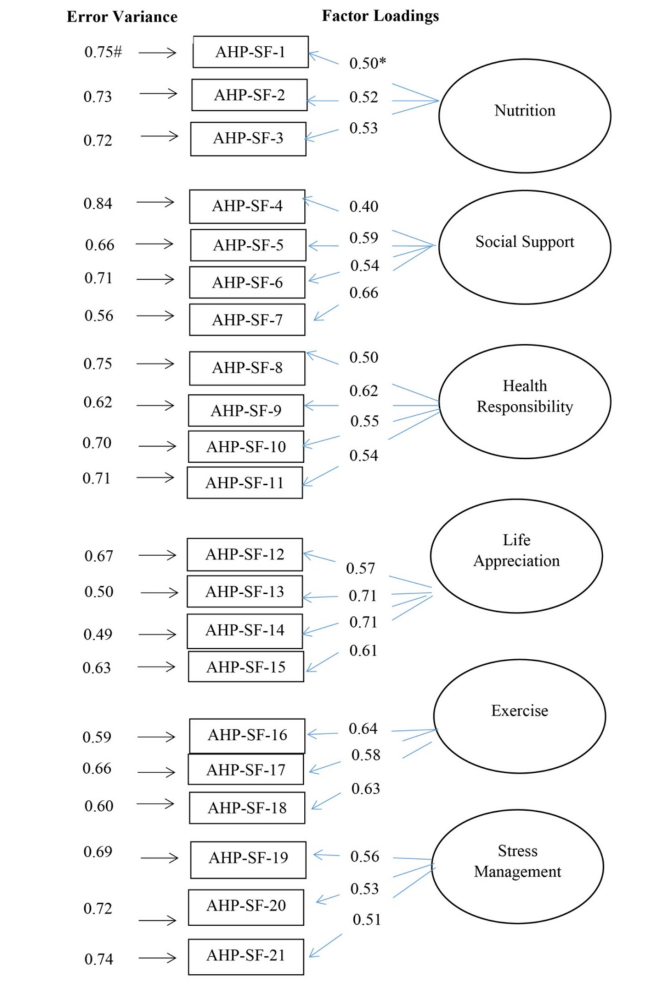

Figure 1. As for the indices, the following values were determined.

AHP-SF: Adolescent Health Promotion: Short Form.

DISCUSSION

In the literature, no adaptation of the Health Promotion Scale: Short Form developed by Chen et al.[15] to another culture was found. Therefore, the discussion part of this study was based on the original scale (short form of health promotion scale-21 items). Content validity relates to whether the items constituting the test are sufficient in terms of quantity and quality to assess the behavior or property it aims to measure. In this study, expert opinion was consulted to ensure content validity. Evaluation of compliance among the experts demonstrated that the content and index validity indices were above 0.80, and there was a high level of agreement among the experts.[21] In light of these results, it was concluded that the expressions of the scale were appropriate to Turkish culture, adequately representing the areas to be measured and providing content validity.

The convenience of the data for factor analysis was examined using the KMO coefficient and Bartlett Sphericity test. In the literature, KMO values between 0.80 and 0.90 show that the sample is large enough to provide correlation reliability and is suitable for factor analysis.[22] If the KMO value is less than 0.50, then the factor analysis cannot be continued.[23] The data in this study were found to be suitable for factor analysis, and the sample size was sufficient.[21,24] It was determined that the KMO value was not considered in the original scale.[15]

The descriptive variance of the original health promotion scale was 51.14%, and it consisted of six subdimensions, and the variance of explanation was similar to the original in the Turkish scale and it consisted of six similar subdimensions. An analysis explaining 50% to 75% of the total variance in the literature is accepted as a valid analysis.[19] According to these results, the explanation variance of the Turkish scale was within an acceptable range and resembled the structure of the original scale.

Factor load is the coefficient which explains the relationship of the item with the factors. The factor loads pertaining to the items accounting for the factors are expected to be high. In order to say that an item measures a structure or factor well, this factor load value should be 0.30 or higher.[19,21,24] In this study, because the factor loadings of all items in the scale were greater than 0.30 and similar to the factor loads in the original scale, it can be said that the Turkish version retained the original structure and had a strong factor structure for the Turkish sample.

The literature indicates that the model compliance indicators GFI, NFI, NNFI, and CFI should be >0.90 and RMSA should be <0.08.[25] In this study, it was shown that these values were suitable, and that the data were compatible with the model; furthermore, results revealed that it was a good model, and it confirmed the single factor structure.[21] Since the model fit indices were not examined in the original scale, no comparison could be made with the Turkish scale. Cronbach's alpha coefficient and test-retest reliability analysis are the most commonly used methods for determining reliability levels in the literature. Whereas a Cronbach's alpha coefficient less than 0.60 means that the scale has lower reliability, when it is between 0.60 and 0.80, it is reliable enough, and when it is between 0.80 and 1.00, it indicates highly reliable.[26] The total Cronbach's alpha coefficient in this study was above 0.80, and the Cronbach's alpha coefficients of the subdimensions were above 0.70, indicating that the scale had a high level of reliability. The Cronbach's alpha value of the Turkish scale was found to be higher than the original scale. In addition, the Cronbach's alpha value of the Turkish scale and the original scale[15] are considered to be consistent. As a result of the test-retest analysis of the Turkish scale, its correlation coefficient was found to be above 0.80, and it had a high level of correlation. The lack of test-retest analysis in the original scale is one of the strengths of our study compared to the original scale. When the item-total score correlations of the Turkish scale were examined, it was seen that all items of the scale exhibited a sufficient correlation with the total score of its own subdimension, and the item-total score correlations of the

subdimensions were high ($p<0.001$, Table 1). Since the item total score correlation was not calculated in the original scale, any similarities or differences with the Turkish scale could not be discussed.

It is assumed that response bias has an adverse effect on the reliability and validity of scales. Therefore, the Hotelling test was performed in this study in order to determine whether or not there was a response bias. The Hotelling t-squared test was used to assess whether or not the answers people gave to the things on the scale were equivalent. The test results demonstrated that adolescents did not interpret every item the same, and there was no response bias while answering the questions.

Study Limitations

This study had several limitations. Concurrent, convergent, and divergent validity were not examined. Moreover, due to the lack of scales organized in different languages, no comparisons of scales could not be made between different cultures; therefore, only the original scale was reviewed in the discussion section of this article.

CONCLUSION

Adolescence is a special period in which health-related behaviors and attitudes develop. Therefore, it is recommended that adolescent health promotion behaviors be determined and adolescents with risky health behaviors be identified using the AHPS-SF. Acquiring positive health behaviors during adolescence is also important in terms of achieving healthy behavior for individuals in the future; therefore, the health promotion behaviors of adolescents should be monitored at certain intervals.

Adolescents, parents, and teachers should be provided with training and counseling relating to risky health behaviors and health promotion behaviors. In addition, it is recommended that nurses working in the field of school health should plan training for risky health behaviors and factors affecting adolescents, and non-invasive interventional studies should be conducted. In addition, determining the factors which affect the health promotion behaviors of adolescents and increasing the awareness of teachers and school health nurses about risky health behaviors which may be detected during adolescence are further recommended. The Health Promotion Behavior Scale: Short Form is believed to have a guiding role in determining the priorities of the content and subjects for training programs intended to prevent or reduce risky health behavior.

MAIN POINTS

- The scale is a valid and reliable means of measurement which can be used to determine the health promotion behaviors of adolescents in a Turkish sample.
- Adolescence is a special period in which health-related behaviors and attitudes develop.
- Adolescent health promotion behaviors can be determined and adolescents with risky health behaviors can be identified using the Adolescent Health Promotion Scale: Short Form.

ETHICS

Ethics Committee Approval: Approval of the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2019/26-33, protocol number: 4884-GOA) and institutional approval were received before this research started.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.A., İ.B., A.A.K., M.B., Design: D.A., İ.B., A.A.K., M.B., Supervision: D.A., M.B., Materials: D.A., Data Collection and/or Processing: D.A., İ.B., A.A.K., M.B., Analysis and/or Interpretation: D.A., İ.B., A.A.K., M.B., Literature Search: D.A., İ.B., A.A.K., M.B., Writing: D.A., İ.B., A.A.K., M.B.

DISCLOSURES

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RESEARCH ARTICLE

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The Relationship Between Type 2 Diabetes Risk and Healthy Lifestyle Behaviours of University Students in North Cyprus

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Abstract

BACKGROUND/AIMS: The development of health-promoting lifestyle behaviours can reduce the risk of lifestyle diseases such as obesity, and type 2 diabetes. This study aimed to determine associated factors and the relationships between health-promoting behaviour and the risk of type 2 diabetes in university students.

MATERIALS AND METHODS: This study was conducted with 374 university students, and type 2 diabetes risk and health promoting lifestyle behaviours were assessed by The Finnish Type 2 Diabetes Risk Score (FINDRISC) and Health Promoting Lifestyle Profile Scale (HPLP)-II, respectively. Data were collected by face-to-face interviews and survey techniques and some anthropometric measurements were also taken.

RESULTS: There was a weak negative relationship between the scores of HPLP-II-total, HPLP-II-physical activity (PA), HPLP-II-nutrition (NT), and type 2 diabetes risk ($r=-0.13$, $p=0.01$; $r=-0.17$, $p<0.001$; $r=-0.16$, $p<0.001$, respectively). The lowest FINDRISC score group had the highest HPLP-II-NT scores ($p<0.05$). Female students had a 2.3-fold increased type 2 diabetes risk in comparison to males and students who were smokers had a 2.1-fold increased type 2 diabetes risk ($p<0.05$). Overweight students had a 3.7-fold increased type 2 diabetes risk compared to underweight students ($p<0.05$).

CONCLUSION: There is a relationship between type 2 diabetes risk and overall healthy lifestyle behaviours and healthy lifestyle behaviours such as NT, and PA. Gender, age, obesity, alcohol consumption, smoking, NT, and PA are the factors affecting type 2 diabetes risk. Parts of university education courses and activities on healthy lifestyles can encourage students to develop their health promoting lifestyle behaviours and can be beneficial in reducing the risk of type 2 diabetes.

Keywords: Healthy lifestyle, diabetes mellitus, diabetes mellitus type 2

INTRODUCTION

Lifestyle can be defined as daily routine activities which may affect an individual's health. A healthy lifestyle is defined as having control over all behaviours affecting an individual's health and their performance of health-promoting daily activities in order to decrease their risk of diseases.[1] A combination of at least four healthy lifestyle factors is associated with the reduction in the all-cause mortality risk by 66%.[2] Smoking, alcohol consumption, physical activity (PA), nutrition (NT), and other lifestyle behaviours are associated with the risk of obesity, type 2 diabetes, cancer, and cardiovascular diseases. The role of genes and lifestyle are contributing to the rapid increase in the incidence of type 2 diabetes.[3] Specifically, changing the dietary and PA behaviours are a target of many effective lifestyle programs which aim to reduce the risk of type 2 diabetes.[4] Therefore, determining the risk of type 2 diabetes is essential in preventing this disease. The International Diabetes Federation (IDF) has introduced three necessary steps for the prevention of diabetes including determining at risk groups, measuring any risk, and interventions aimed at preventing the development of type 2 diabetes. The IDF recommends the use of risk scales such as

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The Finnish Type 2 Diabetes Risk Score (FINDRISC) in order to identify at risk groups.[5] An individual's university years may cause changes in their social environment and health-related behaviour as they are away from their family control. Smoking, alcohol consumption, insufficient fruit and vegetable consumption and a sedentary lifestyle are frequently observed behavioural changes in university students.[6,7] The development of health-promoting lifestyle behaviours of university students includes the development of the current and future quality of life of students as well as social health-promoting lifestyle behaviours within the society, which reduce the risk of lifestyle diseases such as obesity, type 2 diabetes, cardiovascular diseases and cancer. Such changes may be effective in improving students' quality of life.[8,9] This study aimed to determine the associated factors and the relationships between health-promoting behaviour and the risk of type 2 diabetes in university students.

MATERIALS AND METHODS

Place and Time of the Research and Sample Selection

This study was conducted on the Eastern Mediterranean University students in 2016 during the spring semester. The sample size was determined to be 374 university students using a random sampling method with a 95% confidence interval and a 5% sampling error.

Research Techniques and Tools

A questionnaire covering the general characteristics and the nutritional habits of the students, "Type 2 Diabetes Risk" and "Health Promoting Lifestyle Profile Scale-II (HPLP-II)" was used to collect data through face-to-face interviews and a survey technique, which also included some anthropometric measurements. This study was approved by the Ethical Board of Scientific Research and Publication of Eastern Mediterranean University (approval number: 2016/23-06, date: 14.03.2016). All participants were asked to sign an informed consent form according to the Declaration of Helsinki.

Anthropometric measurements: Body weight was measured with a 0.1 kg sensitive digital scale, and height was measured on a frontal plane with a rigid tape measure when the head, back, hips and heels were touching the wall. Waist circumference was measured with a rigid tape measure with the subject standing with their legs together and hands lowered freely over the point in between the iliac crest and the rib cage. The hip was measured with a non-stretching tape measure by standing with legs together, and hands lowered freely at the broadest section of the hip. The body mass index (BMI) was calculated using the formula: weight (kg)/height $(m)^2$. The results were classified as follows: <18.5 kg/m^2 underweight; 18.5-24.9 kg/m^2 normal; 25-29.9 kg/m^2 overweight; and ≥30.0 kg/m^2 obese. In the risk assessment of obesity-associated metabolic complications, waist circumferences which are greater than or equal to 94 cm in males and 80 cm in females are defined as risky, while waist circumferences greater than or equal to 102 cm in males and 88 cm in females are defined as high risk. A waist to hip ratio higher than 1.0 in men and higher than 0.85 in women has been determined as risky.[10] Waist to height ratio is used to determine cardiometabolic risk and type 2 diabetes risk. The optimal cut-off point for Turkish adults of 0.5 or over is accepted as being associated with increased risk.[11]

HPLP-II: This scale was developed to measure the behaviour of various individuals for improving/maintaining health in relation to a healthy lifestyle. HPLP-II consist of 52 items and the Cronbach's alpha coefficient is 0.92 for the Turkish validity and reliability of the scale. The scale consists of 6 sub-dimensions: health responsibility (HR), PA, NT, spiritual growth (SG), interpersonal relations (IR), and stress management (SM).[12,13]

FINDRISC: Although there are many risk scoring models to assess type 2 diabetes risk, they require special blood test results, which limits their widespread use. This scale serves as a fast, cheap, non-invasive, convenient and simple screening tool for students at high-risk of developing type 2 diabetes in the future.[5,14] The FINDRISC questionnaire form consists of eight simple questions regarding risk factors for type 2 diabetes, and higher scores indicate higher risks.[15]

Statistical Analysis

The independent samples t-test and One-Way ANOVA test were used for the deductive statistical evaluation of the data. The One-Way ANOVA post-hoc Tukey's test was used to compare the differences between groups. Additionally, the Pearson correlation test was used to assess the correlation between HPLP-II and FINDRISC scores. Logistic regression analysis was used to assess the effect of factors on type 2 diabetes risk. P-values less than 0.05 were accepted as statistically significant. The Statistical Package for the Social Sciences 21.0 was used for statistical data analysis.

RESULTS

According to Table 1, female students had higher mean scores than male students in the HPLP-II-T and HPLP-II-HR, HPLP-II-NT and HPLP-II-IR ($p<0.05$). Students above 21 years of age had higher scores than those students below 21 years in HPLP-II-NT ($p<0.05$). Students who drank alcohol showed lower mean HPLP-II-NT, HPLP-II-SG and HPLP-II-SM scores than those students who did not drink alcohol ($p<0.05$). Students who smoked had lower HPLP-II-T, HPLP-II-HR, HPLP-II-PA, HPLP-II-NT, HPLP-II-SG and HPLP-II-SM scores and they had higher FINDRISC scores than those students who did not smoke ($p<0.05$).

Type 2 diabetes risk score increased with increased BMI ranges ($p<0.05$). Risky and high-risk groups according to their waist circumference and waist to hip ratios had higher mean scores for type 2 diabetes risk than non-risk groups ($p<0.05$) (Table 2).

The lowest FINDRISC score group had the highest HPLP-II-NT scores (Table 3). There were weak negative relationships between the scores of the HPLP-II-T, HPLP-II-PA, and HPLP-II-NT with the risk of type 2 diabetes ($r=-0.13$, $p=0.01$; $r=-0.17$, $p<0.001$; $r=-0.16$, $p<0.001$, respectively) (Table 4). According to regression results, female students had a 2.3-fold increased type 2 diabetes risk than males and students who were smokers had a 2.1-fold increased type 2 diabetes risk than students who did not smoke ($p<0.05$). Overweight students had a 3.7-fold increased type 2 diabetes risk compare to underweight students ($p<0.05$). Also, according to waist circumferences, type 2 diabetes risk increased 3.8-fold in the risky group and 6.4-fold in the high-risk group compared to the non-risk group ($p<0.05$) (Table 5).

DISCUSSION

The health-promoting lifestyle behaviours of the youth are shaped during their university years and they have effects on the quality of life and the risks of diseases in the future; therefore, it is essential to evaluate lifestyle behaviour. In this study, The HPLP-II-PA demonstrated the lowest

Table 1. HPLP-II and Type 2 Diabetes Risk Scores of students for their gender, age, alcohol consumption, and smoking habits

		HPLP-II-T	HPLP-II-HR	HPLP-II-PA	HPLP-II-NT	HPLP-II-SG	HPLP-II-IR	HPLP-II-SM	FINDRISC
	n	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S
Gender									
Male	215	125.2±20.43	17.8±4.80	17.3±5.36	19.1±4.11	26.4±4.69	25.3±4.56	19.0±3.83	6.6±3.79
Female	159	130.5±18.20	19.7±4.49	16.9±4.38	20.0±3.86	27.1±4.43	27.0±4.22	19.5±3.69	6.5±4.50
p		**0.009***	**<0.001***	0.405	**0.006***	0.167	**<0.001***	0.161	0.830
Age (year)									
≤21	198	126.0±18.39	16.7±4.19	17.1±4.85	20.1±3.68	26.3±4.50	25.9±4.40	19.0±3.72	6.3±3.92
>21	176	129.0±20.93	17.4±4.55	17.2±5.10	21.2±4.58	27.1±4.65	26.1±4.60	19.4±3.83	6.8±4.29
p		0.133	0.113	0.828	**0.015***	0.124	0.682	0.303	0.235
Alcohol consumption									
Yes	185	129.2±18.31	17.3±4.21	17.3±4.60	21.2±4.08	27.3±4.03	25.9±4.39	19.6±3.57	6.1±4.11
No	189	125.6±20.79	16.8±4.53	17.0±5.29	20.1±4.16	26.1±4.99	26.2±4.60	18.8±3.93	6.9±4.07
p		0.077	0.308	0.535	**0.007***	**0.006***	0.537	**0.044***	0.087
Smoking									
Yes	192	124.1±20.14	16.4±4.29	16.5±5.08	19.9±4.29	25.9±4.84	25.8±4.59	18.7±3.84	7.4±4.07
No	182	130.6±17.70	17.6±4.39	17.7±4.79	21.3±3.91	27.4±4.21	26.2±4.40	19.7±3.64	5.7±3.96
p		**0.001***	**0.009***	**0.028***	**0.001***	**0.002***	0.375	**0.009***	**<0.001***
Total	374	127.4±19.66	18.6±4.76	17.1±4.97	19.5±4.03	26.7±4.59	26.0±4.50	19.2±3.78	6.5±4.10

*: P<0.05. x̄: Mean, S: Standard deviation, HPLP: Health Promoting Lifestyle Profile Scale, T: Total, HR: Health responsibility, PA: Physical activity, NT: Nutrition, SG: Spiritual growth, IR: Interpersonal relations, SM: Stress management, FINDRISC: Finnish Type 2 Diabetes Risk Score.

Table 2. HPLP-II and Type 2 Diabetes Risk Scores of students in relation to their anthropometric measurements

		HPLP-II-T	HPLP-II-HR	HPLP-II-PA	HPLP-II-NT	HPLP-II-SG	HPLP-II-IR	HPLP-II-SM	FINDRISC
	n	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S
BMI (kg/m²)									
<18.5	32	132.1±21.66	18.1±4.80	16,8±5.51	21.5±3.99	27.9±4.65	27.4±4.39	19.8±4.02	4.5±3.30[a]
18.5-24.9	242	126.8±19.94	17.0±4.30	17.2±5.11	20.6±4.19	26.5±4.56	25.8±4.49	19.0±3.82	5.5±3.50[b]
25.0-29.9	77	126.4±17.67	16.6±4.19	16.6±4.12	20.5±3.95	26.7±4.39	26.1±4.58	19.3±3.19	9.3±3.84[c]
≥30.0	18	131.2±20.32	17.1±5.27	19.1±5.02	20.4±4.94	27.1±5.54	26.3±4.21	20.1±4.85	11.8±4.16[d]
p		0.413	0.410	0.262	0.639	0.418	0.300	0.490	**<0.001**
WC (cm)									
M: <94; F: <80	277	127.2±20.04	17.2±4.33	17.1±5.12	20.8±4.16	26.5±4.52	26.0±4.56	19.0±3,79	5.2±3.27
M: 94-102; F: 80-88	62	127.4±19.56	16.6±4.45	17.2±4.66	20.0±4.45	27.4±4.24	25.9±3.93	19.6±3.67	9.2±3.25
M: >102; F: >88	35	129.2±17.06	16.8±4.65	17.1±4.29	20.8±3.56	27.2±5.50	26.6±4.94	20.2±3.72	12.4±3.84
p		0.855	0.649	0.980	0.452	0.277	0.765	0.131	**<0.001***
WHR									
M: <1.0 F: <0.8	329	127.6±19.7	17.0±4.41	17.3±4.99	20.7±4.23	26.7±4.51	26.0±4.45	19.2±3.78	6.2±3.80
M: ≥1.0 F: ≥0.8	45	125.9±19.52	17.2±4.13	16.0±4.66	20.4±3.60	26.4±5.12	26.1±4.83	19.2±3.74	9.0±5.30
p		0.583	0.824	0.097	0.619	0.599	0.954	0.980	**<0.001***
WHTR									
<0.5	223	127.4±20.76	17.2±4.53	17.2±5.35	20.6±4.16	26.6±4.58	26.2±4.48	19.0±3.93	5.0±3.26
≥0.5	137	127.0±18.10	16.8±4.24	16.9±4.25	20.5±4.25	26.9±4.74	25.8±4.66	19.4±3.54	8.9±4.24
p		0.467	0.233	0.364	0.394	0.758	0.338	0.577	**<0.001***
Total	374	127.4±19.66	18.6±4.76	17.1±4.97	19.5±4.03	26.7±4.59	26.0±4.50	19.2±3.78	6.5±4.10

[a,b]: BMI is statistically different than 25.0-29.9 kg/m² and 30.0 kg/m² (p<0.05), [c,d]: Statistically different than all other BMI groups (p<0.05), *: All groups are statistically different from each other (p<0.05). x̄: Mean, S: Standard deviation, HPLP: Health Promoting Lifestyle Profile Scale, T: Total, HR: Health responsibility, PA: Physical activity, NT: Nutrition, SG: Spiritual growth, IR: Interpersonal relations, SM: Stress management, FINDRISC: Finnish Type 2 Diabetes Risk Score, BMI: Body mass index, WC: Waist circumference, WHR: Waist to hip ratio, WHTR: Waist to height ratio.

score. In other studies conducted with university students, the lowest score was reported for lifestyle related to PA[16-18]. Moreover, in our study, the mean scores of female students were higher than for male students for HPLP-II-T, HPLP-II-HR, HPLP-II-NT and HPLP-II-IR. Thus, the health-promoting lifestyle behaviour of university students may vary based on their gender.[16,19] Similar results have been found in a study conducted with university students in Japan.[20] Female university students present healthier behaviour than male students, such as attending social activities, the judicious use of alcohol, and visiting a doctor for routine health checks.[21] Students above 21 years of age have higher scores than

Table 3. HPLP-II scores according to FINDRISC groups

FINDRISC groups		HPLP-II-T	HPLP-II-HR	HPLP-II-PA	HPLP-II-NT	HPLP-II-SG	HPLP-II-IR	HPLP-II-SM
	n	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S	x̄ ± S
<7	202	129.2±21.37	17.2±4.66	17.7±5.31	21.2±4.50*	27.0±4.43	26.1±4.45	19.2±3.95
7-11	124	125.1±17.72	16.5±4.09	16.6±4.70	20.0±3.71	26.4±4.61	25.8±4.55	19.3±3.49
12-14	29	125.0±15.57	17.2±3.17	16.0±3.59	19.8±3.70	26.2±4.91	26.1±4.61	18.9±3.66
15-20	19	127.3±17.38	18.1±4.46	16.4±4.08	20.3±2.90	26.1±5.54	26.7±4.60	18.6±3.93
p		0.265	0.363	0.110	**0.037**	0.545	0.839	0.874

*: Statistically different from all other groups (p<0.05), n: Number, x̄: mean, S: Standard deviation, HPLP: Health Promoting Lifestyle Profile Scale, T: Total, HR: Health responsibility, PA: Physical activity, NT: Nutrition, SG: Spiritual growth, IR: Interpersonal relations, SM: Stress management, FINDRISC: Finnish Type 2 Diabetes Risk Score.

Table 4. The relationship between HPLP-II and FINDRISC

		HPLP-II-T	HPLPII-HR	HPLP-II-PA	HPLP-II-NT	HPLP-II-SG	HPLP-II-IR	HPLP-II-SM
FINDRISC	r	-0.130	-0.061	-0.171	-0.174	-0.082	-0.032	-0.051
	p	**0.012***	0.239	**<0.001***	**<0.001***	0.113	0.540	0.322

*P<0.05, n=374, r: Pearson correlation coefficient, HPLP: Health Promoting Lifestyle Profile Scale, T: Total, HR: Health responsibility, PA: Physical activity, NT: Nutrition, SG: Spiritual growth, IR: Interpersonal relations, SM: Stress management, FINDRISC: Finnish Type 2 Diabetes Risk Score.

Table 5. Regression analysis related factors with FINDRISC

	FINDRISC				
	B	(SE)	p	OR	95% CI
Age	0.335	0.312	0.282	1.399	0.759-2.578
Gender	0.869	0.338	**0.010***	2.384	1.229-4.628
Smoking	0.779	0.300	**0.009***	2.180	1.210-3.927
Alcohol usage	-0.165	0.291	0.571	0.848	0.479-1.500
BMI (kg/m²)					
18.5-24.9	0.985	0.497	**0.047***	2.678	1.012-7.089
25.0-29.9	1.326	0.650	**0.041***	3.766	1.054-13.458
≥30.0	1.970	1.410	0.163	7.169	0.452-13.747
WC (cm)					
M: 94-102; F: 80-88	1.354	0.442	**0.002***	3.874	1.631-9.205
M: >102; F: >88	4.118	1.188	**0.001***	6.414	5.980-63.697
WHR	-0.132	0.467	0.777	0.876	0.351-2.187
WHTR	0.368	0.408	0.368	1.444	0.649-3.213
HPLP-II-T	0.617	0.472	0.191	1.853	0.735-4.670
HPLP-II-HR	0.530	0.322	0.100	1.699	0.903-3.197
HPLP-II-PA	-0.709	0.331	0.052	0.492	0.357-0.941
HPLP-II-NT	-0.580	0.323	0.073	0.560	0.297-1.055
HPLP-II-SG	-0.423	0.329	0.198	0.655	0.343-1.248
HPLP-II-IR	0.056	0.317	0.859	1.058	0.568-1.970
HPLP-II-SM	-0.171	0.312	0.582	0.843	0.457-1.552
Constant	-2.376	0.633	0.000	0.093	

*P<0.05, SE: Standard error, OR: Odds ratio, CI: Confidence interval, WC: Waist circumference, WHR: Waist to hip ratio, WHTR: Waist to height ratio, HPLP: Health Promoting Lifestyle Profile Scale, T: Total, HR: Health responsibility, PA: Physical activity, NT: Nutrition, SG: Spiritual growth, IR: Interpersonal relations, SM: Stress management, FINDRISC: Finnish Type 2 Diabetes Risk Score. Age reference category: 21 years, gender reference category: male, cigarette reference category: non-smoker, alcohol reference category: non-drinker, BMI reference category: <18.5 kg/m², WC reference category: M: <94; F: <80, WHR reference category: M: <1.0; F: <0.8, WHTR reference category: <0.5, HPLP-II-T reference category: <127, HPLP-HR reference category: <17, HPLP-PA reference category: <17, HPLP-NT reference category: <20, HPLP-SG reference category: <27, HPLP-IR reference category: <16, HPLP-SM reference category: <19.

those students below 21 for HPLP-II-NT. Previous studies have shown that the highest scores for HPLP-II-HR and HPLP-II-NT were seen in university students between the age range 23-25 years and above 25 years of age.[22,23] There is a positive relationship between the increase in health control focus and health-promoting behaviour.[24,25] Therefore, an increase in health control focus together with the increase in age is associated with an increase in HR and awareness on health-promoting lifestyle behaviours.

In another study conducted with university students, it was found that in addition to age and gender, there was a relationship between the BMI and HPLP-II scores.[24] A study conducted with university students in Syria determined that low intensity and short durations of PA played a role in higher BMI values.[25] In this study, overweight students had a 3.7-fold increased type 2 diabetes risk compared to underweight students. Another study conducted with the Turkish population showed that 10-year cardiovascular risk ratios increased according to waist circumference categories, either calculated according to the World Health Organisation criteria or according to the proposed cut-off levels 90 cm and 100 cm for males and 80 cm and 90 cm for females.[26] In our study, students who had a higher risk of cardiovascular disease according to their waist height ratio had a higher risk score for type 2 diabetes risk. In addition, a weak negative relationship was determined between HPLPII-T, HPLP-II-PA, HPLP-II-NT with FINDRISC scores. Previous studies showed that university students did not perform sufficient PA and had negative nutritional habits such as skipping meals, frequent fast-food consumption and insufficient consumption of fruits and vegetables.[27-29] These could be due to time restrictions for preparing healthy foods and PA due to planning their course and study hours. In a study conducted in Kuwait, students reported that they did not have enough time to prepare healthy diets and could not plan their schedules during the day and also that they did not have enough time for PA due to unfavourable weather conditions.[30]

In this study, it was found that students who consumed alcohol had lower scores for HPLP-II-T, HPLP-II-NT and HPLP-II-SG compared with those students who did not consume alcohol. Moreover, it was indicated that smoking was associated with a 2.1-fold increase in type 2 diabetes risk for university students. In another study which aimed to determine the factors which could predict healthy behaviour in university students, high self-sufficiency, which is a reflective factor of SG, was associated with a decrease in alcohol and smoking and an increase in PA and nutritional behaviour.[6] In this study, students who smoked had lower mean scores for HPLP-II-T, HPLP-II-PA, HPLP-II-NT, HPLP-II-SG and HPLP-II-SM compared with those who did not smoke ($p<0.05$). In a similar study conducted with university students, it was determined that students who smoked had lower scores for HPLP-II-HR, HPLP-II-SG and HPLP-II-NT compared with those students who did not smoke.[31] In a study conducted on the smoking habits of university students, it was determined that the prevalence of respiratory tract infection was higher and physical fitness was lower in those students who smoked than in those who did not smoke. In addition, an increase in PA can be effective in increasing problem-solving ability; thus, it can provide support for SM and SG.[32] Therefore, the interpersonal development and SG of students is an essential factor affecting smoking and other lifestyle behaviours. Thus, the biopsychosocial development of university students affects health-promoting lifestyle behaviours and the risk of disease. Thus, promoting the SG of students would be conducive to adopting health-promoting lifestyle behaviours.[33]

In a study to assess a range of health behaviours and lifestyle characteristics of undergraduate students from seven universities in the United Kingdom, only a few students were found to follow positive health practices above the recommended levels.[34] Another study conducted with university students in Türkiye demonstrated that students did not have enough information about maintaining a healthy lifestyle and were not using effective methods to cope with stress.[35]

Health education programs to target modifiable risk factors such as unhealthy nutritional habits, physical inactivity and smoking habits may increase the knowledge levels and awareness of university students regarding health-promoting lifestyle behaviours and thus may be effective in allowing for the adoption of health-promoting lifestyle behaviours.[36] In addition, organising training and courses on healthy lifestyles, and activities related with healthy lifestyles enhances the health-promoting lifestyle behaviours in university students.[37,38]

Study Limitations

There are several limitations of this study. Firstly, body composition could not be analysed. Thus, the assessment of major anthropometric measurements so as to better understand body composition may lead to a better understanding of the relationships between type 2 diabetes and the factors of NT and PA as main components of quality of life. Secondly, this study was conducted at only one university campus. Multi-centre large sample studies can be beneficial in revealing a stronger relationship between type 2 diabetes and healthy lifestyle behaviours. Thirdly, detailed daily food consumption and PA records could be beneficial for further analysis in order to assess the relationships between type 2 diabetes risk and these two major lifestyle behaviours.

CONCLUSION

There is a relationship between type 2 diabetes risk and overall healthy lifestyle behaviours and healthy lifestyle behaviours such as NT and PA. Gender, age, waist-height ratio, alcohol consumption, smoking, NT and PA habits are the factors affecting healthy lifestyle behaviours and type 2 diabetes risk, and thus, the quality of life. Courses and activities on healthy lifestyles as a part of university education, well-designed and low-cost university food halls which include healthy food choices, as well as sport centres can encourage students to develop health promoting lifestyle behaviours and can be beneficial in reducing the risk of type 2 diabetes. For further studies which include large multi-centre samples, a larger sample size, dietary and PA records, and body composition analysis could be beneficial in obtaining more accurate results on this issue.

MAIN POINTS

- Healthy lifestyle behaviours are related with type 2 diabetes risk among young adults.
- Obesity is related with increased type 2 diabetes risk among young adults.
- Nutritional habits (HPLP-NT) are related with increased type 2 diabetes risk among young adults.
- Physical activity levels (HPLP-PA) are related with increased type 2 diabetes risk among young adults.
- Smoking is related with increased type 2 diabetes risk among young adults.

ETHICS

Ethics Committee Approval: This study was approved by the Ethical Board of Scientific Research and Publication of Eastern Mediterranean University (approval number: 2016/23-06, date: 14.03.2016).

Informed Consent: All participants were asked to sign an informed consent form according to the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.G., M.M.B., Design: C.G., M.M.B., Supervision: C.G., Materials: C.G., M.M.B., Data Collection and/or Processing: M.M.B., Analysis and/or Interpretation: C.G., Literature Search: C.G., M.M.B., Writing: C.G., Critical Review: C.G., M.M.B.

DISCLOSURES

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CASE REPORT

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Recurrent Autonomic Dysreflexia; A Case Report and Review of the Literature

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Abstract

Autonomic dysreflexia is induced by spinal reflex mechanisms which continue to be intact in spite of the patient's injury. Any proprioceptive or noxious stimuli below the injury level generates an afferent impulse. This initiates a generalized sympathetic response. In response, it results in vasoconstriction below the neurologic lesion. We present a case of a male patient with C6 ASIA-A tetraplegia who developed recurrent dysreflexic episodes which were relieved by replacing the clean intermittent catheterization by indwelling Foley catheterization.

Keywords: Autonomic dysreflexia, tetraplegia, rehabilitation

INTRODUCTION

Autonomic dysreflexia (AD) is an emergency syndrome characterized by excessive, uncontrolled sympathetic output seen in patients with spinal cord injury (SCI) at or above the sixth thoracic neurologic level.[1] An acute rise in blood pressure (20-40 mmHg increase in systolic blood pressure), reflex bradycardia, anxiety, visual changes, nasal congestion, headache, flushing and sweating above the level of injury usually occur. Any proprioceptive or noxious stimuli below the level of the injury such as bladder distension or blocked urinary catheter, fecal impaction, pressure ulcers, ingrown toenails, urinary tract infection, or bladder stones can trigger the potentially life-threatening complication of SCI.[2-4] Bladder distension is the most frequent stimulus which is seen in 75% to 85% of cases.[1] A sudden rise in arterial blood pressure may cause seizures, intracerebral hemorrhage, or even death.[2-5] AD is more common and the reaction seems to be more severe in patients with complete lesions.[1,6]

In this report, we present a male patient with C6 ASIA-A tetraplegia who developed recurrent dysreflexic episodes which were relieved by replacing the clean intermittent catheterization (IC) by indwelling Foley catheterization.

CASE PRESENTATION

A 52-year-old man with C6 tetraplegia ASIA-A due to traumatic C5-6 dislocation 3 months prior had urinary and fecal incontinence. He was hospitalized in the pulmonary medicine inpatient service for the treatment of pulmonary embolism and was using warfarin. Clean IC was being administered to manage neuropathic bladder. On the 44th day of hospitalization, his blood pressure, which was usually between 80/50 mmHg and 100/60 mmHg, increased to 180/75 mmHg without any complaints and it decreased to 95/55 mmHg after placing the patient in an upright position. Three hours later, his blood pressure again increased to 190/90 mmHg and decreased to 85/50 mmHg by again placing the patient in an upright position. Two hours later, he

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developed another hypertensive attack characterized by hypertension (190/80 mmHg), pounding headache, cutis anserina, and flushed, sweaty skin at the neck. His heart rate was 66 beats per minute, his respiratory rate was 32 and his temperature was 37 °C. His blood pressure did not decrease after being placed in an upright position for 3 minutes. Suspecting a possible urinary distension, his bladder was emptied via clean IC. Following that, his blood pressure decreased to 120/70 mmHg, and his headache and other symptoms disappeared immediately. Two days later, he had another dysreflexic attack (170/75 mmHg) with a less severe headache which was resolved after bladder emptying. He also had frequent urine leakages between clean ICs. His urinalysis and urinary cultures were normal. Clean IC was stopped and an indwelling Foley catheter was inserted, which prevented the occurrence of furthers autonomic dysreflexic attacks. Informed consent was obtained.

DISCUSSION

AD is induced by spinal reflex mechanisms which continue to be intact in spite of the patient's injury. Any proprioceptive or noxious stimuli below the injury level generates an afferent impulse. This initiates a generalized sympathetic response. In patients with SCI, descending central inhibitory pathways are blocked and cannot modulate the sympathetic response. The loss of inhibitory and excitatory supraspinal input to the sympathetic preganglionic neurons is responsible for unstable blood pressure. It results in vasoconstriction below the neurologic lesion. As a result, peripheral and splanchnic vasoconstriction leads to hypertension. At or above the T6 lesion level, blood pressure increases because of the splanchnic vascular bed's critical vessel mass.[1,7] Hypertension stimulates baroreceptors and a baroreceptor-mediated increase in vagal activity causes vasodilatation above the lesion level to oppose hypertension centrally. As a result of vagal activity, reflex bradycardia is often seen.[1,6]

Above the level of the lesion, peripheral vasodilatation induced by excessive parasympathetic output and a lack of sympathetic tone causes headache, nasal congestion, flushing and sweating in the head and neck region.[1,6]

In bladder management, incidences of symptomatic AD have been reported to be higher in those patients with reflex voiding and indwelling supra-pubic catheterization, even though the indwelling supra-pubic catheter is supposed to prevent AD reactions as opposed to inducing them. The aim of the treatment is to have a balanced bladder, which is completely emptied at regular intervals, thus obtaining low intravesical pressure and being free of urinary tract infections. In patients with SCI, the latest urologic information suggests clean IC as the gold standard for the drainage of the bladder and it supports the discontinuation of indwelling urinary catheter usage.[2,6] A degree of independence is possible with ICs, and also, they negate the disadvantages of permanent urinary catheterization.[8] Urinary tract infections and bacteriuria are more common among patients using ICs.[6] Symptomatic AD risk with ICs was reported to be low. However, bladder distension between ICs was the precipitating factor in our case and the insertion of an indwelling Foley catheter prevented the occurrence of dysreflexic episodes in our patient. For those patients suffering from recurrent episodes of AD, terazosin is effective in the complete improvement of dysreflexic symptoms and the prevention of serious damage caused by AD.[4,8] The best approach would have been the continuation of IC along with terazosin treatment in our patient. However, our patient was receiving warfarin treatment and minor and major bleeding complications may be seen during anticoagulation therapy.[9] IC carries a small risk of localized trauma and urethral perforation.[10] Therefore, we decided to continue the application of the indwelling Foley catheterization and to reassess the patient after the discontinuation of the warfarin treatment. Episodes were immediately resolved after bladder emptying, so bladder distension was thought to be the precipitating factor.

In some SCI patients, recurrent episodes of autonomic dysrefexia may develop due to an underlying reason such as dyssynergic voiding or an indwelling urinary catheter.[4] Bladder distension between ICs was the cause of the recurrent attacks in our patient and indwelling catheterization resolved these attacks in our case.

For the acute management of AD episodes, the aim is to achieve an orthostatic drop in blood pressure, for which the first step is to place the patient in an upright position. The next step is to loosen any tight or restrictive clothing or constrictive devices. Immediately afterwards, possible triggering factors such as an obstruction of the urinary outlet or any fecal mass should be dealt with. Blood pressure should be monitored every 2 to 5 minutes. If systolic blood pressure continues to be 150 mmHg or higher, the use of antihypertensive drugs is necessary.[1,6,7,11] The best and the most commonly used antihypertensive medications to manage AD are nitrates and, especially, nifedipine (immediate release form), which have a rapid onset and short duration of action.[1] Fortunately, the dysreflexic attacks in our patient were resolved without the need for drug treatment.

CONCLUSION

Autonomic dysreflexic attacks due to bladder distension between ICs were totally prevented by the insertion of an indwelling Foley catheter in our patient. Although the avoidance of indwelling urinary catheters is highly recommended and clean IC is the gold standard for drainage of the bladder in SCI patients as is known, it is sometimes not applicable.

MAIN POINTS

- Autonomic dysreflexia is a clinical emergency syndrome which causes an acute rise in blood pressure.
- In patients with spinal cord injury, clean intermittent catheterization is the gold standard for the drainage of the bladder.
- Bladder distension between intermittent catheterizations can precipitate autonomic dysreflexia and indwelling Foley catheters can be used to prevent the occurrence of dysreflexic episodes in these patients.

ETHICS

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.H.Y., A.E., Design: P.H.Y., A.E., Supervision: P.H.Y., A.E., Materials: P.H.Y., A.E., Data Collection and/or Processing: P.H.Y., A.E., L.M.G., F.H., F.R., Analysis and/or Interpretation: P.H.Y., A.E., L.M.G., F.H., F.R., Literature Search: P.H.Y., A.E., Writing: P.H.Y., Critical Review: A.E., L.M.G., F.H., F.R.

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CASE REPORT

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Treatment of Localized Gingival Recession Using Gingival Unit Grafts with a Two-year Follow-Up: Case Report

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Abstract

Gingival recession is the apical movement of the marginal gingiva from the cemento-enamel junction and it results in exposed root surfaces, which cause tooth sensitivity and aesthetic issues. Several methods can be performed for the surgical management of the recession defects of gingiva. A gingival unit graft (GUG) may result in predictable root closure and keratinized tissue improvement and it has shown successful results in gingival recession defects of Miller's class I and II. In this case report, we aimed to present the management of a localized gingival recession of a Miller class II defect with a GUG. A 20-year-old woman with gingival recession and hypersensitivity on left lower second premolar (#35) was referred to our periodontology department. After intraoral examination, gingival recession of Miller's class II defect was observed on #35. The GUG technique was considered for treatment. At baseline, six months and two years following the surgery, clinical measurements showed the efficacy of GUGs in improving soft tissue parameters in gingival recession cases of Miller's class II.

Keywords: Root coverage, gingival unit graft, gingival recession

INTRODUCTION

Gingival recession is the apical migration of the marginal gingiva from the cemento-enamel junction and it results in exposed root surfaces, which cause tooth sensitivity and aesthetic issues.[1] Several methods can be performed for the surgical management of the recession defects of gingiva. Most common among these are free gingival grafts (FGG), connective tissue grafts, different types of pedicle flaps and guided tissue regeneration. Each surgical method offers various success rates. However, further studies are necessary in order to identify issues associated with predictable and successful outcomes.[2-4]

Nabers[5] described FGG as a common gingival augmentation procedure according to its relative ease on increasing keratinized tissue width. However, this technique has several limitations. Compared to other surgical methods, using a FGG in the treatment may lead to a significant color difference among the grafted tissue and the neighboring gingiva.[6] Allen[7] defined the gingival unit graft (GUG) as a modification of the FGG in 2004. The palatal graft which is harvested as a GUG also includes marginal gingiva and interdental tissue, and so differs from FGG.[7]

One of the major points for the success of soft tissue grafts is the relationship between the vascular formation and the related tissues. Gingiva has a complex and unique vascularity. In soft tissue graft procedures, the donor tissue is designed to survive and function especially over root surfaces which are avascular, by including the marginal gingiva and papillae.[7] The existence of the gingival margin and papillary tissue in the graft can stimulate the recovery process, and result in the closure of recession defects and the color adaptation with neighboring gingival tissues.[2,8,9]

In many studies, the GUG technique has shown successful results in gingival recession defects of Miller's class I and II.[2] In this report, we aimed to present a case of the management of a localized Miller's class II gingival recession defect with a GUG.

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CASE PRESENTATION

A 20-year-old woman with gingival recession and hypersensitivity on the left lower second premolar (#35) was referred to our periodontology department. On intraoral inspection, a Miller's class II gingival recession defect in relation to #35 was detected, with a vertical recession depth of 3 mm, a pocket depth of 1 mm and keratinized tissue width of 0.5 mm (Figure 1). As there was a deficiency of keratinized tissue observed, the GUG technique was considered. Clear information was given to the subject about the treatment procedure and an informed consent for surgery and photographs were obtained. After performing local anesthesia, two vertical incisions were made in the recipient area, expanding apically and extending 3 mm beyond the mucogingival line, then split-thickness flap was reflected and interdental papillae was de-epithelized. After scaling and root planing the exposed portion of the root surface, it was rinsed with saline. A split-thickness graft with approximately 1 mm thickness, extending to the interdental papillae and marginal gingiva, was harvested from the left premolar region of palate (Figure 2, 3). After contouring and adapting, it was auto-transplanted to the recipient bed (Figure 4). The patient was instructed regarding their oral hygiene conditions, prescribed an antibiotic (amoxicillin-clavulanic acid) for 5 days and chlorhexidine rinse for 2 weeks. The healing was uneventful over 14 days (Figure 5). After 6 months of recovery, the patient was re-called and a vertical recession depth of 0.5 mm, a pocket depth of 1 mm and keratinized tissue width of 6 mm was observed by clinical measurements (Figure 6). The second-year examination showed no difference among these measurements compared to the clinical values at the sixth month (Figure 7).

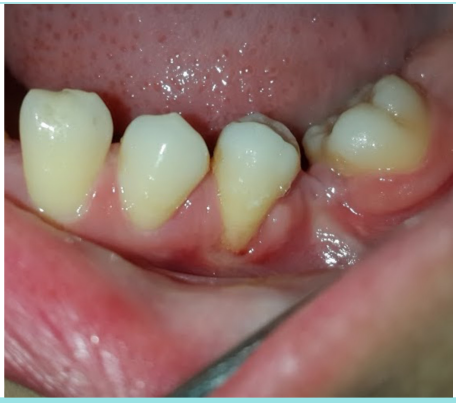

Figure 1. Initial clinical view of recession.

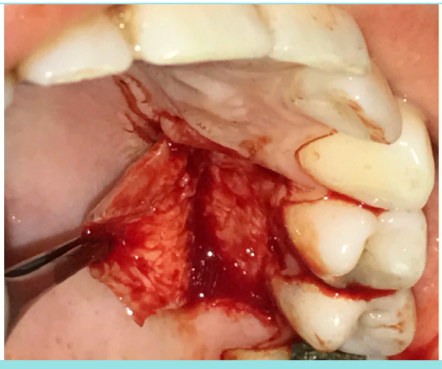

Figure 2. Harvesting from donor site.

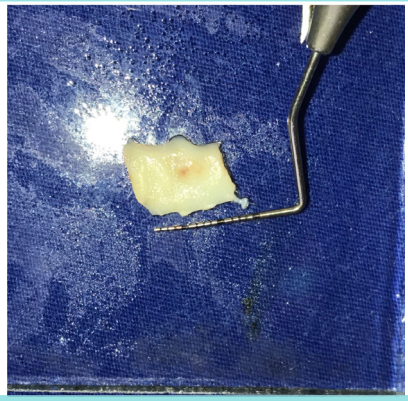

Figure 3. Gingival unit graft.

Figure 4. Graft sutured to the recipient site.

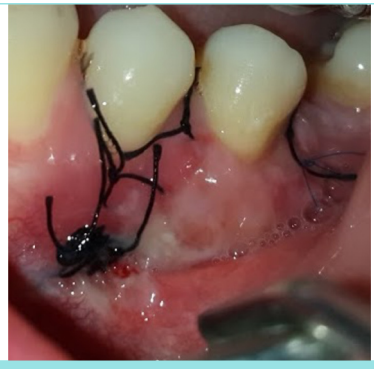

Figure 5. Two weeks after surgery.

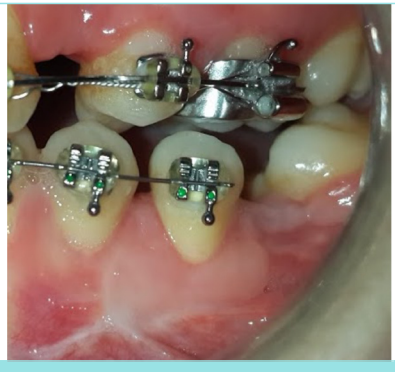

Figure 6. Six months after surgery.

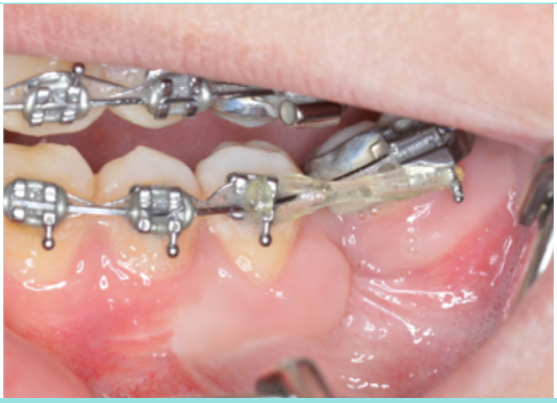

Figure 7. Two years after surgery.

DISCUSSION

This case report with a follow-up of 2 years shows the success of using a GUG in Miller's class II gingival recession cases with notable root coverage and a gain of keratinized tissue. There were no complications observed in the patient throughout the recovery period, neither at the recipient nor at the donor sites. As the patient started orthodontic treatment 5 months after the surgery, long-term results may differ from the normal course.

Conventional FGG was firstly applied in order to recover the deficiency of attached gingiva and shallow vestibular depth. Later on, it was applied to cover recession defects and achieve adequate keratinized tissue, especially if the patient had a reduced vestibular depth.[10]

One study compared the use of FGG and GUG in the management of localized gingival recessions. Eighteen patients with gingival recession on both sides were treated with either a unit graft or a conventional FGG on each side randomly. Clinical parameters defining the recession defect were measured initially and at the following first, third and sixth months. Both techniques showed remarkable improvements in clinical parameters. The GUG demonstrated a better healing index and root closure percentage, as well as giving improved aesthetic content to patients. However, the vertical recession depth was not found to be significantly higher.[8]

Another study compared GUGs with conventional palatal grafts in the management of localized gingival recessions. The probing depth, attachment level, width of keratinized tissue and the depth of vertical recession were measured before surgery and after 8 months. Both treatment procedures showed notable clinical improvements. In the comparison between the groups, the decrease in the depth of recession, the increase of attachment and keratinized tissue were found to be considerably lower in the FGG group.[2]

The gingival unit donor site was clinically recovered more successfully and with fewer complications in these studies. It was noted that some complications such as flap necrosis were not seen in GUGs, while they were frequently seen in subepithelial connective tissue grafts.[11]

This case report shows that using a GUG may be a suitable treatment for the recession of Miller's class I and II defects. GUG procedures may have advantages when compared with the conventional FGG procedure, such as considerably better clinical measurements and aesthetic results. However, further clinical trials with longer follow-ups and a larger population are necessary.

MAIN POINTS

- Gingival recession is the apical displacement of the gingival margin from the cemento-enamel junction and the exposure of root surfaces.
- Gingival recession causes root hypersensitivity and aesthetic problems.
- Treatment methods of gingival recessions are various surgical procedures.
- The gingival unit graft technique may result in predictable root closure and keratinized tissue improvement on gingival recession.

ETHICS

Informed Consent: Clear information was given to the subject about the treatment procedure and an informed consent for surgery and photographs were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., Design: A.Ö., Supervision: A.Ö., A.T., Materials: A.Ö., Data Collection and/or Processing: A.Ö., Analysis and/or Interpretation: A.Ö., Literature Search: A.Ö., A.T., Writing: A.Ö., Critical Review: A.Ö.

DISCLOSURES

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