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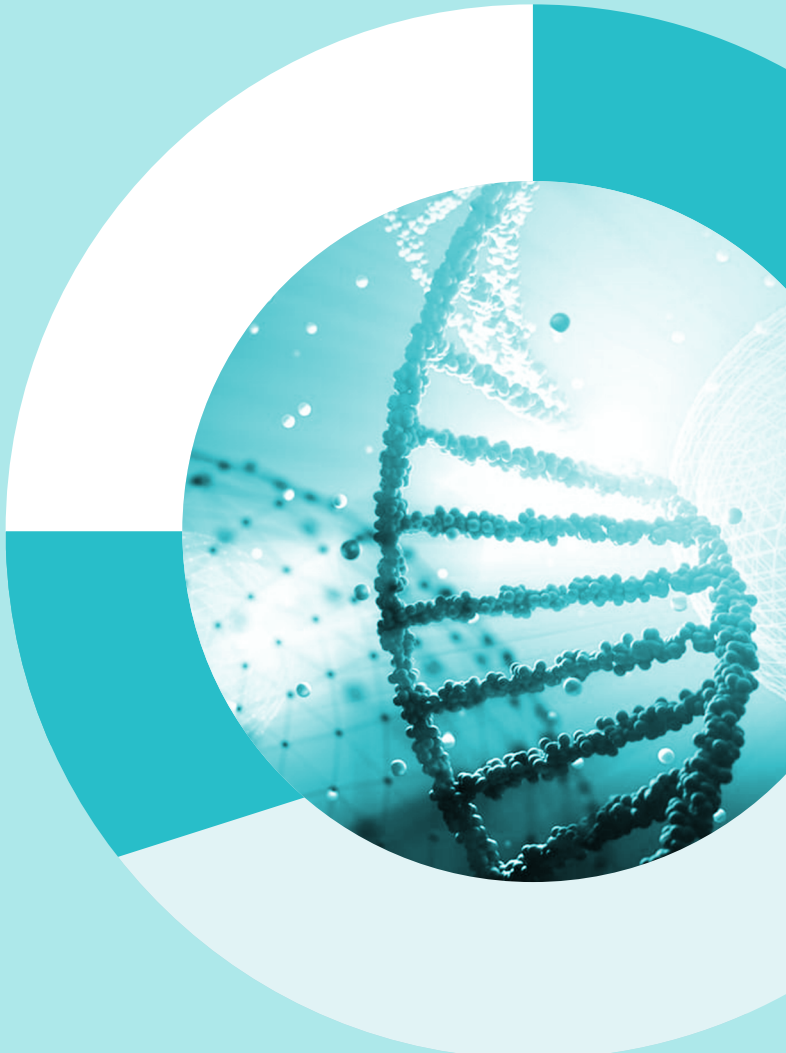

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REVIEW

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Cyprus J Med Sci 2024;9(5):297-301

Oral and Dental Health in Pediatric Oncology Patients

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Abstract

This study aimed to underline the importance of recognizing that pediatric cancer patients should be referred to pediatric dentists to establish preventive and restorative treatment plans before starting cancer therapy, as they are highly susceptible to oral health issues. Oral complications are three times more common in pediatric oncology patients than in adults and constitute the primary non-hematologic side effects of cytotoxic chemotherapy and radiotherapy. Children undergoing immunosuppressive oncology treatments are at risk of acute and long-term oral and dental complications. Current guidelines recommend that children undergo an oral examination before commencing cancer therapy. Pre-treatment examination helps in forming a dentist-child relationship prior to the emergence of oral complications associated with cancer treatment. According to the American Academy of Pediatric Dentistry, these patients are considered high-risk patients and they should visit the dentist every 3 months. Fluoride is a preventive measure against dental caries, and the literature extensively documents the anticariogenic advantages of fluoride therapy. The primary objective of pediatric dentists is to educate pediatric patients and their families on the prevention of oral health problems.

Keywords: Cancer, children, healthcare

INTRODUCTION

According to definitions, cancer is the leading cause of death in affluent countries and the second leading cause in developing countries.[1] Approximately 1 in 285 children under the age of 20 receive a cancer diagnosis, or 150 out of every million.[2] According to cancer incidence studies conducted in the Turkish Republic of North Cyprus (TRNC), the increase in the number of new cases highlights the need for some measures to be taken in this regard. Pervaiz et al.[3] reported in their article published in 2017 that there was an increase in the number of new cases between 2007 and 2012 compared with previous years. Although no specific results were announced for children in the study, the increase in the number of cases suggests that precautions should be taken in terms of oral health before, during, or after treatment. Djamgoz et al.[4] compared the incidence of cancer in patients with National Centre for Truth and Reconciliation (NCTR) with those in Northern and Southern European countries. Although the cancer cases in NCTR are in a similar line with those in European countries, they suggested that programs should be prepared to raise cancer awareness.

Sancar et al.[5] reported cancer incidence in individuals aged 15 years and older in their article published in 2017. The cancer types and incidences of the patients who applied to the Near East University hospitals between 2010-14 were reported, and since there was no pediatric cancer unit, the age group was reported as 15 years and older.

The Ministry of Health of the TRNC reported a survey in 2019 in which the case distribution was based on age groups.[5] In the study, new cases diagnosed between 2012 and 2016 were evaluated. The ratio of cases in the 0-14 age group to total cases was 2.3%. The distribution of this age group according to the population was 36%.

Nevertheless, in Cyprus, where more than 1.26 million people live, the first population-based descriptive epidemiology study of childhood and adolescent cancer discovered that the country has one of the highest age-standardized incidence rates per million children and adolescents worldwide for all pediatric malignancies combined.[6,7]

According to the American Academy of Pediatric Dentistry (AAPD), pediatric dentists play an important role in the diagnosis, prevention,

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stabilization, and management of oral and dental conditions that can impair a child's quality of life before, during, and after immunosuppressive treatments and/or head and neck radiation.[8] Children receiving cancer therapy may have problems with their teeth and oral hygiene during and after treatment. Pediatric patients with cancer may have dental caries that are not treated, periodontal disease, and/or pathological lesions in the oral hard and soft tissues. In addition, patients may experience oral side effects from cancer treatments, show oral cancer symptoms, and experience long-term dental and orofacial problems following cancer therapy.[9] For these reasons, a team consisting of doctors, nurses, dentists, social workers, dietitians, and other medical specialists should work together for children who will receive immunosuppressive therapy and/or head and neck radiation.

Oral Manifestations

A pediatric cancer patient's quality of life is severely impacted by their diagnosis, and their oral hygiene regimen must be customized based on their disease's stage.[10]

The type of cancer, features of the treatment received, age at diagnosis, type of chemotherapy, dosage, and location of the radiation treatment all affect the potential complications that might arise in the mouth. Oral complications can be increased by factors such as pre-existing caries, gingivitis, and poor hygiene.[11,12]

Special short- and long-term complications, including specific and non-specific oral tissue symptoms, may occur in childhood cancers. Specific symptoms are seen in the mucosa, salivary gland, muscle and bone tissue, taste sensation/disfunction, teeth, and gums. Oral mucositis (OM) and related pain, neurotoxicity, mucosal fibrosis, gingival hypertrophy, osteoradionecrosis (ORN), medication-related osteonecrosis, soft tissue necrosis, trismus, secondary tumors, post-transplant lymphoproliferative disorders, dental anomalies and craniofacial changes, dental caries, dry mouth (e.g., salivary gland dysfunction, xerostomia), and dental caries are among the complications.[2,8,10,12,13]

Although bleeding in the mouth is considered an early symptom in some types of cancer (such as acute lymphocytic leukemia, it can be more serious with the direct effect of chemotherapy and radiotherapy.[14] These drugs can cause thrombocytopenia, anemia, and granulocytopenia, increasing the probability of bleeding and susceptibility to infections.[15]

OM generally, mucositis occurs between 3 and 5 months after cancer treatment. It occurs between days after radiotherapy and before chemotherapy. Clinically, the buccal mucosa may initially take on a whitish color, but subsequently, this condition progresses to erythema and a few days later results in a patchy appearance that also contains fibrinous exudate. If high-dose radiation is administered over a short period, ulceration of the covering fibrinous membrane begins earlier.[16]

Opportunistic infections: Candidiasis and herpes simplex virus infections are the most common opportunistic infections. As a result of cancer therapies that cause dryness in the mouth, candida species that are normally inactive in the oral soft tissues become active and develop tiny, sticky lesions on the oral mucosa, tongue, and palate.

Members of the herpesviridae family, such as varicella zoster and herpes simplex, can potentially infect people by causing dry mouth. Herpes simplex manifests as ulcerated sores on the palate, gums, corners of the mouth, and lips. Varicella zoster can cause severe morbidity not only from blister lesions on the lips but also from effects on the lungs, central nervous system, and liver.[16,17]

Dental caries: Neither illness nor therapy directly causes tooth decay. Diseases and treatments do not directly cause tooth decay. Tooth decay develops due to decreased saliva production and flow due to treatments that reduce salivary gland function, children's tendency to eat soft and cariogenic foods, changes in oral flora, and an inability to maintain oral hygiene due to gingivitis.[18] Saliva becomes more acidic due to damage to the salivary glands caused by radiation, which also increases the presence of highly cariogenic oral microbiota, including *Lactobacillus* and *Streptococcus mutans*.[19]

Dry mouth: Hyposalivation (decreased salivation) and/or xerostomia (feeling of dry mouth due to decreased salivation) develop due to salivary gland dysfunction, especially after radiotherapy or chemotherapy.[20] The second most common adverse effect of chemotherapy is xerostomia. Additionally, it has been demonstrated that there is a clear correlation between radiation dosage and salivary gland decrease. As saliva preserves dental health by shielding the teeth and oral mucosa, malfunction of the salivary gland is a significant and sometimes disregarded late consequence that can have a detrimental influence on general health.[21,22] Increased viscosity and slowed flow in saliva make it difficult to chew, swallow, and talk. It also stops taste buds from working, which weakens one's perception of taste.[23,24]

Mucosal fibrosis: Oral submucosal fibrosis is a chronic insidious disease that occurs mainly in the oral cavity and is associated with vesicle formation. Pallor, burning sensations, and ulceration of the oral mucosa are the initial signs of this condition, followed by recurring stomatitis, xerostomia, and, on rare occasions, leukoplakia, as well as difficulties swallowing or phonating. Fibrosis and hardness develop in the buccal mucosa and tongue, leading to trismus and dysphagia.[25]

Gingival hypertrophy: Gingival enlargement and ulcerations cause thickening and pseudopocket formation in the gingiva due to treatment-related neutropenia or infiltration due to an increase in blast leukocytes.[26] Inflamed gum tissues are the main entry route for bacteria and bacterial products, causing sepsis.[27]

Osteoradionecrosis: One of radiation therapy's most dangerous consequences is ORN. It is more common in the mandible than in the maxilla. It is characterized by trauma-induced or spontaneous mucosal degradation leading to a succession of radiation, hypovascular, hypocellular, and hypoxic tissue development, and a non-healing wound.[28]

Medication-related osteonecrosis: In patients without a history of radiation therapy or metastatic disease, it appears as exposed bone in the craniofacial area for >8 weeks. The most significant protective factors against MRONJ include the biological and physiological conditions involved in bone production and growth, as well as the proper dental and oral environment.[29]

Trismus: It is a complication characterized by the inability to completely open the mouth, and it has the potential to cause major morbidity and death.[30] According to reports, 5-38% of individuals with head and neck cancer experience trismus following radiation. Radiotherapy can induce muscular fibrosis, loss of bone growth due to radionecrosis, and inadequate development, culminating in jaw dysfunction.[31]

Craniofacial and dental developmental anomalies: Morphogenesis and calcification of teeth begin in the 5th week of IU life and continues for 14-15 years. During this period, with cancer treatment lasting 1-2 years, complications such as hypodontia, microdontia, regression in root development, hypoplasia, hypomineralization, and premature tooth eruption develop.[32]

Dental Protocols

All patients receiving chemotherapy (immunosuppressive) treatment and/or patients who will receive head and neck radiation should be referred to a pedodontist for condition assessment and precaution planning before starting treatment.[33,34]

The following parameters can be used to guide decisions regarding the need for antibiotic prophylaxis (Table 1).[8,35-39]

Patients receiving cancer therapy are at risk of thrombocytopenia. The following factors can be used to identify the requirement for pre- and post-operative interventions (Table 2).[8,38,39]

Pediatric dentists should evaluate patients' oral health after determining their general health. They keep track of dental hygiene practices, dietary patterns, trauma history, and fluoride exposure through fluoridated water/salt or fluoride supplements (pills, gel, or varnish). Extra-oral and intra-oral examinations are performed, and necessary radiography is performed. According to examination results, pediatric dentists decide preventive and restorative treatment plans. When possible, dental care should be completed before initiating cancer therapy.

Ferrández-Pujante et al.[10] reported a review after searching 114 scientific articles in the databases. They used 29 articles to obtain protocols for pediatric patients receiving immunosuppressive therapy and/or radiation therapy.

The protocols determined the applications in 3 phases.[10]

Phase 1: From the diagnosis of cancer initiate chemo/radiotherapy.

Phase 2: Initial chemotherapy or radiotherapy until 30-45 days post-therapy.

Phase 3: Begins after cancer treatment and may last from 1-2 years to the whole life.

AAPD also made a similar classification and listed recommendations.[8]

In the initial phase, both the AAPD and Ferrández-Pujante et al.[10] noted that the primary priority should be identifying and eradicating potential causes of infection and local irritants in the oral cavity to avoid delaying cancer therapy or causing additional issues. Another goal should be to educate patients and parents about the need for good dental care to avoid issues that might jeopardize the cancer treatment process. It should not be overlooked that communication with an appropriate medical team regarding the patient's oral health status, treatment plan, and timing is critical. To inform patients/parents about the potential short- and long-term negative effects of cancer therapy in the oral cavity and craniofacial complex.[8,10]

In general, the preventive program should include teaching brushing methods, using dental floss, recommending mouthwashes, diet analysis and recommendations, topical fluoride applications, use of lip protectors, use of preventive agents against fungal infections, recommendations for preventing trismus, ensuring that protective measures are taken in radiotherapy to be applied in the head and neck region, and education.[7,9]

Dental procedures must be finished within 7 to 10 days before beginning chemotherapy or radiation therapy. If this is not possible or is delayed, non-acute teeth should receive temporary restoration and therapy. When deciding on dental treatments, more radical decisions like extraction should be made for teeth that pose a risk during cancer treatment. Appliances that can cause mouth injury should not be used. Impacted and persistent primary teeth should be eliminated before treatment initiation. It is recommended to extract teeth with a poor prognosis for at least two weeks or at least seven to ten days prior to the start of cancer treatment.[8,10]

To avoid potential side effects of cancer therapy, patients should be instructed to consume a minimum of two liters of water daily. Lip protective agents should be applied to the lips regularly, chewing sugar-free gum should be recommended to stimulate saliva flow, artificial saliva or pharmacological stimulants should be prescribed, and regular dentist checkups should be recommended.[8,10]

The second phase focuses on where chemotherapy or radiotherapy has begun and lasts until 30-45 days after treatment. This phase should focus on maintaining good oral health throughout cancer treatment, addressing any oral side effects or complications, and educating patients

Table 1. Antibiotic prophylaxis according to absolute neutrophil counts

ANC*	Antibiotic prophylaxis
— >2,000 per cubic millimeter/mm^3	No requirement for antibiotic prophylaxis
1,000-2,000/mm^3	Apply clinical judgment based on the patient's health and scheduled operations
<1,000/mm^3	Defer elective dental treatment. Before initiating treatment in a dental emergency, consult with the medical team about whether to administer a course of antibiotics or just one dose for preventive purposes.

ANC: Absolute neutrophil count.

Table 2. Suggestions as per platelet count

Platelet count	Suggestion
>75,000/mm^3	Does not require any further assistance to carry out the dental procedure.
40,000-75,000/mm^3	Platelet transfusion is necessary before and 24 hours after dental treatment. If the therapy involves bleeding, hemostatic measures such as local hemostatic drugs, sutures, sterile gauze to compress the bleeding location, and/or microfibrillar collagen sponges will be necessary.
— <40,000/mm^3	Dental treatment must be postponed in the event of an emergency. The medical team must also determine whether to treat the patient in a hospital with platelet transfusion, additional bleeding control medication, and bleeding control measures (sutures, sterile compression gauzes, microfibrillar collagen sponges, and local hemostatic agents like topical thrombin).
	Before beginning dental treatment, the dentist should speak with the hematologist about the necessity of a post-transfusion platelet count if platelet transfusions are used. It would be preferable to have extra transfusions in case of severe and protracted intraoperative or postoperative bleeding.

and parents about the value of maintaining good oral hygiene to reduce discomfort from oral issues both during and after cancer treatment.[8,10]

In this phase, the dentist should contribute to the multidisciplinary treatment plan. It should be checked whether the patient maintains oral hygiene practices, and the presence of secondary acute injuries should be checked 1-2 weeks after the start of cancer treatment. To ensure the continuation of oral health, it should be assessed whether all the preventive practices recommended in the first phase are continued, and if pediatric dentists meet with the patient at this stage, these suggestions and practices should be implemented.[8,10]

At this stage, the specific symptoms of the oral mucosa should be examined. In the presence of mucositis, it is recommended that pet owners stay away from acidic, spicy, hard, hot, and irritating foods. Because mucositis causes pain, cryotherapy (ice chips), saline 0.9% rinses, topical anesthetics, or mucous rinses containing anesthetics such as benzocaine (aerosol, gel), lidocaine 2% (viscose, ointment, or aerosol), diphenhydramine, and dyclonine hydrochloride 0.5 or 1.0% solution-dyclonine) should be recommended. In cases of severe mucositis, non-opioid and opioid analgesics as well as low-power laser therapy are preferred. To treat secondary infections, your dentist may prescribe allopurinol, leucovorin, or nystatin.

If particular musculoskeletal difficulties emerge that limit mouth opening, regular stretching of the masticatory muscles, muscle relaxants, and analgesics should be administered. If local bleeding is detected in the gums, tamponade with sterile gauze and topical hemostatic agents should be recommended. In case of systemic bleeding problems, surgical procedures and blockage of local anesthesia should be avoided.

In this stage, if a patient requires dental care, only procedures for emergencies should be performed in-hospital following a collaborative evaluation with the cancer team to determine the best time to administer the treatment (during the intervals between cancer treatment cycles, when the patient's hemoglobin level is more constant, or by utilizing local or systemic hemostatic procedures and antibiotic prophylaxis).[8,10,39]

"Begins after cancer treatment and may last from 1-2 years to the whole life" is the definition of the third phase. The goal of this phase is to preserve ideal oral health following cancer treatment, manage oral problems or long-term oral side effects caused by cancer therapy, and improve patient and parent education regarding the need for lifelong excellent oral hygiene.[8,10]

To maintain preventive strategies, dentists should continue with patient/parent training and general oral maintenance and prevention measures. The use of topical fluoride applications, mouthwash recommendations, and bicarbonate solution should be continued. The patient should maintain regulated dietary habits and continue trismus-preventing exercises.

Non-invasive dental treatments should be initiated in the first year, and orthodontic treatment should be started at least 2 years later. Maintaining proper hydration requires the application of lip lubricants.

CONCLUSION

Using standard protocols that prioritize prevention from the early stages to prevent or minimize complications that cancer treatments may cause in the mouth can improve children's quality of life.

For this reason, the importance of teamwork in cancer treatment should be frequently emphasized among healthcare professionals, and the contribution of pedodontists who will be part of this team should be considered. To contribute to the quality of life of children who undergo a difficult treatment process, relevant specialist organizations need to work together to develop protocols that can be applied as standard in all pediatric oncology centers.

MAIN POINTS

- Main point of review is to underline the importance of coordinated work of pediatric oncology and pedodontics at early stages of cancer treatment, in order to prevent further complications.
- Most common oral manifestations that can occur during cancer treatment.
- To form standardized dental prevention protocol for pediatric patients to be followed.

ETHICS

DISCLOSURES

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RESEARCH ARTICLE

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Comparison of the Complications of Knee Replacement Using Fixed or Mobile Inserts

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Abstract

BACKGROUND/AIMS: Knee replacement surgery or total knee arthroplasty is a widely performed procedure to alleviate pain and improve function in patients with severe knee joint degeneration or injury. The choice between fixed and mobile inserts for knee replacement implants remains critical. Fixed-bearing implants provide stability, whereas mobile-bearing implants offer increased conformity and potential for improved range of motion. This study aimed to compare the complications of knee replacement using fixed and mobile inserts.

MATERIALS AND METHODS: A retrospective analysis was conducted on 412 knee replacement patients who underwent surgery between 2011 and 2021 using either the Smith & Nephew GENESIS-II fixed insert knee prosthesis or Zimmer-Mobile insert knee prosthesis. Data collection involved rigorous evaluation of patient files, radiographs, and postoperative outcomes. Data on age, gender, side of the knee prosthesis, preoperative and postoperative tibiofemoral angle, proximal tibia angle, osteolysis around the prosthesis, and complications, such as instability, infection, extensor mechanism problems, aseptic loosening, and radiological osteolysis, were recorded. Complications requiring surgical intervention were also noted.

RESULTS: The mean age of patients was 65.18 years, and 88.5% were female. The mobile insert group included younger patients with a higher incidence of bilateral knee arthroplasties. Radiological evaluation revealed a higher incidence of patella changes and subsequent patella replacement in the mobile insert group. However, the overall complication rate was not significantly different between the two groups. Although postoperative joint alignment did not significantly differ between the groups, the postoperative proximal tibial angles were higher in the mobile insert group. Specific complications, including instability, infection, extensor mechanism problems, aseptic loosening, and radiological osteolysis, did not significantly differ between the two groups.

CONCLUSION: The choice of fixed or mobile insert during knee replacement did not significantly affect the incidence of specific complications. Surgeons should consider individual patient factors, surgeon preference, and technical expertise when selecting the appropriate implant type for knee replacement surgery.

Keywords: Fixed insert, knee arthroplasty, mobile insert

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INTRODUCTION

Knee replacement surgery, also known as total knee arthroplasty (TKA), is commonly performed in individuals with severe knee joint degeneration or injury. This treatment aims to alleviate pain, improve function, and enhance the overall quality of life of patients.[1] Over the years, advancements in implant design and surgical techniques have led to improved outcomes and long-term success rates in knee replacement surgery.[2]

One crucial aspect of knee replacement surgery is the choice between fixed and mobile inserts, which are components of the implant that facilitate joint movement.[3] Fixed-bearing implants have been traditionally used in TKA, providing stable articulation between the femoral and tibial components. In contrast, mobile-bearing implants offer increased conformity and potential for improved range of motion because of their ability to rotate within the tibial tray.[4]

Although both fixed and mobile-bearing implants have demonstrated satisfactory clinical outcomes, there is an ongoing debate regarding the incidence and nature of complications associated with each type. Complications following knee replacement surgery can include a range of issues, such as infection, implant loosening, instability, wear, and revision surgery, among others.[5] Understanding the comparative risks and complications of fixed and mobile inserts is crucial for optimizing patient outcomes and informing surgical decision-making.

To address this knowledge gap, the current study aimed to compare the complications encountered in patients undergoing knee replacement using fixed and mobile inserts. By examining a large cohort of patients who underwent knee replacement surgery and analyzing their postoperative complications, this study aims to provide valuable insights into the relative advantages and disadvantages of these two implant types. The findings of this investigation may help guide surgeons in selecting the most appropriate implant option based on individual patient needs, ultimately leading to improved surgical outcomes and patient satisfaction.

In conclusion, this study investigated and compared the complications associated with fixed and mobile inserts in patients undergoing knee replacement. The results are expected to contribute to the existing literature and inform clinical decision-making in the field of knee arthroplasty.

MATERIALS AND METHODS

Knee prostheses applied by the authors between 2011 and 2021 were retrospectively scanned. Approval was obtained from the İzmir Bakırçay University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 1122, date: 20.07.2023). Patients who underwent the Smith & Nephew GENESIS-II fixed and Zimmer-Mobile knee prostheses were included in the study. The tibiofemoral and proximal tibial angles were measured as described in Kim et al.'s[6] study. A valgus angulation of 3-7.5 degrees in the evaluation of femorotibial anatomic alignment as a neutral alignment. Valgus angulation 3° was evaluated as varus angulation, and >7.5° angulation was evaluated as valgus.[6] Postoperative radiographs showed osteolysis loosening and periprocetic fracture.[7] Measurements were made by 2 different orthopedic specialists, and the intraclass correlation coefficient was >90%.

Patients who underwent revision knee prosthesis, those who did not undergo adequate preoperative and postoperative knee radiography and follow-up, and those who underwent surgery due to tumor were excluded from the study.

Infection and revision status were checked in the patient files. The complications were instability, infection, extensor mechanism problems, aseptic loosening, and radiological osteolysis. Complications that were surgically treated were also noted.

A tourniquet was used in all knee arthroplasty procedures. At 30 minutes before the operation, prophylactic 1gr cephazolin sodium i.v. Done. 200 mg ciprofloxacin i.v. in patients with allergies Done. An anterior incision was made in all patients. The joint was reached by medial parapatellar intervention. Incisions were made with intramedullary and extramedullary guidance to the femur and an extramedullary guide to the tibia. After appropriate incisions, the prosthesis was fixed to the bone with cement. Patellar component placement was performed in some patients according to the surgeon's preference. Patellar denervation was performed after osteophyte excision in patients without a patellar component. A hemovac drain was placed from the suprapatellar region in all patients.

After surgery, low-molecular-weight heparin was administered for 1 month. (clexan or oxapar 0.4 cc 1x1 or clexan 0.6 cc 2x1 in patients using anticoagulants). The hemovac drain was removed at 12 hours postoperatively. The next day, full load mobilization and controlled passive motion were started. Active knee flexion was initiated as tolerated by the patient. Postoperative film controls were followed up on the 1st day, 1st month, 3rd month, 6th month, 1st year, and 2nd year.

The data obtained from the patients were uploaded into Microsoft Excel. Age, gender, side, bilaterality, preoperative and postoperative tibiofemoral angle, proximal tibia angle, osteolysis around prosthesis, instability (lateral-medial collateral ligament failure, anterior-posterior knee dislocation), extensor mechanism problems [(patella-quadriceps tendon) tear, patella fracture], deep infection requiring prosthesis removal, aseptic loosening, and osteolysis (tibia-femur) around the components that did not show clinical signs were noted.

Statistical Analysis

Means, medians, and standard deviations were used in the statistical evaluation of numerical data, and percentage values were used in the evaluation of cross-sectional data. The conformity of the numerical data of the groups to the normal distribution was evaluated using the Shapiro-Wilk test. Parametric tests were used when it was suitable for the normal distribution, and nonparametric tests were used when it did not. The chi-square test was used for the evaluation of cross-sectional data. Pearson's correlation test was used as the correlation test. statistical significance was set as 95% confidence interval and $p<0.05$.

RESULTS

In the scan, 354 patients had the knee prosthesis applied. However, 412 series of 287 patients with adequate follow-up were included in the study. The mean age of the patients was 65.18±9,267. Other demographic data about the patients are given in Table 1. In the statistical evaluation, gender distributions were similar between the two

groups. There was a significant difference between age and bilaterality. but the distribution of control times was similar (Table 1).

In the radiological evaluation, there was a statistically significant difference between the patella replacement rates and the average postoperative proximal tibial angles between the two groups. There were no statistically significant differences between the average preoperative tibiofemoral angle, postoperative tibiofemoral angle, and preoperative proximal tibial angle (Table 2).

Complications were detected in a total of 22 patients (5.3%). There was a significant difference in the total complication rates between the two groups. however, there was no significant difference between specific complications (Table 3).

DISCUSSION

The present study aimed to compare the complications of knee replacement using fixed and mobile inserts. The analysis of a large cohort of patients who underwent knee replacement provided valuable insights into the relative advantages and disadvantages of these two types of implants.

In terms of patient demographics, the study included a total of 412 knee replacement patients, with a mean age of 65.18 years. The majority of patients were female (88.5%), which is consistent with the higher prevalence of knee osteoarthritis in women.[8] In the analysis of general demographic data, patients who received the mobile insert application were found to be younger than those who received the fixed insert application (63.93 and 66.53, p=0.017). In the patient group with mobile insert application, a higher percentage of bilateral knee arthroplasties were performed (51.7%, 34.8%, p=0.004). More total complications were observed in younger patients who underwent bilateral knee prostheses. Similar studies have also reported more complications in older patients undergoing bilateral knee arthroplasty.[9,10] In this patient group, we recommend using a fixed insert instead of a mobile one.

Table 1. General demographic data of patients

		Mobile insert	Fix insert	All patients	p	Statistical test
Number of patients, (%)		149 (48.1%)	138 (51.9%)	287	-	-
Number of knees, (%)		226 (54.9%)	186 (45.1%)	412	-	-
Age, (mean ± SD)		63.93±9,941	66.53±8,305	65.18±9,267	**0.017**	T-test
Gender, (%)	Male	22 (14.8%)	11 (8.0%)	33 (11.5%)	0.071	Pearson chi-square
	Female	127 (85.2%)	127 (92%)	254 (88.5%)		
Side, (%)	Right	28 (18.8%)	49 (35.5%)	77 (26.8%)	**0.002**	Pearson chi-square
	Left	44 (29.5%)	41 (29.7%)	85 (29.6%)		
	Bilateral	77 (51.7%)	48 (34.8%)	125 (43.6%)		
Bilateral (%)	Yes	77 (51.7%)	48 (34.8%)	125 (43.6%)	**0.004**	Pearson chi-square
	No	72 (48.3%)	90 (65.2%)	162 (56.4%)		
Follw up (months), (mean ± SD)		15.97±7,411	17.88±11,717	16.89±9,752	0.098	T-test

SD: Standard deviation.

Table 2. Radiological results

Radiological evaluation		Mobile insert	Fix insert	All patients	p	Statistical test
Patella change (%)	Yes	138 (61.1%)	24 (12.9%)	162 (39.3%)	**<0.001**	Pearson chi-square
	No	88 (38.9%)	162 (87.1%)	250 (60.7%)		
Preoperative tibiofemoral angle, (mean ± SD)		3.44±7,388	4.05±6,056	3.71±6,817	0.366	T-test
Postoperative tibiofemoral angle, (mean ± SD)		-5.90±3,031	-5.75±2,312	-5.83±2,727	0.590	T-test
Preoperative proximal tibial angle, (mean ± SD)		82.51±3,951	82.09±2,955	82.32±3,538	0.229	T-test
Postoperative proximal tibial angle, (mean ± SD)		90.41±2,155	89.41±1,112	89.96±1,829	**<0.001**	T-test

SD: Standard deviation.

Table 3. Complications

Complications	Mobile insert	Fix insert	All patients	p	Statistical test
	Number (%)	Number (%)	Number (%)		
Total complications	17 (7.5%)	5 (2.7%)	22 (5.3%)	**0.030**	Pearson chi-square
Complications leading to revision	11 (4.9%)	4 (2.2%)	15 (3.6%)	0.143	Pearson chi-square
instability	3 (1.3%)	1 (0.5%)	4 (1.0%)	0.630	Fisher's exact test
Infection	3 (1.3%)	1 (0.5%)	4 (1.0%)	0.630	Fisher's exact test
Aseptic loosening	4 (1.8%)	0 (0.0%)	4 (1.0%)	0.130	Fisher's exact test
Periprocetic osteolysis	5 (2.2%)	1 (0.5%)	6 (1.5%)	0.229	Fisher's exact test
Extensor mechanism problem	4 (1.8%)	2 (1.1%)	6 (1.5%)	0.694	Fisher's exact test

Radiological evaluation revealed differences in patella changes between the two groups. The mobile insert group exhibited a higher incidence of patella changes, leading to a significantly higher rate of patella replacement (61.1%, 12.9% $p<0.001$). This finding is consistent with those of previous studies reporting increased rates of patella-related complications in mobile-bearing knee prostheses.[11] Some complications observed in patients undergoing patella replacement may be due to implant-related issues.[12] However, it is important to note that patella changes did not translate into a higher overall complication rate in the mobile insert group.

There were no significant differences in preoperative and postoperative tibiofemoral angle values between the two groups. However, the postoperative proximal tibial angles differed significantly, with the mobile insert group showing higher values (90.41°, 89.41° $p<0.001$). This difference may be attributed to the unique design characteristics of the mobile-bearing inserts, which allow for greater conformity and potential for improved range of motion.[13] There are publications reporting that neutral varus alignment is more advantageous than valgus alignment.[14] Further studies are suggested to investigate the relationship between postoperative valgus angulation and insert use.

The overall complication rate was statistically significant, with a higher rate observed in the mobile insert group. However, when examining specific complications, such as instability, infection, extensor mechanism problems, aseptic loosening, and radiological osteolysis, there were no statistically significant differences between the two groups. These findings suggest that although the overall risk of complications may differ between fixed and mobile inserts, the incidence of specific complications remains comparable.[15,16]

The results of this study are consistent with those of previous studies reporting similar clinical outcomes and complication rates between fixed- and mobile-bearing knee prostheses.[17] It is important to note that the choice of implant type should be based on individual patient factors, including age, activity level, and surgeon preference. Factors such as surgeon experience and technical expertise in implantation may also influence the choice of implant type.

Study Limitations

It is worth mentioning that the present study has some limitations. First, the study design was retrospective, which may have introduced inherent biases and limitations associated with data collection and analysis. Prospective studies with longer follow-up periods could provide further insights into the long-term outcomes and complications associated with fixed and mobile inserts. Additionally, the current study focused on short-term complications and did not evaluate functional outcomes or patient-reported outcomes, which are important considerations in assessing the success of knee replacement surgery.

CONCLUSION

The present study compared the complications of knee replacement using fixed and mobile inserts. While specific complications, such as patella changes, may differ between the two groups, the overall risk of experiencing complications is similar regardless of the insert type. Surgeons and orthopedic specialists can use these findings to inform their decision-making when selecting the appropriate insert type for knee replacement, taking into account patient-specific characteristics and functional requirements.

MAIN POINTS

- The use of mobile inserts may increase the incidence of total complications in young patients who have undergone patella replacement and bilateral application.
- Postoperative proximal tibial angle remaining at the valgus may increase the overall complication rate.
- However, since the general results of mobile and fixed inserts are similar, a patient-specific decision on which insert to use should be made.

ETHICS

Ethics Committee Approval: Approval was obtained from the İzmir Bakırçay University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 1122, date: 20.07.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: M.A., A.İ.K., C.K., S.Ç., Design: M.A., E.K., A.İ.K., C.K., S.Ç., Data Collection and/or Processing: M.A., E.K., A.İ.K., C.K., S.Ç., Analysis and/or Interpretation: M.A., E.K., A.İ.K., C.K., S.Ç., Literature Search: M.A., E.K., A.İ.K., C.K., S.Ç., Writing: M.A.

DISCLOSURES

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

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RESEARCH ARTICLE

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Investigation of the Sleep-Awake Bruxism Habit Experienced by People Who Quarantined Different Places During the COVID-19 Pandemic

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Abstract

BACKGROUND/AIMS: This study aimed to investigate the sleep and awake bruxism habits experienced by people who were quarantined in different places during the coronavirus disease-2019 (COVID-19) pandemic in the North Cyprus.

MATERIALS AND METHODS: A 25-question self-reported questionnaire was sent to the patients' mobile phones to measure their demographic information and the level of bruxism they experienced before and during their quarantine period while sleeping and awake. The answers were evaluated statistically using percentage and chi-square tests.

RESULTS: A total of 241 people participated in our research. During the quarantine period, there was an increase in awake bruxism and a slight decrease in sleep bruxism. The feelings of worry, fear, panic, and hopelessness felt by the participants in the first days of the quarantine decreased in the last days of the quarantine, regardless of place and length of stay in the quarantine. Teeth clenching, teeth grinding, and earache were mostly observed in those who stayed in dormitory quarantine.

CONCLUSION: People's anxiety is increasing during the COVID-19 pandemic, and there is a positive correlation between anxiety and both sleep and awake bruxism. Dentists should pay more attention to the signs of bruxism during examinations, especially in people who say that they are in quarantine during anamnesis. Although the reason for a patient's visit to the doctor may seem like a simple toothache, underlying factors, such as clenching, should not be forgotten with a holistic approach, and awareness should be created for the patient.

Keywords: Awake bruxism, coronavirus, COVID-19, quarantine, sleep bruxism

INTRODUCTION

Coronavirus is a disease that causes severe acute respiratory syndrome. The outbreak started in Wuhan in 2019, and a few months later, the World Health Organization (WHO) labeled the virus spread across the globe as a pandemic. The risk assessment according to the WHO guidelines for coronavirus disease-2019 (COVID-19) is extremely high, with a global impact. As of April 12, 2020, there were 1,696,588 confirmed cases of COVID-19, including 105,952 deaths, reported by the WHO.[1]

To date, all countries that have suffered from COVID-19 have taken measures, as stated by health authorities, to prevent further spread of the virus and ensure infection control. Some of these strategies include the provision of virus tests, extreme social isolation, localized quarantine, and monitoring of the most vulnerable populations; the measures taken are largely guided by the official WHO website based on the number of cases in each country.[2]

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With the first Coronavirus case in North Cyprus, the Turkish Republic of North Cyprus (TRNC) government implemented stricter measures than other countries because Cyprus is an island. Because of uncertainty about the ways of virus spread, appropriate modes of treatment, insufficient availability of health services, and no existing vaccine or efficient drug for treatment, all entrances and exits to the island by sea, air, and land were closed, and the country was lockdown.[3]

A filiation team was formed in TRNC to prevent the spread of the disease. The filiation team uses a contact tracking algorithm published by the Republic of Türkiye (TR) and the TRNC health ministries. This algorithm allows users to determine whether they are at high or low risk of COVID-19. People who did not take protective measures (without a mask or wore an inappropriate mask) and were in contact with a patient with COVID-19 in the situations presented in Table 1 were considered at high risk.

The main duty of the filiation team is to contact COVID-19-positive individuals and/or their close contacts. Close contact, in this case, would mean anyone who had been in contact with the positive person within the last 48 hours after being tested positive.[4]

The filiation team called the people they considered as close contacts by phone and placed them in dorms or hotels or left them at home. To stay in quarantine at home, people had to either live alone or have rooms for themselves at home, and they had to have bathrooms and toilets in the room. Otherwise, people were randomly placed in dorms and hotels. In these centers, patients were isolated until two negative polymerase chain reaction (PCR) results were obtained. The average duration was 7 to 21 days.

Bruxism is characterized by the clenching and/or grinding of teeth, bracing, or thrusting of jaw muscles. There are 2 different types of bruxism; sleep and awake. Awake bruxism is a form that is seen during the waking period, and it is usually conscious of the person. Sleep bruxism occurs while the person is sleeping. In sleep bruxism, patients either complain of jaw pain when they wake up in the morning or are observed to clench their teeth during the night. While the diagnosis of bruxism is obtained by asking questions that give the person the possible diagnosis, a dental examination is essential for a definitive diagnosis.[5-8]

Table 1. Increased COVID-19 risk conditions

The increasing risk of COVID-19
Face and talk to a patient with COVID-19 at a distance of less than 1 m for 15 minutes at a time.
Provide direct care to patients with COVID-19.
Teachers or students who share the classroom with students or teachers who have COVID-19.
Come into physical contact with a patient with COVID-19 (kissing, hugs, etc.).
Unprotected contact with secretions (saliva, sputum, etc.) of patients with COVID-19, such as sneezing and coughing.
The same closed environment as the COVID-19 patient (hospital or bank standby halls, title deed, tax office, those waiting in official institutions such as municipality, bus, shuttle, etc. persons with means of transport).
Passengers traveling on the same plane with a patient with COVID-19 (sitting two fronts, two back and two side seats).
Living in the same house with a patient with COVID-19.
Work in the same office as a patient with COVID-19.
Sharing the same room with a patient with COVID-19 in a dormitory or hotel.
Traveling on the same bus with a patient with COVID-19.

Many studies have shown that one of the most important reasons for bruxism is psychosocial stress. The quarantine process has caused many changes in people's social lives, which has affected the habit of bruxism.[3,5,6,9-12] During the quarantine period, people have different problems such as; losing their jobs, decreased income level, starting to have marital problems, being away from their children, thinking that their health will deteriorate, getting bad news from social media, immobility, deterioration of their appearance (weight gain, hair growth, hair dye coming in, etc.), being dissatisfied with their stay, not being social, learning that they have lost their relatives or been hospitalized during their stay in. They experienced varied emotional states like worry, fear, panic, hopelessness, and calmness in their lives.[2,9,13]

With this research, which is conducted for the first time in TRNC, we aim to evaluate the bruxism habits of people who were in contact due to the COVID-19 pandemic and who remained in quarantine while they were asleep and awake, as well as the effect of differences in the quarantine environment on bruxism.

MATERIALS AND METHODS

This was a retrospective, descriptive study. The sample of the study consists of people who were accepted as close contacts between July 1 and 31, 2021, and who remained in quarantine. Information about the patients was obtained from the sources of the filiation team.

The messages were sent to 2,528 participants. The message could not be delivered to 160 of them because their phones were switched off or could not be reached. To obtain information from the respondents, a questionnaire consisting of 25 questions prepared by the researcher in light of the literature was used. The questionnaire was designed to determine 6 questions to obtain demographic information and then 19 questions to measure bruxism habits before and during the quarantine period.

Our inclusion criteria were as follows: staying in quarantine between July 1 and 31, 2021, being in close contact with a person infected with coronavirus, being 18 years old and over, speaking Turkish, and using a mobile phone. Since the study was based on volunteerism, the survey was sent to individuals, and those who responded within a week were included in the study. The questionnaire was sent to a total of 2,368 people, and 241 of them responded.

The study protocol was approved by Dr. Burhan Nalbantoğlu State Hospital Ethics Committee (approval number: 38/21, date:12.07.2021). All procedures in studies involving human participants were conducted in accordance with the ethical standards of the hospital and/or hospital research committee and with the 1964 Helsinki Declaration. Written informed consent to publish this paper was obtained from the patients.

Statistical Analysis

The data obtained in this study were analyzed using the SPSS 22 package. The relationship between categorical data was examined using chi-square analysis. The method to be used may vary depending on the theoretical frequency calculated for each cell. When the smallest theoretical frequency was <5, "Fisher's exact test" was used and when the frequency was >20, "Monte Carlo Simulation" was used. The

confidence interval was set at 95%, and significance was set at 0.05. It is stated that there is a significant difference/relationship if $p<0.05$ and that there is no significant difference/relationship if $p>0.05$.

RESULTS

Participants were 152 females (63.1%) and 89 males (36.9%) in our study with a sample size of 241. 103 (42.8%) were between the ages of 18-29, 79 (32.8%) were between the ages of 30-39, 43 (17.8%) were between the ages of 40-49 and 16 (6.6%) were between the ages of 50 and up. The participants were at 151 (62.7%) university level, 45 (18.7%) high school level, 12 (5%) master's level, and 10 (4.1%) doctoral level.

The answer to the question of relationship status was 123 (51%) married, 62 (25.7%) single, 28 (11.6%) I have a relationship,16 (6.6%) engaged, 9 (3.7%) divorced-separated, and 3 (1.4%) widow. 121 (50.2%) of the study participants had children, and 97 of them were younger than 18 years old.

When asked the participants "Have you ever been to a dental checkup?" 215 (89.2%) answered "Yes" to the question, and 75 (31.1%) told their dentist that they had clenched or ground their teeth. After the quarantine period, 85 (35.3%) participants went to the dentist control, and 26 (10.8%) said that the dentist clenched or grinded their teeth.

Before the quarantine period, 67 (27.8%) of the participants said "Yes" to the question "Did you notice that you were clenching your teeth while awake or did someone tell you", this rate increased to 68 (28.8%) during the quarantine period. Before the quarantine period, 69 (28.6%) of the participants said "Yes" to the question "Did you notice that you were clenching your teeth in sleep or did someone tell you", this rate decreased to 67 (27.8%) during the quarantine period (Table 2).

When you woke up in the morning before the quarantine period, 70 (29%) of the participants answered yes to the question of whether they had fatigue, tension, or jaw pain, while this rate increased to 72 (29.8%) participants during the quarantine period.

51.9% of the participants stated that they stayed under home quarantine, 37.8% under hotel quarantine, and 10.4% under dorm quarantine. It was found that 78.8% of the participants answered once, 16.2% two times, 3% three times, and 2% four or more times to the question of how many times they stayed in quarantine. To the question "How many days did you stay in quarantine," 61.4% of the participants answered 8-14 days, 20.7% 1-7 days, 12% 15-21 days, and 5.8% answered 22 days and above.

In the first days of the quarantine, 28% of those staying in the dorm quarantine, 31.9% of those staying in the hotel quarantine, and 33.6% of those staying in home quarantine felt much or too worried. 24% of those staying in the dorm quarantine, 18.7% of those staying in the hotel quarantine, and 21.6% of those staying in home quarantine felt much or too scared. 24% of those staying in the dorm quarantine, 17.6% of those staying in the hotel quarantine, and 19.2% of those staying in home quarantine felt much or too much hopelessness. 28% of those staying in the dorm quarantine, 34.1% of those staying in the hotel quarantine, and 25.6% of those staying in home quarantine felt much or too calm (Table 3).

In the last days of the quarantine, 12% of those staying in the dorm quarantine, 14.3% of those staying in the hotel quarantine, and 12.8% of those staying in the home quarantine felt much or too worried. 16% of those staying in the dorm quarantine, 8.8% of those staying in the hotel quarantine, and 11.2% of those staying in the home quarantine felt much or too scared. 12% of those staying in the dorm quarantine, 7.7% of those staying in the hotel quarantine, and 8.8% of those staying in home quarantine felt much or too much in panic. 20% of those staying in the dorm quarantine, 5.5% of those staying in the hotel quarantine, and 12.8% of those staying in home quarantine felt much or too much hopelessness. 32% of those staying in the dorm quarantine, 40.7% of those staying in the hotel quarantine, and 38.4% of those staying in home quarantine felt much or too calm (Table 4).

The factors that affected you during your quarantine were asked. 8% of those staying in the dorm quarantine, 3.3% of those staying in the hotel quarantine, and 5.6% of those staying in home quarantine chose the option to lose their job. 36% of those staying in the dorm quarantine, 23.1% of those staying in the hotel quarantine, and 19.2% of those staying in home quarantine chose the option to decrease their

Table 2. Difference analysis table between the variable of "teeth grinding" variable and the answers to the questions

		Teeth grinding								Chi-square analysis	
		Nothing-less		Moderate		Much-too much		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
Have you noticed or asked someone to grind your teeth while awake?	Yes	51	76.1	10	14.9	6	9.0	67	100.0	*	0.0001
	No	164	94.3	4	2.3	6	3.4	174	100.0		
	Total	215	89.2	14	5.8	12	5.0	241	100.0		
During quarantine, have you noticed or someone told you that you are grinding your teeth while awake?	Yes	47	69.1	10	14.7	11	16.2	68	100.0	*	0.0001
	No	168	97.1	4	2.3	1	0.6	173	100.0		
	Total	215	89.2	14	5.8	12	5.0	241	100.0		
Before the quarantine period, have you noticed or someone told you that you were grinding your teeth in sleep?	Yes	33	47.8	20	29.0	16	23.2	69	100.0	66,159	0.0001
	No	160	93.0	3	1.7	9	5.2	172	100.0		
	Total	193	80.1	23	9.5	25	10.4	241	100.0		
During quarantine, have you noticed or someone told you that you are grinding your teeth while sleeping?	Yes	29	43.3	19	28.4	19	28.4	67	100.0	79,049	0.0001
	No	164	94.3	4	2.3	6	3.4	174	100.0		
	Total	193	80.1	23	9.5	25	10.4	241	100.0		

Table 3. Describes the answers given to the question of where you were in quarantine and how emotional they felt during the first few days

Which emotional states did you experience during the first few days of quarantine?		Where did you stay in quarantine?								Chi-square analysis	
		Dorm		Hotel		Home		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
Worried	Nothing-less	10	40.0	43	47.3	52	41.6	105	43.6	1,747	0.782
	Moderate	8	32.0	19	20.9	31	24.8	58	24.1		
	Much-too much	7	28.0	29	31.9	42	33.6	78	32.4		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Scared	Nothing-less	13	52.0	59	64.8	75	60.0	147	61.0	1.54	0.819
	Moderate	6	24.0	15	16.5	23	18.4	44	18.3		
	Much-too much	6	24.0	17	18.7	27	21.6	50	20.7		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
In panic	Nothing-less	16	64.0	64	70.3	89	71.2	169	70.1	1,395	0.845
	Moderate	4	16.0	8	8.8	11	8.8	23	9.5		
	Much-too much	5	20.0	19	20.9	25	20.0	49	20.3		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Hopeless	Nothing-less	15	60.0	68	74.7	79	63.2	162	67.2	*	0.21
	Moderate	4	16.0	7	7.7	22	17.6	33	13.7		
	Much-too much	6	24.0	16	17.6	24	19.2	46	19.1		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Calm	Nothing-less	13	52.0	38	41.8	60	48.0	111	46.1	2,342	0.673
	Moderate	5	20.0	22	24.2	33	26.4	60	24.9		
	Much-too much	7	28.0	31	34.1	32	25.6	70	29.0		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		

Table 4. Describes the answers given to the question of where you were in quarantine and how they felt in the last few days

Which emotional states have you experienced in the last few days of your stay in quarantine?		Where did you stay in quarantine?								Chi-square analysis	
		Dorm		Hotel		Home		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
Worried	Nothing-less	16	64.0	69	75.8	76	60.8	161	66.8	*	0.036
	Moderate	6	24.0	9	9.9	33	26.4	48	19.9		
	Much-too much	3	12.0	13	14.3	16	12.8	32	13.3		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Scared	Nothing-less	16	64.0	76	83.5	94	75.2	186	77.2	*	0.234
	Moderate	5	20.0	7	7.7	17	13.6	29	12.0		
	Much-too much	4	16.0	8	8.8	14	11.2	26	10.8		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
In panic	Nothing-less	19	76.0	79	86.8	103	82.4	201	83.4	*	0.649
	Moderate	3	12.0	5	5.5	11	8.8	19	7.9		
	Much-too much	3	12.0	7	7.7	11	8.8	21	8.7		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Hopeless	Nothing-less	18	72.0	79	86.8	94	75.2	191	79.3	*	0.12
	Moderate	2	8.0	7	7.7	15	12.0	24	10.0		
	Much-too much	5	20.0	5	5.5	16	12.8	26	10.8		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Calm	Nothing-less	12	48.0	34	37.4	50	40.0	96	39.8	0.978	0.913
	Moderate	5	20.0	20	22.0	27	21.6	52	21.6		
	Much-too much	8	32.0	37	40.7	48	38.4	93	38.6		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		

income level. 8% of those staying in the dorm quarantine, 7.7% of those staying in the hotel quarantine, and 0.8% of those staying in home quarantine chose the option to start to have marital problems. 28% of those staying in the dorm quarantine, 17.6% of those staying in the hotel quarantine, and 15.2% of those staying in home quarantine chose the option of being away from my children. 32% of those staying in the dorm quarantine, 23.1% of those staying at the hotel quarantine, and 22.4% of those staying in home quarantine chose the option thinking that their health would deteriorate. 12% of those staying in the dorm quarantine, 13.2% of those staying in the hotel quarantine, and 15.2% of those staying in home quarantine chose the option of getting bad news from social media. 44% of those staying in the dorm quarantine, 41.8% of those staying in the hotel quarantine, and 33.6% of those staying in home quarantine chose the option of immobility. 16% of those staying in the dorm quarantine, 6.6% of those staying in the hotel quarantine, and 3.2% of those staying in home quarantine chose the option of deterioration of my appearance. 24% of those staying in the dorm quarantine, 20.9% of those staying in the hotel quarantine, and 3.2% of those staying in home quarantine chose the option of being dissatisfied with my stay. 36% of those staying in the dorm quarantine, 24.2% of those staying in the hotel quarantine, and 35.2% of those staying in home quarantine chose the option of not being social. 4% of those staying in the dorm quarantine, 4.4% of those staying in the hotel quarantine, and 10.4% of those staying in home quarantine chose the option of learning that I have lost a relative or being hospitalized during my stay (Table 5).

Table 5. Describe the answers given to the question of where you will stay in quarantine and which of the following will be effective for you as long as you stay

During the quarantine period, which of the following things have been effective for you?		Where did you stay in quarantine?								Chi-square analysis	
		Dorm		Hotel		Home		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
I lost my job	Yes	2	8.0	3	3.3	7	5.6	12	5.0	*	0.42
	No	23	92.0	88	96.7	118	94.4	229	95.0		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Decreased income levels	Yes	9	36.0	21	23.1	24	19.2	54	22.4	3.42	0.181
	No	16	64.0	70	76.9	101	80.8	187	77.6		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Starting to have marital problems	Yes	2	8.0	7	7.7	1	0.8	10	4.1	*	0.014
	No	23	92.0	84	92.3	124	99.2	231	95.9		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Being away from my children	Yes	7	28.0	16	17.6	19	15.2	42	17.4	2,374	0.305
	No	18	72.0	75	82.4	106	84.8	199	82.6		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Thinking that your health will deteriorate	Yes	8	32.0	21	23.1	28	22.4	57	23.7	1,09	0.58
	No	17	68.0	70	76.9	97	77.6	184	76.3		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Bad news from social media	Yes	3	12.0	12	13.2	19	15.2	34	14.1	0.278	0.87
	No	22	88.0	79	86.8	106	84.8	207	85.9		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Immobility	Yes	11	44.0	38	41.8	42	33.6	91	37.8	1,954	0.377
	No	14	56.0	53	58.2	83	66.4	150	62.2		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Deterioration in my appearance	Yes	4	16.0	6	6.6	4	3.2	14	5.8	6,403	0.041
	No	21	84.0	85	93.4	121	96.8	227	94.2		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Dissatisfied with my stay	Yes	6	24.0	19	20.9	4	3.2	29	12.0	19,323	0.0001
	No	19	76.0	72	79.1	121	96.8	212	88.0		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Not being social	Yes	9	36.0	22	24.2	44	35.2	75	31.1	3,296	0.192
	No	16	64.0	69	75.8	81	64.8	166	68.9		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Learning that I have lost a relative or have been hospitalized during my stay	Yes	1	4.0	4	4.4	13	10.4	18	7.5	3,233	0.199
	No	24	96.0	87	95.6	112	89.6	223	92.5		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		

During your stay in quarantine, you were asked which of the following(s) you experienced. 16% of those staying at the dorm quarantine, 7.7% of those staying at the hotel quarantine, and 4% of those staying at home quarantine chose the option pain in my jaw as much or too much. 8% of those staying in the dorm quarantine, 2.2% of those staying at the hotel quarantine, and 1.6% of those staying at home quarantine chose the option earache as much or too much. 32% of those staying in the dorm quarantine, 12.1% of those staying in the hotel quarantine, and 4.1% of those staying in home quarantine chose the option of clenching teeth as much or too much. 28% of those staying in the dorm quarantine, 3.3% of those staying in the hotel quarantine, and 1.6% of those staying at home quarantine chose the option of grinding teeth as much or too much. 16% of those staying in the dorm quarantine, 17.6% of those staying in the hotel quarantine, and 19.2% of those staying at home quarantine chose the option headache as much or too much. 4% of those staying in the dorm quarantine, 7.7% of those staying in the hotel quarantine, and 5.6% of those staying in home quarantine chose the option noise from the jaw when opening and closing the mouth as much or too much. 8% of those staying in the dorm quarantine, 4.4% of those staying in the hotel quarantine, and 0.8% of those staying in home quarantine chose the option difficulty in mouth opening as much or too much. 4% of those staying in the dorm quarantine, 1.1% of those staying in the hotel quarantine, and 0.8% of those staying in home quarantine chose the option of locking their jaw as much or too much. 4% of those staying in the dorm quarantine, 3.3% of those staying in the hotel quarantine, and 1.6% of those staying at home quarantine chose the option of facial swelling as much or too much. 8% of those staying in the dorm quarantine, 3.3% of those staying in the hotel quarantine, and 4% of those staying in home quarantine chose the option of eating difficulty as much or too much (Table 6).

Table 6. Describe the answers given to the questions regarding where you stayed in quarantine and which of the following experiences did you experience during your stay in quarantine

Which of the following experiences did you have during your stay in quarantine?		Where did you stay in quarantine?								Chi-square analysis	
		Dorm		Hotel		Home		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
Pain in my jaw	Nothing-less	19	76.0	74	81.3	105	84.0	198	82.2	*	0.272
	Moderate	2	8.0	10	11.0	15	12.0	27	11.2		
	Much-too much	4	16.0	7	7.7	5	4.0	16	6.6		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Earache	Nothing-less	20	80.0	77	84.6	119	95.2	216	89.6	*	0.012
	Moderate	3	12.0	12	13.2	4	3.2	19	7.9		
	Much-too much	2	8.0	2	2.2	2	1.6	6	2.5		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Clenching teeth	Nothing-less	17	68.0	72	79.1	104	83.2	193	80.1	*	0.002
	Moderate	0	0.0	8	8.8	15	12.0	23	9.5		
	Much-too much	8	32.0	11	12.1	6	4.8	25	10.4		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Teeth grinding	Nothing-less	16	64.0	84	92.3	115	92.0	215	89.2	*	0.001
	Moderate	2	8.0	4	4.4	8	6.4	14	5.8		
	Much-too much	7	28.0	3	3.3	2	1.6	12	5.0		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Headache	Nothing-less	10	40.0	50	54.9	66	52.8	126	52.3	3,011	0.556
	Moderate	11	44.0	25	27.5	35	28.0	71	29.5		
	Much-too much	4	16.0	16	17.6	24	19.2	44	18.3		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Noise from the mouth opening and closing	Nothing-less	19	76.0	77	84.6	111	88.8	207	85.9	*	0.195
	Moderate	5	20.0	7	7.7	7	5.6	19	7.9		
	Much-too much	1	4.0	7	7.7	7	5.6	15	6.2		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Difficulty in mouth opening	Nothing-less	21	84.0	83	91.2	115	92.0	219	90.9	*	0.132
	Moderate	2	8.0	4	4.4	9	7.2	15	6.2		
	Much-too much	2	8.0	4	4.4	1	0.8	7	2.9		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Locking the jaw	Nothing-less	23	92.0	89	97.8	124	99.2	236	97.9	*	0.096
	Moderate	1	4.0	1	1.1	0	0.0	2	0.8		
	Much-too much	1	4.0	1	1.1	1	0.8	3	1.2		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		

Table 6. Continued

Which of the following experiences did you have during your stay in quarantine?		Where did you stay in quarantine?								Chi-square analysis	
		Dorm		Hotel		Home		Total			
		n	%	n	%	n	%	n	%	Chi-square	p
Facial swelling	Nothing-less	23	92.0	86	94.5	120	96.0	229	95.0	*	0.605
	Moderate	1	4.0	2	2.2	3	2.4	6	2.5		
	Much-too much	1	4.0	3	3.3	2	1.6	6	2.5		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		
Eating difficulty	Nothing-less	21	84.0	78	85.7	112	89.6	211	87.6	*	0.538
	Moderate	2	8.0	10	11.0	8	6.4	20	8.3		
	Much-too much	2	8.0	3	3.3	5	4.0	10	4.1		
	Total	25	100.0	91	100.0	125	100.0	241	100.0		

DISCUSSION

COVID-19 has interfered with global and socioeconomic activities such as travel plans, work, and normal life activities, causing unexpected deaths and illnesses. Studies have reported that moderate and severe anxiety occurs in a high percentage of COVID-19 cases. Suspicious and even inaccurate information about the disease, the lack of information on the affected areas, the number of infected people, and the actual death rate have led to fear and distrust among the public. People and states preferred social isolation, which is the safest method of protection, to fully understand what the existing disease is and to prevent its spread. Social isolation is associated with physical and mental health. Many factors such as were dismissed, decreased income level, marital problems, staying away from children, thinking that their health would deteriorate, getting bad news from social media, immobilization, deterioration of appearance, dissatisfaction with the living environment, not being able to socialize, hospitalization, or death of a relative caused increased stress levels in people who were in quarantine.[11,13,14] In our study, we asked the participants to answer these questions. Receiving bad news from social media and learning that a relative's condition deteriorated and was hospitalized or died was higher among those who remained in home quarantine. In all other questions, those who remained in dorm quarantine were observed to be affected at a higher rate.

There is a positive correlation between bruxism and stress. It has been observed that the frequency of bruxism increases in populations with high stress levels.[7-9,11,12] Bruxism during sleep and awake states are recognized as different entities with different etiologies. Awake bruxism is associated with psychological factors such as anxiety, stress, and negative emotions. It has been reported that the frequency of awake bruxism is 5-6 times higher than normal in individuals experiencing high stress, but the role of psychology in sleep bruxism remains controversial.[2,9] According to a researcher, stress impairs sleep quality and increases the transition between REM and non-REM sleep periods, thus increasing micro-stimulation in the jaw muscles.[7] In our study, it was observed that the frequency of those who stated that they had a higher level of teeth-grinding problems while awake increased during the quarantine period compared to before. An increase was also reported during the quarantine for those who responded excessively to the clenching problem while sleeping before the quarantine period.

In awake bruxism, possible bruxism can be identified using self-report questionnaires. However, diagnosing bruxism while sleeping is difficult in people who live alone and when no measurement (polysomnographic measurement) is made. To give a definitive diagnosis in both types of bruxism, the patient should be examined and diagnosed by a dentist.[5,7] In our study, most of the participants gave importance to oral and dental health and visited the dentist. It was observed that of those participating in the study, one-third had a habit of clenching, which the dentist detected and informed the patient before the quarantine. It was found that one-third of those who went to the dentist before the quarantine period went to the dentist again after the quarantine period due to dental problems.

It has been observed that there was a slight increase in the quarantine period among people who noticed that they were clenching their teeth while awake, or someone told them this before the quarantine period. On the other hand, there has been a decrease in the proportion of people who noticed that they were grinding their teeth while sleeping, or someone else told them before the quarantine period. In self-reported approaches, pain or fatigue in the masticatory muscles of patients can be considered as bruxism. However, in clinical evaluation, pain in the masticatory muscles is used to diagnose both TMD and bruxism.[8] In our study, when the participants were asked about fatigue, tension, and jaw pain when they woke up in the morning, no significant difference was observed between what they felt before and during the quarantine period.

In the study by Cotrin et al.[14], participants were aware of the seriousness of the coronavirus, and high anxiety levels were observed in those who remained in quarantine. Studies have observed that home quarantine is usually applied to people during pandemics. Unlike other studies, our study consisted of people who were considered contacts who stayed under hotel and dorm quarantine apart from home quarantine. Participants in our study were asked about their emotional states (worried, scared, in a panic, hopeless, and calm) they felt in the first and last days of quarantine, how many times they had been in quarantine, and how long they had been in quarantine. The length and frequency of the quarantine period did not affect the mood of the groups. Those who stayed at home during the first few days of quarantine showed more worry than those who stayed in dorms and hotels. It can be thought that the reason for this is the possibility of infection of the disease by other people at home. On the other hand, the feelings of fear, panic, and hopelessness were most common among those staying in the dorm quarantine. The reason for this may be that they are far from their relatives and live in dormitories. Hotel stayers were found to be the calmest during the first days of quarantine. The reason for

this may be that they feel like they are in a holiday environment. In the last days of the quarantine, regardless of place, length, and frequency of stay, worry, fear, panic, and hopelessness decreased, whereas calm increased in all groups. Psychological and somatic reactions experienced by people may be relieved within hours. For this reason, time is spent in the same place, and the person adapts to the situation.[2,3,6,9,11,14-16]

One of the common causes of ear pain in the temporomandibular region is bruxism, which is often accompanied by stress and anxiety.[17] Those who stayed in quarantined dorms experienced statistically significant complaints of earache, clenching, and grinding teeth compared with other hotel and home quarantined groups.

Relationship status can also affect stress, anxiety, and depression. Married people have more anxiety during quarantine.[18] In our study, more than half of the participants were married; however, it was observed that those who stayed at the dorm quarantine and the hotel quarantine started to experience marital problems in a statistically significant way compared with those who stayed at home quarantine.

In our study, most of those who were married had children under the age of 18, which means they needed parental care and family support. Being away from their homes and children due to quarantine causes more stress for parents, and they may not receive sufficient support from the people with whom they are together.

Self-reported questionnaires are a reliable tool for measuring possible bruxism habits.[5,8] This method provides an advantage in terms of seeing the problem quickly, but it is difficult to get people to answer the questionnaire because it is voluntary.[14] Because of this, this research does not include the entire country but only individuals who remain in contact with other individuals under quarantine within 1 month.

Study Limitations

As criteria for exclusion from the study, those whose PCR results were positive during the quarantine process were classified as foreign nationals and people under the age of 18 who remained in quarantine. Moreover, if the phone numbers were the same for a family, only one participant participated in the study.

CONCLUSION

Regardless of the source, anxiety has a serious and positive relationship between anxiety and dental health. For this reason, especially in a high-stress situation like a pandemic; dentists should perform a detailed anamnesis to evaluate the patient's situation well and make a diagnosis and treatment accordingly.

Although the reason for the patient's visit to the doctor may appear to be a simple toothache, underlying factors, such as clenching, should not be forgotten, and the possible etiologies of the patient should be investigated with a holistic approach. It is possible to prevent bruxism habits by increasing awareness among people. Tooth erosion, jaw pain, and locking can be reduced in the following years for these people.

In our research group, it was determined that the awareness of clenching was low. Considering the temporomandibular joint problems and muscle spasms that clenching may cause in the future, it is important to increase this awareness.

MAIN POINTS

- The worry, scared, panic, and hopelessness felt in the first days of the quarantine period gave way to calmness in the following days. This shows how people adapt to adverse situations.
- Clenching, grinding of teeth, and earache were mostly seen in those whose quarantine place was dormitory.
- The COVID-19 pandemic, which affects the whole world and health, has been effective in the increase of awake bruxism.

ETHICS

Ethics Committee Approval: The study protocol was approved by Dr. Dr. Burhan Nalbantoğlu State Hospital Ethics Committee (approval number: 38/21, date:12.07.2021).

Informed Consent: Written informed consent to publish this paper was obtained from the patients.

Authorship Contributions

Surgical and Medical Practices: B.G.Ç.G., Concept: B.G.Ç.G., K.O., Design: B.G.Ç.G., K.O., Data Collection and/or Processing: B.G.Ç.G., Analysis and/or Interpretation: B.G.Ç.G., Literature Search: B.G.Ç.G., Writing: B.G.Ç.G.

DISCLOSURES

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

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RESEARCH ARTICLE

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Refractory Vasovagal Syncope Despite Tilt Training: Should Paroxetine be Included in the Treatment?

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Abstract

BACKGROUND/AIMS: To investigate the efficacy of selective serotonin reuptake inhibitors (SSRI) for preventing spontaneous vasovagal syncope (VVS) in patients with refractory VVS despite home-based tilt training (TT).

MATERIALS AND METHODS: We included 111 consecutive patients with VVS. All patients were instructed to increase salt and fluid intake, perform counterpressure maneuvers, and perform TT. The first control visit was scheduled within 2 months of the initial treatment. Paroxetine 20 mg was added to TT in patients with refractory VVS despite TT (TT plus SSRI group) at the first control visit, and patients without refractory VVS who continued TT (TT group). The clinical features of the patients, spontaneous VVS attacks before and after treatment, and follow-up data were recorded.

RESULTS: A total of 111 consecutive patients (67 females; age: 32±12 years) were treated with TT (64 patients) or TT plus SSRI (47 patients). The mean follow-up was 8.9±3.3 months after the first control visit. During follow-up, 38 (80.9%) patients in the TT + SSRI group and 30 (46.9%) in the TT group were asymptomatic ($p<0.001$). In the univariate analyses, TT plus SSRI treatment and TT treatment during follow-up were predictors of an asymptomatic course. Multivariate analysis showed that TT plus SSRI therapy (odds ratio: 4,785, 95% confidence interval: 4,784-11,501, $p<0.001$) as the sole predictor of asymptomatic course at follow-up.

CONCLUSION: The addition of paroxetine to the treatment of patients with recurrent VVS who do not respond to TT and conventional treatment is an effective and well-tolerated treatment method for preventing vasovagal attacks.

Keywords: Refractory vasovagal syncope, tilt training, drug treatment, selective serotonin re-uptake inhibitor, paroxetine

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INTRODUCTION

Recurrent vasovagal (neurocardiogenic) syncope (VVS) is a common and important clinical presentation, accounting for 66% of syncope cases presenting to the emergency department.[1,2] The diagnosis of VVS, which causes deterioration in quality of life, limitation and inadequacy, increased hospital admissions, and serious health expenditures in many young patients, started to be made more frequently after the application of the head-up tilt test (HUTT).[3,4]

Although many randomized and non-randomized clinical trials have investigated various treatments for VVS, an effective treatment for VVS has not yet been identified.[3-7] Various pharmacological and non-pharmacological approaches are available for the treatment of VVS.[4-7] VVS treatment includes a multi-layered approach consisting of lifestyle changes, physical maneuvers, drug treatments, and, if necessary, pacemaker implantation. HUTT is greatly helpful in identifying younger patients but has also been shown to be beneficial in prophylactic treatment.[6,8,9] Tilt training (TT), or passive standing, is a non-pharmacological VVS treatment that involves repeated and prolonged exposure of the cardiovascular system to an orthostatic stimulus. However, there are inconsistencies in subsequent studies that vary according to the training protocol and patient compliance. Previous studies have shown that TT is a promising treatment for VVS.[9-12]

Non-invasive treatment of VVS includes both pharmacological and non-pharmacological interventions. Conversely, studies have been conducted on various drugs with different mechanisms of action for the treatment of VVS.[13] The central serotonergic system, which appears to be associated with the pathogenesis of VVS, has been investigated in several clinical studies.[13-15] In these studies, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, and paroxetine, were shown to be effective in preventing vasovagal events.[15] In a placebo-controlled study involving severely symptomatic patients, paroxetine was found to be effective in preventing syncope attacks; however, this finding has not been supported by a small number of subsequent studies.[16] In this study, in patients with resistant VVS despite TT, the effectiveness of adding paroxetine to existing non-pharmacological therapy in preventing syncope attacks.

MATERIALS AND METHODS

The Study Group

This was a multicenter prospective observational study including 632 consecutive patients who were admitted to or referred to 3 different state hospital cardiology clinics with a diagnosis of transient loss of consciousness (TLoC) over a 1-year period. VVS was found in 183 (29.0%) patients, situational syncope in 38 (6.0%), carotid sinus syncope in 6 (0.9%), and orthostatic hypotension in 92 (14.6%) (including primary or secondary autonomic failure, postural orthostatic tachycardia syndrome and drug-induced), cardiac arrhythmia in 104 (16.5%), structural cardiovascular disease or pulmonary diseases in 27 (4.3%), neurological disorders (epilepsy, transient ischemic attack, non-epileptic drop attack) in 66 (10.4%), psychogenic disorders in 17 (2.7%), metabolic disorders (diabetic patients with or without hypoglycemia), in 34 (5.4%), inner ear-related vertigo in 5 (0.8%), and uncertain or unknown diagnosis (idiopathic) in 60 (9.5%) patients as the cause of TLoC.

Of the 183 patients with a diagnosis of VVS, 56 were excluded due to a history of syncope for 6 months (n=37), antidepressants, or anxiolytics use [(n=19) (12 of them using non-SSRI and 3 of them using SSRI antidepressants, and 4 of them using anxiolytics] (Figure 1). Of the remaining 127 patients with a diagnosis of VVS, those who attended at least 2 follow-up visits (provided that the first control visit was in the outpatient clinic) were included in the study. Patients who did not attend the second control visit were contacted via telephone, and a telephone-mediated control visit was conducted. Patients were advised to measure their own pulse and blood pressure, and if they could not measure it, they were advised to apply to the nearest health institution, and the obtained data were recorded. After treatment, 10 patients who did not come to the first control visit and 6 patients who could not be reached by telephone for the second control visit were excluded from the study. The remaining 111 patients constituted the study group (Figure 1). This study was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Ethical Committee of Türkiye's Yüksek İhtisas Training and Research Hospital approved the study (approval number: 091023-310-EPK). All patients enrolled in the study provided informed consent to participate in the study.

VVS Diagnosis

In the study group, patients with no pathological findings in the results of 12-lead electrocardiography (ECG), 72-hour Holter ECG follow-up, exercise ECG test, transthoracic echocardiography, and HUTT examinations were diagnosed with VVS. The HUTT (for 10 minutes in an upright position) was performed by an experienced nurse; previously it had been explained in a detailed version.[17]

Treatment and Follow-up

Patients were informed about the etiology of VVS, prodrome, and physical counterpressure maneuvers and how to avoid possible triggers. Adequate water and fluid intake, targeting 2-3 liters of fluid and 10 g of sodium chloride per day was recommended for the patients. In addition, the patients were educated about a strict daily TT program at home and additional flexible exercise training (ET) programs.

1. TT program: Patients were educated to practice TT at home while leaning against a wall (20 cm away from the wall with their ankles). The sessions were planned to be conducted in a safe and comfortable environment to prevent physical trauma and to be completed under the supervision of a family member. Patients were educated with sustained standing training and were encouraged to quit early if symptoms of presyncope developed; otherwise, TT was terminated at 30 minutes. Patients were informed that they would start the training with 5 min sessions twice a day, morning, and evening, increasing the session duration by 5 min each week, and extending the session duration up to 30 min. Two months later, patients were instructed to perform the alternate-day TT program.

2. ET program: Patients were educated about the flexible ET program consisting of 45-60 minutes exercise sessions three times a week. Each exercise session was planned to consist of stretching and relaxation exercises, such as 5 min stretching, 30-40 minutes cycling or brisk walking, 2-10 minutes local strengthening (sitting, pushing, and pulling), and 5 min stretching. In cases of symptoms, it was recommended to interrupt training and switch to a horizontal position.

The first control visit was planned within the first 2 months after the start of treatment. In the event of spontaneous syncope between the initiation of therapy and the first control visit, patients were

considered symptomatic, and 20 mg of paroxetine (at the first control visit) was added to the existing therapy. Patients without spontaneous syncope between the first treatment and the first control visit were considered asymptomatic, and their current treatment was continued. Asymptomatic patients who visited the first control visit were named the TT group, whereas symptomatic patients who were administered paroxetine were named the TT plus SSRI group.

Definitions and Data Collection

Side effects related to paroxetine or reasons for discontinuing paroxetine treatment were recorded at the control visits. The expected side effects are drowsiness, headache, transient sexual dysfunction, constipation, dry mouth, nausea, and diarrhea. The patients were examined by a psychiatrist. The psychiatrist applied the Beck Depression Inventory (Symptom Checklist-90) during the examination. Minor psychiatric disorders (MPD) diagnosed according to the DSM-IV-TR criteria[18] were included in the study. However, patients with dysthymia, major depressive episodes, or chronic psychiatric disorders were excluded from the study group by inclusion in the psychogenic syncope group (Figure 1). Routinely, each patient was asked to record the number of training sessions per day and their duration. In addition, each patient was asked to record their spontaneous and presyncope episodes. The efficacy of paroxetine treatment was evaluated by comparing the symptomatic status of patients in the TT and TT plus SSRI groups between the first and last control visits.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation in the presence of a normal distribution, as median (minimum-maximum) in the presence of an abnormal distribution, and categorical variables were expressed as percentages. For comparisons between patient groups, (χ^2 test was used for categorical variables, the t-test for independent groups for normally distributed continuous variables, and the Mann-Whitney U test for abnormally distributed variables. The paired t-test was used for normally distributed values, and McNemar test was used for categorical variables (percentages and ratios) to compare changes in the first and last control visit values. Univariate regression analysis was used to measure the relationship of variables with the asymptomatic (absence of syncope) condition during the first and last control visits. Variables with a p value of <0.1 in the univariate analysis were included in the multivariate analysis. The TT program, TT program plus SSRI, adequate ET program, average daily TT duration, and average daily TT number were included in the multivariate logistic regression analysis using the forward stepwise method to identify independent indicators of asymptomatic status during follow-up. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

RESULTS

Study Population

The characteristics of the study population are shown in Table 1. A total of 111 consecutive patients were included in the study. Of these patients, 44 were male and 67 were female. The mean age was 32±12 years. The median numbers of syncopes and presyncope per year were 4 and 10, respectively. Twenty (15%) patients had a history of severe trauma due to a previous syncope attack. The median duration of VVS history was 2.5 years (Table 1). The first control visit was made to all patients in the cardiology outpatient clinic 28±5 days after the first treatment. During the period between the start of treatment and the first visit, 47 patients were symptomatic, whereas 64 (57.7%) patients were asymptomatic (Table 1, Figure 1).

The baseline characteristics of patients who were asymptomatic and symptomatic at the first control visit were similar (Table 1). Symptomatic patients presented to the first control visit earlier than asymptomatic patients (30±4 days versus 27±5 days; p=0.001). The mean duration and number of daily TTs were statistically higher in the asymptomatic group than in the symptomatic group (609±172 min compared to 54±7 min, p<0.001 and 421±187 min, 40±10 min, respectively; p<0.001). However, the mean duration and number of daily TT were statistically greater in the asymptomatic group than in the symptomatic group (20.0±3.0 min vs. 15.0±4.9 min and 1.8±0.1 vs. 1.5±0.3, respectively, p<0.001 for both). Compliance with an adequate ET program was statistically higher in the asymptomatic group than in the symptomatic group (73.4% compared to 42.6%; p=0.001), whereas there were no differences between the groups in compliance with adequate salt and fluid intake treatment (p=0.445) (Table 1).

Follow-up Data After the First Control Visit

Additional paroxetine was added to TT (TT + SSRI group) for treating symptomatic patients (n=47) at the first control visit, and TT treatment was continued in asymptomatic patients (n=64) (TT group) (Figure 1). Patients were followed for 8.9±3.3 months after the first control visit (Table 2). During follow-up, 30 patients (46.9%) in the TT group and 38 (80.9%) in the TT plus SSRI group were asymptomatic (p<0.001). However, the mean number and duration of daily TT were statistically higher in the asymptomatic group than in the symptomatic group (12.6±2.0 min vs. 9.6±3.1 min and 1.1±0.1 vs. 0.9±0.2, respectively, p<0.001 for both). Compliance with an adequate ET program was higher in the asymptomatic group than in the symptomatic group (59.4% vs. 36.2%; p=0.016), whereas adequate salt and water intake levels were similar between the groups (p=0.487) (Table 2).

In the TT group, the mean daily TT duration, mean daily TT number, and adequate compliance with the ET program during follow-up were significantly decreased compared with the values at the first control visit (p<0.001, p<0.001, and p=0.004, respectively). Similarly, the mean daily TT duration and mean daily TT number during follow-up were significantly decreased in the TT plus SSRI group (p<0.001 and p<0.001, respectively). However, in the TT plus SSRI group, there was no significant difference in compliance with the ET program during follow-up compared with the value at the first control visit (p=0.250).

In 7 patients (14.9%) in the TT plus SSRI group, paroxetine-related side effects (drowsiness, transient sexual dysfunction, constipation, dry mouth, nausea, and diarrhea) were observed; however, treatment was continued in these patients. Paroxetine treatment was discontinued in one patient at the fifth month of follow-up because of weight gain (according to the patient, this was related to paroxetine). The patient was asymptomatic during the follow-up, and no syncope attacks were recorded after treatment was discontinued.

Independent Predictors of Asymptomatic Patients at Follow-up

The results of univariate and multivariate analyses performed to determine the predictors of asymptomatic status (absence of VVS attacks) during follow-up (the time between the first control visit and

Table 1. Characteristics of the study group

Variables	All patients, (n=111)	Asymptomatic during the first visit, (n=64)	Symptomatic during the first visit, (n =47)	p
Basal parameters				
Age	32±12	32±12	33±12	0.589
Female gender, n (%)	67 (60.4)	41 (64.1)	26 (55.3)	0.352
BMI, kg/m^2	23.6±4.6	23.2±3.9	24.2±5.3	0.266
Smokers, n (%)	45 (40.5)	27 (42.2)	18 (38.3)	0.680
Number of syncopes per year	4 (1-54)	4 (1-30)	4 (1-54)	0.388
Number of presyncope annually	10 (3-54)	8.5(13-50)	12 (3-54)	0.103
Number of syncopes per year >2, n (%)	99 (89.2)	57 (89.1)	42 (89.4)	1.0
Syncope causing severe trauma, n (%)	20 (15.0)	9 (14.1)	11 (23.4)	0.310
Prodromal symptoms, n (%)	78 (70.3)	49 (76.6)	29 (61.7)	0.138
History of positive HUTT, n (%)	75 (67.6)	43 (67.2)	32 (68.1)	0.920
VVS history duration (years)	2.5 (1-11)	2.5 (1-11)	2.5 (1-10)	0.507
History of head trauma, n (%)	16 (14.4)	8 (12.5)	8 (17.0)	0.692
Minor psychiatric disorders, n (%)	42 (37.8)	22 (34.4)	20 (42.6)	0.380
Parameters of the first control visit				
Systolic blood pressure (mmHg)	123±14	123±12	124±15	0.899
Diastolic blood pressure (mmHg)	71±10	73±10	72±10	0.590
Heart rate, beats per minute	75±11	76±10	75±12	0.687
Days of the first visit	28±5	30±4	27±5	0.001
Total number of TTs	48±11	54±7	40±10	<0.001
Total TT time (minute)	529±200	609±172	421±187	<0.001
Average daily TT time, minute	18.0±4.6	20.0±3.0	15.0±4.9	<0.001
Average number of daily TTs	1.7±0.3	1.8±0.1	1.5±0.3	<0.001
Adequate treatment adherence				
Salt and fluid intake, n (%)	92 (82.9)	55 (85.9)	37 (78.7)	0.445
ET program, n (%)	67 (60.4)	47 (73.4)	20 (42.6)	0.001

ET: Exercise training, HUTT: Head-up tilt test, TT: Tilt training, BMI: Body mass index, VVS: Vasovagal syncope.

the last follow-up visit) are presented in Table 3. Univariate analysis revealed that TT plus SSRI [odds ratio (OR): 4,785, 95% confidence interval (CI): 4,784-11,501, p<0.001)] and TT (OR: 0.209, 95% CI: 0.087-0.502, p<0.001) were predictors of asymptomatic patients at follow-up. Multivariate analysis revealed that only TT plus SSRI treatment (OR: 4,785, 95% CI: 4,784-11,501, p<0.001) was an independent predictor of asymptomatic patients at follow-up.

DISCUSSION

The main findings of this study, which investigated the effect of adding paroxetine (SSRI) to the treatment of resistant VVS despite TT, are as follows: 1) TT treatment initially seemed effective in preventing syncope attacks; however, loss of efficacy was observed during follow-up, probably due to decreased compliance of patients with TT programs; 2) the addition of paroxetine to TT treatment resulted in a reduction in syncope attacks in patients with resistant syncope attacks despite TT; 3) paroxetine has been shown to have a lasting effect on preventing syncope attacks in patients with TT-resistant VVS, as long as it is used; 4) paroxetine was observed to be well-tolerated in patients with VVS; 5) TT plus SSRI treatment was found to be the only independent predictor of being asymptomatic during follow-up.

To date, few pathophysiological suggestions have been made regarding the underlying mechanisms of VVS.[3,4,6] Susceptibility to VVS has been associated with insufficient sympathetic activation, resulting in sympathetically mediated peripheral vascular resistance reduction.[10,18] Upright posture induces gravity-induced pooling of venous blood in the lower extremities. This pooling and displacement of intravascular volume decreases cardiac output, activates arterial baroreceptor reflexes, and increases sympathetic stimulation. The activation of ventricular mechanoreceptors produces a strong afferent signal in the brainstem and inhibits sympathetic stimulation.[16] Another possible mechanism is stimulation of the Bezold-Jarisch reflex because of strong contraction of the myocardium against insufficient filling of the heart chamber, resulting in paradoxical hypotension and bradycardia; this may also be responsible for VVS. In general, VVS is caused by three main mechanisms: low vasoconstrictor reserve variability, increased autonomic tone, and changes in baroreflex sensitivity. Most triggers consist of prolonged sitting or standing in an upright position, or muscle activation with a reduction in cardiac preload.[6]

VVS has different treatment options, and it continues to be an important health problem. Various non-pharmacological approaches are effective for treating VVS.[6] The initial strategy is patient education, which is very helpful and necessary. Patients should be advised to avoid heat

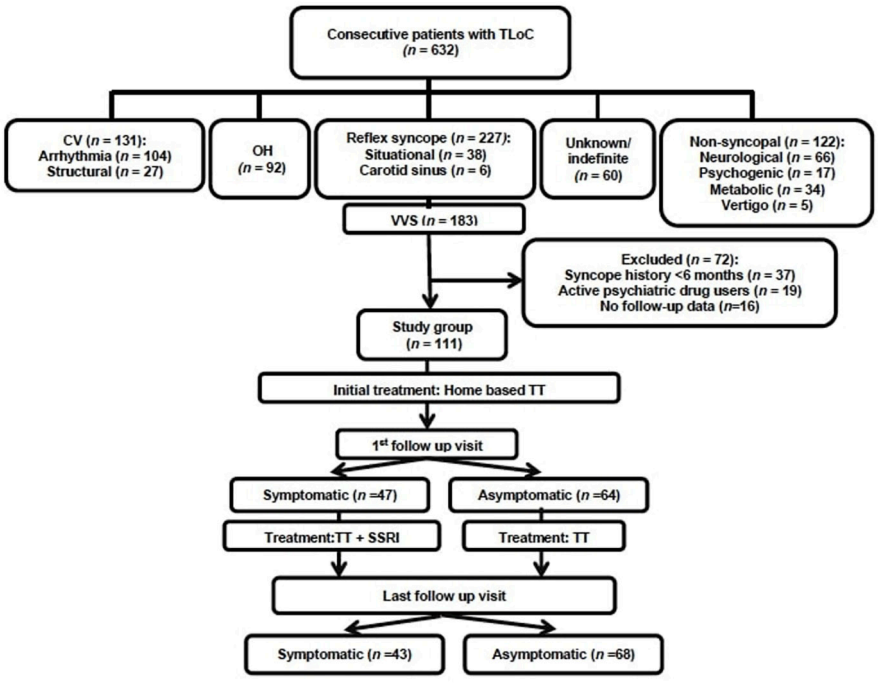

Figure 1. Flow chart showing patients who participated in the treatment-based study at follow-up and the distribution of patients into subgroups according to drug therapy.

TLoC: Transient loss of consciousness; CV: Cardiovascular, TT: Tilt training, OH: Orthostatic hypotension, SSRI: Selective serotonin reuptake inhibitor, VVS: Vasovagal syncope.

Table 2. Follow-up data of the study group after the first control visit

Variables	All patients, (n=111)	TT group, (n=64)	The TT + SSRI group, (n=47)	p
Systolic blood pressure (mmHg)	123±14	124±14	122±14	0.276
Diastolic blood pressure (mmHg)	71±8	70±9	73±8	0.134
Heart rate, beats per minute	74±11	73±12	76±9	0.259
Duration until last visit (months)	8.9 ±3.3	9.0±3.3	8.8±3.2	0.717
Asymptomatic at follow-up, n (%)	68 (61.3)	30 (46.9)	38 (80.9)	<0.001
Syncope during follow-up, n (%)	43 (37.8)	34 (53.1)	9 (19.1)	<0.001
Syncope causing severe trauma, n (%)	11 (9.9)	10 (15.6)	1 (2.1)	0.023
Average TT time per day, minute	11.4±2.9	12.6±2.0	9.6±3.1	<0.001
Average number of daily TTs	1.1 ±0.2	1.1±0.1	0.9±0.2	<0.001
Adequate treatment adherence				
Salt and fluid intake, n (%)	97 (84.7)	56 (87.5)	38 (80.9)	0.487
ET program, n (%)	55 (49.5)	38 (59.4)	17 (36.2)	0.016

ET: Exercise training, TT: Tilt training, SSRI: Selective serotonin re-uptake inhibitor.

and beware of early prodromal symptoms. Aydin et al.[19] showed that a significant reduction in syncope frequency could be achieved using the standard training protocol. Isometric muscle contractions increase cardiac output and arterial blood pressure while reducing syncope in non-randomized and randomized studies.[20,21] Communication with the patient is important during treatment because treatment is usually tailored to the patient's response. TT was developed after repeated HUTT observations. It has been suggested that repetitive HUTTs gradually increase peripheral sympathetic nervous system function and may decrease positive test results.[8,22]

Several studies have shown that training for continuous exposure to orthostatic stress effectively reduces the risk of syncope recurrence.[9,22] Ector et al.[8] found that patients could tolerate all HUTTs after 3-6 sessions, if they repeated daily HUTTs to hospitalized patients until the patients developed a vasovagal response and tolerated the entire test period. Therefore, many researchers have prescribed TT at home, which involves standing against a wall for 30 minutes twice a day; however, it was reported that outpatient TT has no beneficial effect on spontaneous episodes of syncope during follow-up.[10,23] It has been reported that patient compliance is necessary for a continuous TT program, and it may be difficult to achieve a high rate of patient compliance in each patient

Table 3. Univariate and multivariate predictors of asymptomatic at follow-up

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
TT + SSRI	4,785	4,784-11,501	<0.001	4,785	4,784-11,501	<0.001
TT program	0.209	0.087-0.502	<0.001			
ET program	0.489	0.223-1,058	0.069			
Number of presyncope annually	1,026	0.987-1,067	0.199			
TT duration per day	0.862	0.746-0.997	0.045			
TT per day	0.116	0.009-1,430	0.093			

CI: Confidence interval, ET: Exercise training, TT: Tilt training, OR: Odds ratio, SSRI: Selective serotonin reuptake inhibitor.

group.[24] A study conducted by Foglia-Manzillo et al.[25] revealed that only 34% of patients fulfilled all the requirements of the TT session, even at short-term follow-up. In our study, it was found that patient compliance with TT was better at the beginning and decreased significantly over time. In our study, 53.1% of the patients who were asymptomatic at the first follow-up visit became symptomatic during follow-up, in parallel with a decrease in compliance with TT. Numerous physical therapy strategies and maneuvers have been tried for the treatment of VVS.[6] The ET program was formerly widely used because it increases blood volume and improves or modulates baroreceptor function.[25,26] Aerobic and core strengthening exercises were also included in these studies.[26,27]

Serotonin is a neurotransmitter known to affect blood pressure and heart rate by modulating the central nervous system. Several studies have investigated the use of SSRIs for treating VVS.[13,15,16] In a randomized, double-blind, placebo-controlled study, Di Girolamo et al.[16] showed that compared with placebo, paroxetine significantly reduced episodes of syncope in patients with refractory VVS who did not respond to conventional therapy during a 2-year follow-up. Theodorakis et al.[13] published the results of a randomized, placebo-controlled, double-blind study showing that fluoxetine and propranolol were not superior to placebo for the treatment of VVS. Paroxetine has high selectivity and low affinity for adrenergic, cholinergic, and histamine receptors.[16] Therefore, not all SSRIs are equally effective against recurrent VVS. In this case, the group effect of SSRIs for treating VVS can be misinterpreted.

A high rate of MPD has been reported in patients with VVS.[28,29] These disorders are associated with increased vasovagal reflex excitability and relatively high rates of VVS attack.[30] Leftheriotis et al.[30] showed that psychiatric drug therapy can improve VVS attacks and psychiatric symptoms in MPD patients.

Several pathophysiologic mechanisms similar to the vasovagal reflex are believed to be mediated by changes in central serotonin levels.[31] Grubb[32] proposed that SSRIs downregulate postsynaptic serotonin receptors by promoting neuronal transmission. This reduction in receptor density is thought to blunt the response to rapid changes in central serotonin levels.[14,15,32]

Study Limitations

This study has a few limitations. First, this was a prospective observational study and did not have a randomized placebo-controlled design. Second, the sample size was relatively small. Third, patients from three health centers followed by different healthcare providers were included in the study. Fourth, it would have been more beneficial for all patients to undergo a psychiatric evaluation to better understand the response to the SSRI. Fifth, to better understand the pathophysiological impact of SSRIs, patients could be evaluated using pre- and post-treatment quality of life and psychiatric measures. Sixth, quantitative methods can be used to assess patient adherence to TT and ET. Last but not least, the follow-up period of our study was relatively short compared with that of other randomized studies on SSRIs. Therefore, large-scale, multicenter, randomized, and prospective studies are needed to determine the efficacy of paroxetine in VVS.

CONCLUSION

TT is an acceptable treatment for VVS for motivated patients who are willing to follow the program. However, the effectiveness of TT in preventing VVS attacks decreased during the follow-up period, probably due to decreased compliance of patients with the TT program. In patients with recurrent VVS who do not respond to conventional treatments, the addition of paroxetine appears to be an effective and well-tolerated treatment modality for preventing vasovagal attacks.

MAIN POINTS

- TT treatment initially appeared effective in preventing syncope; however, a loss of efficacy was observed during follow-up.
- Paroxetine has a lasting effect on preventing syncope attacks in patients with TT-resistant VVS.
- Paroxetine was well tolerated in patients with VVS.
- Tilt training plus paroxetine treatment was the only independent predictor of asymptomatic patients during follow-up.

ETHICS

Ethics Committee Approval: The Institutional Ethical Committee of Türkiye's Yüksek İhtisas Training and Research Hospital approved the study (approval number: 091023-310-EPK).

Informed Consent: All patients enrolled in the study provided informed consent to participate in the study.

Authorship Contributions

Concept: L.D.A., O.B., Y.A., M.B.Y., Design: L.D.A., O.B., Y.A., M.B.Y., Data Collection and/or Processing: L.D.A., O.B., B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., Y.A., Analysis and/or Interpretation: L.D.A., O.B., B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., M.B.Y., Literature Search: B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., Y.A., Writing: L.D.A., O.B., B.A., N.B., H.B., G.Z., N.Y., H.K., R.K., M.B.Y.

DISCLOSURES

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RESEARCH ARTICLE

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The Effect of *Lactobacillus rhamnosus* GG in Infants with Food Protein-Induced Allergic Proctocolitis

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Abstract

BACKGROUND/AIMS: Most infants with food protein-induced allergic proctocolitis (FPIAP) achieve clinical tolerance between 1 and 3 years of age. The aim of this study was to investigate the effect of *Lactobacillus rhamnosus* GG on the development of tolerance in infants who are exclusively breastfed and diagnosed with FPIAP.

MATERIALS AND METHODS: Sixty infants with FPIAP were divided into two groups: group 1 (study); who received probiotic *Lactobacillus rhamnosus* GG for 3 months, and group 2 (control); who did not. Clinical characteristics, allergy tests, and tolerance development were examined. Randomized controlled study.

RESULTS: Thirty patients [mean age: 3.9±1.3, range: 2-6 months, male/female (M/F): 1.7] in group 1 and 30 patients (mean age: 4.1±1.3, range: 1.4-6 months, M/F: 0.7) in group 2 were included in the study. The reintroduction of trigger foods into the mothers' diet at 9 months was significantly higher in group 1 than in group 2 (63.3% versus 26.7% of the patients, respectively, p=0.004). No significant difference was observed in terms of the resolution time of symptoms and time of tolerance development between groups and subgroups.

CONCLUSION: A significant difference was observed in the mean time to reintroduce trigger foods into the maternal diet, the number of mothers who first reintroduced trigger foods back into their diet at 9 months, and the resolution of symptoms at 9 and 12 months in infants with multiple food allergies.

Keywords: Food protein-induced allergic proctocolitis, *Lactobacillus rhamnosus* GG, probiotics, tolerance, treatment

INTRODUCTION

Food protein-induced allergic proctocolitis (FPIAP) is usually characterized by fresh rectal bleeding and stool mucus in otherwise healthy, well-appearing infants during the first months of life. A definitive diagnosis is made by eliminating the trigger foods thought to be responsible from the diet and reintroduceing the foods after the symptoms improve.[1]

It has been reported that the deterioration of the gut microbiota may play a role in the development of food allergy by negatively affecting immune system development in the early stages of life.[2] Therefore, the gut microbiota may be a potential target for preventing food allergy and its treatment. It has been suggested that the relationship between diet, probiotics, the immune system, and gut microbiota determines the susceptibility to allergy.[3]

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Lactobacillus rhamnosus GG is a preferred probiotic for the prevention and treatment of intestinal microbiota degradation by strengthening intestinal epithelial barriers, binding to mucous surfaces stronger due to its surface exopolysaccharide and piles, preventing the attachment of pathogenic bacteria, and contributing to the regulation of the immune system.[4,5]

Although there are studies about the addition of probiotics such as *Lactobacillus rhamnosus* GG or *Bifidobacterium breve* to formula feed in formula-fed infants,[6-10] there are few studies about the addition of probiotics exclusively in breastfed infants. The aim of this study was to determine whether *Lactobacillus rhamnosus* GG has an effect on the development of tolerance in exclusively breastfed infants with FPIAP.

MATERIALS AND METHODS

Sixty infants who were exclusively breastfed and followed up for diagnosis of FPIAP at the departments of pediatric gastroenterology and pediatric allergy between 2018 and 2019 were enrolled in this single-center, prospective, randomized, controlled clinical study.

The diagnosis of FPIAP was based on detailed history and physical examination findings according to the food allergy and anaphylaxis guidelines recommended by The European Society for Pediatric Gastroenterology Hepatology and Nutrition and European Academy of Allergy and Clinical Immunology (EAACI).[11,12]

The exclusion criteria were; the patients younger than 1 month and older than 6 months, those fed with formula, those given prebiotics or probiotics during the 4 weeks before enrollment, those with known allergies to probiotics, patients with chronic diseases, immunodeficiency, a central venous catheter, and other diseases causing gastrointestinal findings or bleeding.

The patients were divided into two groups: Group 1 (study); exclusively breastfed infants whose mothers were on an elimination diet and received probiotic *Lactobacillus rhamnosus* GG (Maflor® 1x5 drops once a day) for 3 months, and group 2 (control); whose mothers were on only milk and dairy products elimination diet. The control group did not receive any placebo. These groups were divided into two separate subgroups: Those diagnosed in the first 3 months (groups 1a and 2a) and those diagnosed in the last 3 months (groups 1b and 2b). Our aim in dividing the patients into two subgroups was to homogenize both groups as we switched to complementary foods in both groups at 6 months.

Infants were followed up monthly for the first 3 months after diagnosis and every 3 months thereafter until 1 year of age at outpatient clinics of pediatric gastroenterology. Allergy tests were performed by the same trained allergist during the follow-up period after six months of age. Allergy tests were performed in those with non-IgE symptoms, family history of atopy, and who accepted the allergy tests.

Food-Specific Immunoglobulin E and Skin Prick Test

Sensitization in patients with a preliminary diagnosis of FPIAP, especially those with concomitant atopic diseases such as atopic dermatitis and recurrent wheezing, was evaluated by serum food-specific immunoglobulin E (IgE) and/or skin prick test (SPT). SPT was performed on the forearm by microneedling method using commercial extracts for common offending food proteins, including cow's milk, soy, egg, wheat, fish, sesame, and peanut (Stallargenes SA. Antony, France). The prick-to-prick method was used for the other suspected foods, particularly those reported by the parents. Histamine (10 mg/mL) was used as the positive control, and physiological saline was used as the negative control. Skin reactions were evaluated after 20 min, and a wheal >3 mm was considered positive SPT.

Serum-specific IgE concentrations in suspected foods were measured using the ImmunoCAP system (PHADIA AB, Uppsala, Sweden). A serum specific IgE concentration >0.10 kU/L was considered sensitization.

Atopy Patch Test

One drop (50 µL) of milk, scrambled eggs, soy milk, and 1 g of flour dissolved in 10 mL of water and physiological saline as a negative control were adsorbed with filter paper and placed in 12 mm diameter aluminum chambers ("Finn chamber") on adhesive tapes. The patch adhered to the patient's back. Reactions were evaluated at 48 and 72 h according to the European Task Force for atopic Dermatitis Consensus Report.[13]

Diagnostic Food Elimination

A maternal elimination diet was started with the most common offending triggers, milk and dairy products. Food elimination was explained in detail to the mothers and caregivers. In patients with persistent symptoms, other foods such as egg and wheat were also excluded from the diet, based on frequency, parent's suspicion, and symptoms. The occult blood test was not performed, and the evaluation was performed with the resolution of bloody stool.

Oral Food Challenge Test

After a food elimination diet for 2-4 weeks and the disappearance of the complaints, the patients underwent oral food challenge test (OFC) at home or in the hospital, depending on the severity of the patient's symptoms. Provocation tests and protocols were performed according to the recommendations of the World Allergy Organization Food Allergy Working Group and EAACI.[11,14,15] An open food challenge test was performed in all patients. The dosing intervals of the given foods were 15 minutes and were given gradually increasing doses as; peanut and walnut 6, 12, 48, 240, 480, 1200, and 2000 mg; hazelnut 12, 25, 100, 500, 860, 2500, and 4000 mg; cow's milk 0.1,0.5, 1, 3, 10, 30, 50, 100, and 200 mL; egg 0.5, 1, 3, 6, 10, 15, 16, and 32 g. If symptoms appeared at any stage of the test, the test was considered positive. When no reaction developed, the diet was opened to trigger food and was given daily as cooked. Each child was observed for 4 hours after provocation. The families contacted by telephone at 24, 48, and 72 hours and 1 week after the provocation to ask whether any symptoms had occurred. The mothers were also asked to keep an allergy diary at home.

Tolerance Development

All patients on the elimination diet were reevaluated at 3-6 months intervals. OFC was performed in patients who had resolved their symptoms and healthy growth and development. No symptoms were observed after OFC, which was considered as tolerance achieved.

The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 911, date: 08/07/2018). Written informed consent was obtained from all parents.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 15.0 package program (SPSS Inc, Chicago, Illinois, U.S.A.). The descriptive statistics; were given as mean, standard deviation, minimum and maximum for numerical variables, and numbers and percentages for categorical variables. Comparisons of the ratios between the groups were made using the chi-square test. Because the normal distribution condition was not met, numerical variables in the groups were compared using the Mann-Whitney U test. P values of <0.05 were considered statistically significant.

RESULTS

Thirty patients [mean age: 3.9±1.3, range: 2-6 months, male/female (M/F): 1.7] in group 1 and 30 patients (mean age: 4.1±1.3, range: 1.4-6 months, M/F: 0.7) in group 2 were included in the study. The demographic and clinical characteristics of the patients are presented in Table 1.

22.7% (n=5) of the patients in group 1 and 44.8% (n=13) in group 2 had food-specific IgE positivity (p=0.10). SPT was performed in 22 (73.3%) patients in group 1 and 23 (79.3%) patients in group 2. Approximately 13.6% of the patients in group 1 and 8.7% in group 2 had positive SPT (p=0.66). Atopy patch test (APT) was positive in 7 of 13 (53.8%) patients in group 1 and 3 of 13 (23.1%) of 13 patients in group 2 (p=0.10). No significant difference was observed in the APT and SPT results according to the food allergens between the groups and subgroups (Table 1).

Eleven (36.7%) patients with multiple food allergies in group 1 and 11 (36.7%) patients in group 2 reacted to egg, cow's milk, and dairy products (p=1.00). Six common food allergens (nuts, wheat, fish/seafood, chicken, and veal) were restricted from the diet of 8 (26.7%) patients in group 1 and 6 (20%) in group 2 (p=0.54). Six (54.5%) patients in group 1a, 2 (40%) in group 2a, 5 (26.3%) in group 1b, and 9 (36%) in group 2b reacted to both egg, cow's milk, and dairy products (p>0.05). Six food allergens were restricted from diet in 2 (18.2%) patients in group 1a, 2 (40%) in group 2a, 6 (31.6%) in group 1b, and 4 (16%) in group 2b (p>0.05).

No significant difference was observed in the resolution time of the first symptom (bloody stool) between groups (p=0.78) (Table 2). A statistically significant difference was observed in the mean time from the reintroduction of trigger food into the maternal diet between groups (9.1±2.1 months in group 1, and 10.3±1.5 in group 2, p=0.041).

The reintroduction of trigger foods into the mothers' diet at 9 months was significantly higher in group 1 than in group 2 (63.3% versus 26.7% of the patients, respectively, p=0.004), whereas it was observed higher in group 1b than in group 2b (p<0.001) (Tables 2, 3). The distribution of patients according to the reintroduction of trigger foods into the maternal diet and tolerance development is shown in Figure 1.

When the mothers who only had egg and milk elimination diet were evaluated, no significant difference was observed in terms of the resolution time of all symptoms and the reintroduction of trigger food

Table 1. Demographic and clinical characteristics of the patients

	<3 months at diagnosis		p	≥3 months at diagnosis		p
	Group 1a	Group 2a		Group 1b	Group 2b	
	Probiotics (+)	Probiotics (-)		Probiotics (+)	Probiotics (-)	
	(n=11)	(n=5)		(n=19)	(n=25)	
Age at diagnosis (mean ± SD, months)	2.5±0.3 (2-2.9)	2.0±0.6 (1.4-2.8)	0.12	4.7±0.8 (3.3-6)	4.5±1.0 (3-6)	0.61
Gender (M/F)	1.2 (6/5)	0.6 (2/3)	1.00	2.1 (13/6)	0.78 (11/14)	0.10
Type of birth						
Normal spontaneous vaginal	4 (36.4%)	1 (20%)	1.00	11 (57.9%)	11 (44%)	0.36
Cesarean	7 (63.6%)	4 (80%)		8 (42.1%)	14 (56%)	
Duration of symptoms (mo)	1.1±0.5 (0.5-2)	1.1±0.7 (0.5-2)	0.81	2.2±1.1 (0.5-4.5)	2.0±1.0 (0.5-4)	0.53
Gestational age						
Term	10 (90.9%)	5 (100%)	1.00	19 (100%)	25 (100%)	1.00
Post-term	1 (9.1%)	-		-	-	
Birth weight	3502±466.8 (2760-4380)	3420±255 (3000-3680)	0.73	3288.4±452 (2540-3990)	3380.6±372 (2800-4200)	0.48
Birth weight classification						
Normal	9 (81.8%)	5 (100%)	1.00	19 (100%)	24 (96%)	1.00
LGA	2 (18.2%)	-		-	1 (4%)	
SGA	-	-		-	-	
Smoking	1 (9.1%)	1 (20%)	1.00	3 (15.8%)	5 (20%)	1.00
Antibiotics	4 (36.4%)	1 (20%)	1.00	2 (10.5%)	8 (32%)	0.14
Consanguineous marriage	-	-		1 (5.3%)	2 (8%)	1.00
Family history of atopy	11 (100%)	3 (60%)	0.08	15 (78.9%)	17 (68%)	0.41
Mother	6 (54.5%)	3 (60%)	1.00	8 (42.1%)	10 (40%)	0.83
Father	5 (45.5%)	2 (40%)	0.24	11 (57.9%)	15 (60%)	0.57
Symptoms on admission						

Table 1. Continued

	<3 months at diagnosis		p	≥3 months at diagnosis		p
	Group 1a	Group 2a		Group 1b	Group 2b	
	Probiotics (+)	Probiotics (-)		Probiotics (+)	Probiotics (-)	
	(n=11)	(n=5)		(n=19)	(n=25)	
Vomiting	3 (27.3%)	2 (40%)	1.00	7 (36.8%)	10 (40%)	0.83
Diarrhea	4 (36.4%)	3 (60%)	0.59	11 (57.9%)	13 (52%)	0.69
Constipation	1 (9.1%)	1 (20%)	1.00	2 (10%)	3 (12%)	1.00
Bloody stool	6 (54.5%)	1 (20%)	0.30	10 (52.6%)	14 (56%)	0.82
Stool with mucus	10 (90.9%)	4 (80%)	1.00	18 (94.7%)	24 (96%)	1.00
Colic	10 (90.9%)	4 (80%)	1.00	13 (68.4%)	13 (52%)	0.27
Breastfeeding refusal	4 (36.4%)	1 (20%)	1.00	10 (52.6%)	7 (28%)	0.09
Skin rash	6 (54.5%)	3 (60%)	1.00	11 (57.9%)	7 (28%)	0.04
Diaper dermatitis	8 (72.7%)	4 (80%)	1.00	7 (36.8%)	13 (52%)	0.31
Persistent cough/wheezing	2 (18.2%)	1 (20%)	1.00	5 (26.3%)	3 (12%)	0.26
Low weight gain	1 (9.1%)	-	1.00	2 (10.5%)	8 (32%)	0.14
Physical examination						
Atopic dermatitis	6 (54.5%)	3 (60%)	1.00	5 (26.3%)	9 (36%)	0.49
Seborrheic dermatitis/eczema	8 (72.7%)	3 (60%)	1.00	14 (73.7%)	13 (52%)	0.14
Failure to thrive	-	-		-	-	
Laboratory examinations						
Anemia	-	-		3 (15.8%)	1 (4.2%)	0.30
Eosinophilia (n, %)	4 (36.4%)	3 (60%)	0.59	7 (36.8%)	15 (60%)	0.12
Eosinophil count (µ/L)	360.9±238 (330)	624±556.7 (300)	0.61	325±179.8 (270)	450.8±277 (320)	0.11
Total IgE positivity	6 (54.5%)	-	0.09	2 (10.5%)	5 (20%)	0.68
Serum total IgE (U/L)	108±309.4 (16)	7.1±4.4 (6.2)	0.39	20.7±55.3 (4.4)	14.5±23.6 (6.4)	0.61
Skin prick test positivity	1 (12.5%)	-	1.00	2 (14.3%)	2 (10.5%)	1.00
Cow's milk	-	-	-	1 (7.1%)	1 (5.3%)	1.00
Egg	1 (12.5%)	-	1.00	1 (7.1%)	1 (5.3%)	1.00
Soy	-	-		-	-	
Wheat	-	-		-	-	
Nuts	-	-		1 (8.3%)	-	0.42
Sea food/chicken	-	-		-	-	
Specific IgE positivity	2 (22.2%)	2 (40%)	0.58	3 (23.1%)	11 (45.8%)	0.28
Cow's milk	1 (11.1%)	1 (20%)	1.00	2 (15.4%)	8 (34.8%)	0.27
Egg	1 (12.5%)	1 (20%)	1.00	1 (8.3%)	8 (40%)	0.10
Soy	-	-		-	-	
Wheat	-	-		-	-	
Nuts	-	-		1 (50%)	-	1.00
Sea food/chicken	-	-		-	-	
Atopy patch test positivity	3 (50%)	1 (33.3%)	1.00	4 (57.1%)	2 (20%)	0.16
Cow's milk	1 (16.7%)	-	1.00	1 (14.3%)	2 (20%)	1.00
Egg	2 (40%)	1 (33.3%)	1.00	4 (57.1%)	1 (11.1%)	0.10
Soy	-	-		-	-	
Wheat	1 (20%)	-	1.00	-	-	
Nuts	-	-		-	-	
Sea food/chicken	-	-		-	-	

P<0.05 is statistically significant. LGA: Large for gestational age, SGA: Small for gestational age.

back into the maternal and infant diets at 9 and 12 months between groups (p>0.05). Five (100%) mothers in group 1b versus 2 (22.2%) mothers in group 2b who were on egg and milk elimination diet only had the first reintroduction of trigger food back into their diet at 9 months (p=0.021). The resolution of all symptoms at 12 months was achieved in 5 (100%) patients in group 1b and 2 (22.2%) patients in group 2b who were on egg and milk elimination diet (p=0.021). Three patients (60%) in group 1b who received egg and milk elimination diet switched to normal diet at 12 months, but none of the patients in group 2b achieved tolerance (p=0.02).

When patients who were on elimination diet with six trigger food allergens in groups and subgroups were compared, no statistically significant difference was observed in the first time of reintroducing trigger foods back into the maternal diet, resolution of all symptoms, and time of tolerance development. No probiotic-related adverse effects were observed.

Table 2. Comparison of tolerance development between groups

	Group 1, (n=30)	Group 2, (n=30)	p
Resolution time of first symptom*	22.7±16.3 (21)	22±17.3 (17.5)	0.78
First resolved symptom			
Vomiting	3 (10%)	2 (6.7%)	0.2
Diarrhea	1 (3.3%)	6 (20%)	
Bloody stool	13 (43.3%)	8 (26.7%)	
Stools with mucus	3 (10%)	6 (20%)	
Colic	2 (6.7%)	4 (13.3%)	
Breastfeeding refusal	2 (6.7%)	-	
Skin rash	5 (16.7%)	4 (13.3%)	
Diaper dermatitis	1 (3.3%)	-	
Introduction of trigger foods back into maternal diet*	9.1±2.1 (9)	10.3±1.5 (10)	0.04
At 9 months	19 (63.3%)	8 (26.7%)	0.004
At 12 months	28 (93.3%)	24 (80%)	0.25
Resolution of all symptoms*	10.1±2.1 (10)	10.8±1.6 (12)	0.42
At 9 months	5 (16.7%)	4 (13.3%)	1.00
At 12 months	15 (50%)	12 (40%)	0.43
Time for free diet*	11.1±1.4 (12)	11.9±0.4 (12)	0.24
At 9 months	2 (6.7%)	-	0.49
At 12 months	14 (46.7%)	7 (23.3%)	0.05
Multiple food allergies	(n=19)	(n=17)	
Introduction of trigger foods back into maternal diet*	9.0±1.8 (9)	10.3±1.7 (10)	0.05
At 9 months	13 (68.4%)	5 (29.4%)	0.01
At 12 months	17 (89.5%)	14 (82.4%)	0.65
Resolution of all symptoms*	9.6±2.2 (10)	11.8±0.5 (12)	0.09
At 9 months	5 (26.3%)	-	0.04
At 12 months	11 (57.9%)	4 (23.5%)	0.03
Time for free diet*	10.7±1.5 (11)	12 (1)	0.008
At 9 months	2 (10.5%)	-	0.48
At 12 months	9 (47.4%)	1 (5.9%)	0.008

*Mean ± standard deviation (mean). P<0.05 is statistically significant.

DISCUSSION

In breastfed children with FPIAP, no significant difference was detected in the time to resolution of bloody stools or the first symptoms between the groups in terms of probiotic use. Bloody stools were not the only symptoms in the babies, and other accompanying digestive system symptoms, such as sucking refusal, vomiting, and colic, could occur even if there was no bloody defecation when a trigger food was added. Mothers could state that they avoided going on a diet. One limitation of our study was perhaps the lack of evaluation of multiple symptoms. We performed an evaluation based on the family's major symptoms when bringing them to the hospital. Tolerance assessments were conducted every 3 months based on the child's symptoms and anthropometry during physical examination.

In our study, mothers in the probiotic-treated group were able to open their diet earlier in the 9th month, but we did not find a significant difference in the resolution of all symptoms. It may take longer in groups with multiple food allergies. In different studies, it was reported that 30.4-31.5%, that is, one third of the cases with FPID, have multiple food allergies.[16,17] Approximately one-third of patients with food allergies have multiple food allergies. In non-IgE-mediated food allergy, a single nutrient (the most common cow's milk protein) is responsible in the majority of cases (65-80%), and in 10%, three or more nutrients are responsible.[18] Recent studies conducted in our country reported multiple food allergies at rates of up to 50%.[17] In addition, the responsible allergenic foods may vary according to country and culture. Cultural differences may also affect altitude. Moreover, we were one of the reference centers for pediatric allergy and gastroenterology at that time, and it was a center to which many patients were referred. Our rate of allergy testing was high; thus, we may have found it to be too high compared with the literature. The diagnosis of multiple food allergies has been more common since we performed allergy testing for study purposes at that time when we did not perform routine allergy testing to diagnose FPIAP.

In the absence of clinical response to cow's milk protein elimination within 2 weeks in FPIAP and 4-8 weeks in food protein-related enteropathy,[19] food protein-related enterocolitis syndrome within hours,[20] and recurrence of findings after intake of certain foods, multiple food allergies should be considered, and allergenic foods should be avoided. Gradual elimination from the diet should be planned.

Cows' milk was the most common trigger food in this study, similar to the other studies,[21-23] followed by eggs. Family history of atopy was reported in 86.7% of patients in group 1 and 66.7% in group 2, which was higher than that reported in the literature.[24,25] Multiple food allergies were reported to be 4-42.9% in studies from our country,[21,22,24,25] whereas it was found to be 60% in our study.

It has been suggested that gut microbiota play an important role in immune system maturation, maintaining the Th1/Th2 balance, which is the key mechanism involved in allergic diseases and tolerance acquisition.[3,6,26,27] The gastrointestinal microbiota may also modulate mucosal physiology, barrier function, and systemic immunologic and inflammatory responses.[3-5] Yang et al.[3] reported that sIgE, sIgG1, interleukin 4 (IL-4), IL-5, and IL-13 levels were significantly decreased, resulting in improved diarrhea in mice with food allergy who were administered the probiotic *Bifidobacterium* infantis. It has been reported that the administration of probiotics in early-life stimulate Th1 cytokines to reverse Th2 imbalance.[28]

Table 3. Comparison of tolerance development between subgroups

	<3 months at diagnosis		p	≥3 months at diagnosis		p
	Group 1a	Group 2a		Group 1b	Group 2b	
	Probiotics (+)	Probiotics (-)		Probiotics (+)	Probiotics (-)	
	(n=11)	(n=5)		(n=19)	(n=25)	
Resolution time of first symptom (day)*	21.4±1 (1.9)	23.2±17.3 (15)	0.9	23.4±1 (8.6)	21.8±17.6 (20)	0.77
First resolved symptom						
Vomiting	1 (9.1%)	1 (20%)	0.19	2 (10.5%)	1 (4%)	0.32
Diarrhea	-	2 (40%)		1 (5.3%)	4 (16%)	
Bloody stool	4 (36.4%)	-		9 (47.4%)	8 (32%)	
Stools with mucus	1 (9.1%)	1 (20%)		2 (10.5%)	5 (20%)	
Colic	1 (9.1%)	-		1 (5.3%)	4 (16%)	
Breastfeeding refusal	-	-		2 (10.5%)	-	
Skin rash	4 (36.4%)	1 (20%)		1 (5.3%)	3 (12%)	
Diaper dermatitis	-	-		1 (5.3%)	-	
Introduction of trigger foods back into maternal diet*	9.7±2.2 (9)	9.2±1.6 (9)	0.67	8.8±2.1 (9)	10.6±1.4 (11)	0.008
At 9 months	5 (45.5%)	4 (80%)	0.30	14 (73.7%)	4 (16%)	<0.001
At 12 months	9 (81.8%)	5 (100%)	1.00	19 (10%)	19 (76%)	0.12
Resolution of all symptoms*	9.7±2.2 (9)	9.2±1.6 (9)	0.84	10.4±2.1 (11)	11±1.6 (12)	0.49
At 9 months	3 (27.3%)	1 (20%)	1.00	2 (10.5%)	3 (12%)	1.00
At 12 months	5 (45.5%)	2 (40%)	1.00	10 (52.6%)	10 (40%)	0.40
Time for free diet*	10.8±1.8 (12)	12±0.0 (12)	0.33	11.3±1.1 (12)	11.8±0.4 (12)	0.50
At 9 months	1 (9.1%)	-	1.00	1 (5.3%)	-	0.43
At 12 months	5 (45.5%)	2 (40%)	1.00	9 (47.4%)	5 (20%)	0.05
Multiple food allergies	**(n=8)**	**(n=4)**		**(n=11)**	**(n=13)**	
Introduction of trigger foods back into maternal diet*	9.5±2.5 (9.5)	9.3±1.9 (8.5)	1.00	8.7±1.3 (9)	10.7±1.5 (11)	0.006
At 9 months	3 (37.5%)	3 (75%)	0.54	10 (90.9%)	2 (15%)	<0.001
At 12 months	6 (75%)	4 (100%)	0.51	11 (100%)	10 (76.9%)	0.22
Resolution of all symptoms*	9.3±1.9	-		10±2.3	12±0.0	
At 9 months	3 (37.5%)	-	0.48	2 (18.2%)	-	0.19
At 12 months	4 (50%)	1 (25%)	0.57	7 (63.6%)	3 (23.1%)	0.09
Time for free diet*	10.5±1.9 (11)	12±0.0		10.8±1.3 (11)	-	0.01
At 9 months	1 (12.5%)	-	1.00	1 (9.1%)	-	0.45
At 12 months	4 (50%)	1 (25%)	0.57	5 (45.5%)	-	0.01

*Mean ± standard deviation (median). P<0.05 is statistically significant.

Thus, probiotics may treat food allergy by restoring imbalanced indigenous microbiota and controlling inflammatory responses (activation of local macrophages, modulation of local and systemic IgA production, and alteration of the pro- and anti-inflammatory cytokine profile).[29]

Morisset et al.[30] reported a significant decrease in the proportion of positive SPT in cows' milk and a decrease in positive IgE tests against other foods than cow's milk in the probiotic group after 12 months. Berni Canani et al.[6] noted a risk reduction in infants receiving *Lactobacillus rhamnosus* GG for additional atopic diseases (eczema, asthma, rhinoconjunctivitis, and other food allergies) and a decrease in oral tolerance development in children with IgE-mediated cow's milk allergy in their two studies. Baldassarre et al.[7] showed significant improvement in hematochezia in infants fed an extensively hydrolyzed casein formula containing *Lactobacillus rhamnosus* GG. Cukrowska et al.[8], Kirjavainen et al.[9], and Majamaa and Isolauri[10] observed a decrease in the Severity Scoring of the Atopic Dermatitis Index in patients with atopic eczema and cows' milk allergy who received probiotics. Although Qamer et al. [31] stated that probiotics (*Lactobacillus rhamnosus* GG) can lead to an earlier acquisition of tolerance to cows' milk in children aged 36 months, and probiotic supplementation was not associated with an earlier resolution of hematochezia. In contrast to these studies, others reported no significant effects of probiotics on clinical tolerance, SPTs, and the rate of symptomatic food allergy.[32,33] Fiocchi et al.[34] reported very low quality of evidence for probiotics in preventing eczema, and Hojsak et al.[35] mentioned that probiotics cannot be recommended for the prevention of atopic diseases.

In our study, we observed that 10^9 *Lactobacillus rhamnosus* GG-containing drops added to the diet of exclusively breastfed infants diagnosed with FPIAP over a 3-month period shortened the average time to reintroduce trigger foods into the maternal diet, and more mothers in the study group were able to reintroduce trigger foods back into

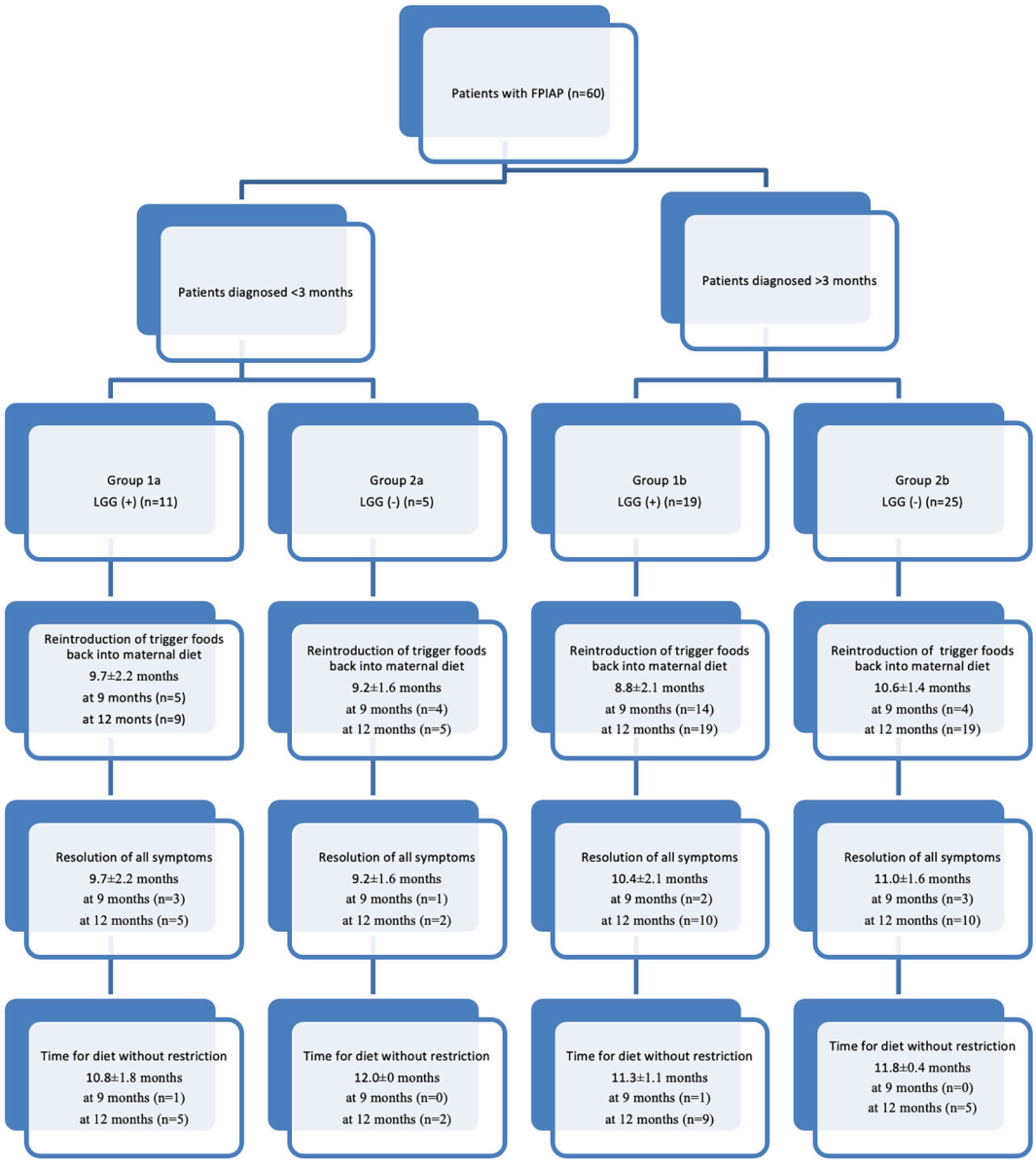

Figure 1. Distribution of patients according to tolerance development.

FPIAP: Food protein-induced allergic proctocolitis, LGG: Lactobacillus rhamnosus GG.

their diet at 9 months. Significant differences were also found in both groups and their subgroups who had multiple food allergies in terms of reintroducing trigger foods back into the maternal diet at 9 months in the study group, tolerance development, resolution of all symptoms at 9 and 12 months, and return to a normal diet at 12 months.

20% of breastfed infants with FPIAP have spontaneous resolution, and nearly all infants become tolerant to the trigger food by the age of 1-3 years.[1] Tolerance to trigger foods by 1 year of age in infants with FPIAP was reported to be 40% in Erdem et al.[25] The frequency of tolerance development was found to be higher in patients who had a single food allergy than in patients with multiple food allergies (86.6% vs. 44.7%, respectively, $p<0.001$)[22] and among the patients who developed tolerance at >24 months, most had multiple food allergies. In our study, no significant difference was observed in tolerance development between patients with single or multiple food allergies at the age of 1 year.

A significantly greater number of patients with single and multiple food allergies in both group 1 and group 1b who received probiotics and switched to a free diet at 12 months in this study. The tolerance was achieved in more patients with multiple food allergies who received probiotics.

Study Limitations

The limitations of the study were its single-center nature with a small number of participants, and being not placebo controlled.

CONCLUSION

It is important to achieve tolerance to trigger foods earlier to prevent inappropriate, unnecessary, or prolonged elimination diet intake, which may affect dietary nutritional intake, health-related quality of life, and growth in children with FPIAP. Further studies with larger sample sizes are needed to clarify the beneficial effects of probiotics on food allergy.

MAIN POINTS

- Most of the infants with food protein-induced allergic proctocolitis achieve clinical tolerance between 1 and 3 years of age.
- Most of patients with single and multiple food allergies who received probiotics, switched to free diet at 12 months in this study.
- The tolerance development was achieved in more patients with multiple food allergies who received probiotics.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 911, date: 08/07/2018).

Informed Consent: Written informed consent was obtained from all parents.

Authorship Contributions

Surgical and Medical Practices: Ö.A., M.U., A.K., N.K., N.U., Concept: Ö.A., M.U., Design: Ö.A., M.U., Data Collection and/or Processing: Ö.A., M.U., A.K., N.K., N.U., Analysis and/or Interpretation: M.U., A.K., N.K., N.U., Literature Search: Ö.A., M.U., Writing: Ö.A., M.U.

DISCLOSURES

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

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RESEARCH ARTICLE

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Olfactory Dysfunction and Cognitive Impairment After COVID-19

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Abstract

BACKGROUND/AIMS: The coronavirus disease-2019 (COVID-19) pandemic has brought to mind the long-known relationship between loss of smell, cognitive functions, and neurodegenerative processes and raised the question, "Can COVID-19 trigger or accelerate the development of neurodegenerative diseases?". This study aimed to investigate cognitive functions and their relationship with loss of smell, temporal changes in cognitive functions, and factors that may have an effect on this possible change in individuals with COVID-19.

MATERIALS AND METHODS: Individuals between the ages of 18-60, who had mild-moderate COVID-19 were included in the study within 3-6 months following the disease. COVID-19-related olfactory dysfunction and its duration were evaluated. Cognitive functions were assessed using the Addenbrooke's Cognitive Examination-Revised test battery and the Symbol Digit Modalities test. After six months, neuropsychological tests were repeated.

RESULTS: Ninety-seven patients who had COVID-19 (52 patients with COVID-19-related loss of smell and 45 patients without) were included in the study. Fifty patients were re-evaluated 6 months after their initial examination. Loss of smell was found to be continued for ≤3 months in 42 patients and >3 months in 10 patients. Neuropsychological test results showed that cognitive function was affected by loss of smell at the first examination. Additionally, the cognitive impact was more pronounced in the group with >3 months of smell loss than in the group with ≤3 months of smell loss. Six months later, test results were better than those at the first examination in both groups, regardless of loss of smell or not.

CONCLUSION: Our results indicate that cognitive function may be affected with or without loss of smell in patients with COVID-19, and that cognitive dysfunction and the duration of loss of smell may be related. It was found that cognitive functions were recovered substantially over time, and it was considered that COVID-19-related damage affecting cognitive functions was recoverable.

Keywords: Cognitive impairment, COVID-19, long-COVID, loss of smell, olfactory dysfunction

INTRODUCTION

Experiences during the coronavirus disease-2019 (COVID-19) pandemic revealed that neurological and neuropsychiatric symptoms related to the disease may develop over a wide spectrum and spread over time. A high frequency of cognitive complaints after COVID-19 was reported, and the effect of COVID-19 on cognitive function was almost invariably shown in many studies.[1-9] During the COVID-19 pandemic, olfactory dysfunction became a common symptom that was frequently observed and attracted attention.[10,11]

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Olfactory dysfunction may develop as a result of a wide range of factors and pathological events, ranging from viral infections including Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) to neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). Olfactory dysfunction is also a sensitive biomarker of neurodegenerative diseases.[12-17] It was suggested that a connection between SARS-CoV-2 infection and olfactory dysfunction may play a potential role in the development of neurodegenerative diseases or occurrence of predisposition to these diseases in individuals with COVID-19.[12]

Although it is not known whether SARS-CoV-2 is neurotropic and the extent of its damage to the central nervous system (CNS), several hypotheses have been suggested to clarify its entry into the CNS. First, SARS-CoV-2 probably proceeds via axonal/transsynaptic transport in olfactory neurons innervating the nasal epithelium and reaches the olfactory bulb, olfactory cortex, other structures in the temporal lobe, and possibly the brain stem.[18,19] The other hypotheses are that SARS-CoV-2 may spread to many parts of the brain by being transmitted into the cerebrospinal fluid surrounding the olfactory nerve bundles, enter the CNS hematogenously, and infect vascular endothelial cells, pericytes, and possibly neurons.[10,12,18,20,21]

It has been suggested that SARS-CoV-2, like other coronaviruses, may remain in certain neurons without causing acute toxicity, cause abnormal folding and aggregation of proteins, and lead to neurodegenerative processes that may arise in individuals who have COVID-19 within the subsequent years.[22-24] Coronaviruses affect endosomal cathepsins, cell surface transmembrane or serine proteases, and host proteases, such as furin and trypsin.[25,26] Most of these proteases have an important role in the degradation of altered neural proteins, such as alpha-synuclein, amyloid precursor protein, and huntingtin, and play a role in the pathogenesis of neurodegenerative diseases, such as PD and AD.[25,27] Another comment for clarifying the relation between COVID-19 and neurodegenerative diseases is that after entering the olfactory bulb, viral proteins are released by the replication of SARS-CoV-2, activating the release of proinflammatory cytokines; the resulting inflammatory environment also triggers oxidative stress mediators, leading to the loss of dopamine neurons or the aggregation of proteins, such as amyloid fibrils and α-synuclein responsible for the pathogenesis of PD and AD.[12,28-30]

The long-known relationship between loss of smell and cognitive function and neurodegenerative processes brings into mind the question of whether olfactory dysfunction in patients with COVID-19 can predict cognitive impairment. The answer to the question of whether COVID-19 will increase the risk of dementia in the future is not yet clear. In this study, we aimed to investigate the relationship between loss of smell and its duration and cognitive function in patients after COVID-19. The changes in cognitive function over time and the factors that may have affected this change were also investigated.

MATERIALS AND METHODS

Patients aged 18-60 years with COVID-19 and at least primary school graduates were included in the study within 3 to 6 months following the illness. The study participants were selected from relatives of patients who applied to the neurology outpatient clinic. The study was conducted prospectively. Patients were included in the study between August 2021 and October 2021.

Patients with a confirmed diagnosis of COVID-19 (positive SARS-CoV-2 polymerase chain reaction test result in nasopharyngeal swabs with viral symptoms), those with mild/moderate illness (with COVID-19 severity score between 1-4)[31] and those who did not require hospitalization at the intensive care unit were included in the study. Patients with a history of neurological disease, head trauma, systemic-induced cognitive impairment, psychiatric disease, and psychotropic drug use, diagnosed with depressive emotional disorder, a history of olfactory disorder symptoms that developed for any reason before COVID-19, a history of nasopharyngeal surgery, and in whom COVID-19-related encephalopathy developed were excluded from the study.

The participants were interviewed face-to-face, and the information forms developed for the study were completed. It was queried whether the patients had any complaints related to their sense of smell (anosmia, hyposmia, hyperosmia, parosmia, phantosmia or cacosmia) due to COVID-19, and if so, how long it continued/whether it still continues. The education level of the patients was categorized as primary school, high school, or university graduate, and their education periods were recorded. Whether the patient was currently smoking and their body mass index (BMI) were determined. BMI ≥30 kg/m^2 was considered obesity. History of hypertension, diabetes mellitus (DM), coronary artery disease, and chronic lung disease (chronic obstructive pulmonary disease, asthma) were recorded.

Cognitive functions were evaluated with Addenbrooke's Cognitive Examination-Revised (ACE-R) test battery, which evaluates orientation, attention, memory, verbal fluency, language, and visuospatial ability, and the Symbol Digit Modalities test (SDMT), which evaluates attention, concentration, and speed of information processing. In addition, the participants were evaluated using Beck's Depression Inventory, and patients with scores ≥17 (moderate and severe depressive mood disorder) were excluded from the study because there may have been confusion in determining cognitive dysfunctions. The tests were performed by a clinical psychologist that was blind to patient information.

Comparisons were made in terms of cognitive function between patients with and without olfactory dysfunction for ≤3 months and >3 months as well as between patients with and without COVID-19-related olfactory dysfunction. A part of the participants of the study were called for a check-up 6 months after the initial examination, their neuropsychological tests were repeated, and it was determined whether any changes in cognitive functions and smell-related complaints had occurred over time. Factors that may affect temporal changes in neuropsychological test results were examined.

The study was conducted in accordance with the Declaration of Helsinki and with the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (approval number: 116/16, date: 26.07.2021). Written informed consent was obtained from all patients who participated in the study.

Statistical Analysis

SPSS 23.0 software (Statistical Package for the Social Sciences, version 23.0 for Windows, SPSS Inc., Chicago, IL). Conformity of continuous variables to normal distribution was researched by Shapiro-Wilk test. Descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum) for continuous variables and number (%) for categorical variables. Independent two-sample t-test was used if

continuous variables had normal distribution and Mann-Whitney U test was used if continuous variables did not have a normal distribution. In the comparison of two dependent groups, the paired two-sample t-test was applied for data with normal distribution, and the Wilcoxon test was applied for the data not having normal distribution. Pearson's chi-square test was used to assess categorical variables, and Fisher's exact test was used when chi-square test conditions were not met. A linear regression model was used to analyze the independent variables affecting the changes in ACE-R, SDMT, and ACE-R memory sub-scores. The statistical significance level was set as $p<0.05$ in the analyses.

RESULTS

Participants

Ninety-seven people (59 females, 38 males; mean age 40.2±10.8) who had COVID-19 were included in the study, and initial cognitive assessment was performed within 3-6 months following the illness (mean: 128.6±25.1 days). Fifty of the 97 patients were evaluated at the second examination 6 months later.

In 52 of the patients (53.6%), COVID-19-related loss of smell developed. Loss of smell continued for ≤3 months in 42 patients (80.8%) and >3 months in 10 patients (19.2%). In 2 of 10 patients, the duration of loss of smell was >12 months.

The demographic and clinical characteristics of the patients, ACE-R scores, ACE-R memory subscore, and SDMT scores at the first examination and during the checkup after 6 months are presented in Table 1.

Loss of Smell

No statistically significant difference was detected between patients with and without COVID-19-related loss of smell in terms of demographic characteristics, comorbid conditions, and diseases, ACE-R score, SDMT score, and ACE-R memory subscore in the first and second examinations (Table 2).

The patients in whom loss of smell continued for more than 3 months had lower ACE-R scores in the first examination and lower SDMT scores in their checkups after 6 months compared with the patients in whom loss of smell continued for 3 months or less ($p=0.018$ and $p=0.044$, respectively) (Table 3).

Olfactory dysfunction persisted 12 months after COVID-19 in 2 patients. In a 47-year-old female patient who was a high school graduate, the ACE-R and SDMT scores in the first examination were significantly lower than the group averages. The test scores of another 19-year-old female patient were lower but not as significant as those of the first patient. An increase was found in the test scores of both patients in the second examination after 6 months, but a significant decrease in the test scores of the first patient was observed.

Changes in Cognitive Function After COVID-19 within the 6-Month Period

Fifty of the 97 patients whose initial examinations were performed were re-evaluated after 6 months (29 patients with loss of smell, 21 patients without loss of smell).

ACE-R scores in the second examination were found to have a statistically significant increase compared with ACE-R scores in the first examination in all patients with COVID-19 and in the subgroups with and without olfactory dysfunction ($p<0.001$, $p<0.001$ and $p=0.001$, respectively). In the ACE-R scores at the second examination, a statistically significant increase was observed in the patients with loss of smell lasting for ≤3 months and for >3 months ($p<0.001$ and $p=0.017$, respectively) (Table 4).

An increase was found in ACE-R memory subscore in the second examination compared with the first examination in all patients with COVID-19 and in the subgroups with and without loss of smell ($p<0.001$, $p<0.001$ and $p<0.001$, respectively). It was observed that there was a statistically significant increase in ACE-R memory sub-scores in both patients with 3-month loss of smell lasting ≤3 months and patients with >3-month loss of smell lasting >3 months ($p<0.001$ and $p=0.016$, respectively).

Table 1. Demographic and clinical characteristics of patients with COVID-19

	Patients with COVID-19, (n=97)
Age (years)	40.24±10.80
Gender	
Female	59 (60.8)
Male	38 (39.2)
Years of education	11.89±4.30
Level of education	
Primary school	31 (32)
High school	27 (27.8)
University	39 (40.2)
COVID-19 severity score	
1	23 (23.7)
2	66 (68)
3	4 (4.1)
4	4 (4.1)
Smoking	28 (28.9)
Obesity (BMI >30 kg/m^2)	23 (23.7)
Hypertension	14 (14.4)
Diabetes mellitus	9 (9.3)
Coronary heart disease	2 (2.1)
Chronic lung disease	2 (2.1)
Loss of smell	52 (53.6)
Loss of smell ≤3 months	42 (43.3)
Loss of smell for 3-12 months	8 (8.2)
Loss of smell >12 months	2 (2.1)
Loss of taste	46 (47.4)
Forgetfulness	79 (81.4)
ACE-R score (initial)	79.81±10.86
ACE-R memory subscore (initial)	15.32±4.42
SDMT score (initial)	49.68±17.05
ACE-R score (6 months later)	82.92±11.41
ACE-R memory subscore (6 months later)	17.24±3.99
SDMT score (6 months later)	54.69±16.71

Data are presented as mean ± standard deviation or number (%). Twenty-nine and 21 patients with and without loss of smell, respectively, were evaluated 6 months after their initial examination. BMI: Body mass index, ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modalities test, COVID-19: Coronavirus disease-2019.

SDMT scores in the second examination were found to have a statistically significant increase as compared with SDMT scores in the first examination in all patients who had COVID-19 and in the subgroups with and without olfactory dysfunction ($p<0.001$, $p<0.001$ and $p=0.002$, respectively). In SDMT scores at the second examination, a statistically significant increase was observed in patients with loss of smell lasting for ≤3 months ($p<0.001$). In patients with olfactory dysfunction lasting for >3 months, the change in the control SDMT scores was not statistically significant compared with that at the first examination (Table 4).

Independent variables that may affect changes in ACE-R, SDMT, and ACE-R memory sub-scores over 6 months (duration of olfactory loss ≤3 months or >3 months, age, gender, level of education, obesity, hypertension and DM) were evaluated using linear regression models. Regression models for the ACE-R, SDMT, and ACE-R memory subscore were not significant ($p=0.346$, $p=0.242$ and $p=0.281$, respectively) (Table 5).

Table 2. Comparison of demographic and clinical characteristics between patients with and without loss of smell

	Patients with loss of smell, (n=52)	Patients without loss of smell, (n=45)	p
Age (year)	38.73±10.77	41.98±10.69	0.141[1]
Gender			
Female	36 (69.2)	23 (51.1)	0.106[2]
Male	16 (30.8)	22 (48.9)	
Years of education	11.98±4.23	11.78±4.42	0.825[3]
Level of education			
Primary school	17 (32.7)	14 (31.1)	0.974[5]
High school	14 (26.9)	13 (28.9)	
University	21 (40.4)	18 (40)	
Smoking	33 (63.5)	36 (80)	0.117[2]
Obesity (BMI >30 kg/m^2)	9 (17.3)	14 (31.1)	0.176[2]
Hypertension	5 (9.6)	9 (20)	0.161[4]
Diabetes mellitus	4 (7.7)	5 (11.1)	0.729[4]
Coronary heart disease	2 (3.8)	0 (0)	0.497[4]
Chronic lung disease	2 (3.8)	0 (0)	0.497[4]
COVID-19 severity score (1-4)	2±0.68	1.75±0.60	0.312[2]
Forgetfulness	37 (71.2)	27 (60)	0.346[2]
ACE-R score (initial)	79.04±10.75	80.71±11.04	0.454[3]
ACE-R memory subscore (initial)	14.62±3.93	16.13±4.85	0.158[3]
SDMT score (initial)	49.33±16.40	50.09±17.94	0.828[1]
ACE-R score (6 months later)	83.36±11.87	82.33±11.04	0.760[1]
ACE-R memory subscore (6 months later)	17.07±3.91	17.48±4.19	0.729[1]
SDMT score (6 months later)	57.89±16.26	50.43±16.72	0.123[1]

Data are presented as mean ± standard deviation or number (%). Twenty-nine and 21 patients with and without loss of smell, respectively, were evaluated 6 months after their initial examination. [1]Independent two sample t-test, [2]Yates Correction, [3]Mann-Whitney U test, [4]Fisher's exact test, [5]Pearson's chi-square test. BMI: Body mass index, ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, COVID-19: Coronavirus disease-2019.

DISCUSSION

The effect of COVID-19 on cognitive function was almost invariably demonstrated in many studies.[1-9] However, it remains unclear how often it affects, how long the effect lasts, whether it is permanent, and whether olfactory disorders that develop during the disease are markers for cognitive impairment. The reasons such as the fact that cognitive evaluations were performed in the acute phase of the disease or in the following months, the characteristics of the patients included in the study population, the variability in disease severity between studies, and the evaluation of different cognitive domains may have led to contradictory results.

In this study, there was no difference in cognitive function between patients with and without COVID-19-related loss of smell. However, in the first examination of patients whose loss of smell persisted for more than 3 months, ACE-R scores were found to be lower, indicating widespread cognitive dysfunction, including orientation, attention,

Table 3. Comparison of demographic and clinical characteristics among patients with loss of smell for ≤3 months or >3 months

	Patients with loss of smell for ≤3 months, (n=42)	Patients with loss of smell for >3 months, (n=10)	p
Age (years)	38.52±10.28	39.60±13.20	0.745[1]
Gender			
Female	29 (69)	7 (70)	1.000[2]
Male	13 (31)	3 (30)	
Years of education	12.40±4.31	10.20±3.55	0.114[3]
Level of education			
Primary school	12 (34.3)	2 (20.0)	
High school	10 (28.6)	3 (30.0)	0.658[4]
University	13 (37.1)	5 (50.0)	
Smoking	26 (61.9)	7 (70.0)	0.729[2]
Obesity (BMI >30 kg/m^2)	8 (19)	1 (10)	0.670[2]
Hypertension	5 (11)	0 (0)	0.569[2]
Diabetes mellitus	4 (9.5)	0 (0)	0.576[2]
Coronary heart disease	1 (2.4)	1 (10)	0.351[2]
Chronic lung disease	2 (4.8)	0 (0)	0.649[2]
COVID-19 severity score (1-4)	1.97±0.64	2.1±0.87	0.792[4]
Forgetfulness	29 (69)	8 (80)	0.704[2]
ACE-R score (initial)	80.76±9.96	71.80±11.44	**0.018[3]**
ACE-R Memory subscore (initial)	15.07±4.03	12.70±2.87	0.080[3]
SDMT score (initial)	50.90±16.15	42.70±16.60	0.157[1]
ACE-R score (6 months later)	84.95±11.49	78.57±12.59	0.159[3]
ACE-R Memory subscore (6 months later)	17.76±3.92	15.00±3.27	0.106[1]
SDMT score (6 months later)	61.43±14.95	47.29±16.43	**0.044[1]**

Data are presented as mean ± standard deviation or number (%). Twenty-nine and 21 patients with and without loss of smell, respectively, were evaluated 6 months after their initial examination. [1]Independent two sample t-test, [2]Fisher's exact test, [3]Mann-Whitney U test, [4]Pearson chi-square test; ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, COVID-19: Coronavirus disease-2019.

Table 4. ACE-R and SDMT scores over a 6-month period and their relationship with loss of smell

	ACE-R score (initial)	ACE-R score (6 months later)	p	SDMT score (initial)	SDMT score (6 months later)	p
Patients with COVID-19	79.81±10.86	82.92±11.41	**<0.001***	49.68±17.05	54.69±16.71	**<0.001****
Patients without loss of smell	80.71±11.04	82.33±11.04	**0.001***	50.09±17.94	50.43±16.72	**0.002***
Patients with loss of smell	79.04±10.75	83.36±11.87	**<0.001***	49.33±16.40	57.89±16.26	**<0.001***
Patients with loss of smell ≤3 months	80.76±9.96	84.95±11.49	**<0.001***	50.90±16.15	61.43±14.95	**<0.001****
Patients with >3 months of loss of smell	71.80±11.44	78.57±12.59	**0.017***	42.70±16.60	47.29±16.43	0.688**

Data are presented as mean ± standard deviation. *Wilcoxon test, **Paired two sample t-test. Twenty-nine of the patients with loss of smell and 21 of the patients without loss of smell, 22 of the patients with olfactory dysfunction for ≤3 months and 7 of the patients with olfactory dysfunction for >3 months were evaluated 6 months after their initial examination. ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, COVID-19: Coronavirus disease-2019.

Table 5. Linear regression models for the ACE-R and SDMT scores

Linear regression model of independent variables that may affect changes in ACE-R scores

	β_0 (95% CI)	β_1	t	p	r_1	r_2	VIF
Constant	2,380 (1.14-3,621)		4,048	0.001			
Patients with >3 months of loss of smell (no reference)	-0.371 (-0.97-0.228)	-0.272	-1,307	0.209	-0.196	-0.302	1,155
Age	-0.062 (-0.688-0.565)	-0.051	-0.208	0.837	-0.104	-0.050	1,597
Gender (no reference)	0.036 (-0.667-0.739)	0.027	0.108	0.915	-0.036	0.026	1,725
Education (reference: university)							
Primary school	0.514 (-0.215-1,242)	0.376	1,488	0.155	0.009	0.339	1,710
High school	0.461 (-0.236-1,158)	0.362	1,395	0.181	0.134	0.320	1,799
Obesity	-0.795 (-1,705-0.115)	-0.517	-1,843	0.083	-0.405	-0.408	2,106
Hypertension	0.380 (-1,017-1,778)	0.201	0.574	0.573	-0.056	0.138	3,262
Diabetes mellitus	-0.530 (-2,472-1,412)	-0.233	-0.576	0.572	-0.245	-0.138	4,385

F=1,219, p=0.346, R^2=36.5%, corrected R^2=6.6%, β_0: Unstandardized beta coefficient, β_1: Standardized beta coefficient, r_1: Zero order correlation, r_2: Partial correlation. As the ACE-R changes did not have a normal distribution, Ln conversion was applied.

Linear regression model of independent variables that may affect changes in SDMT scores

	β_0 (95% CI)	β_1	t	p	r_1	r_2	VIF
Constant	**1,619 (0.547-2,692)**		**3,218**	**0.006**			
Patients with loss of smell >3 months (no reference)	-0.467 (-1,093-0.159)	-0.382	-1,589	0.133	-0.423	-0.380	1,550
Age	-0.457 (-0.993-0.08)	-0.431	-1,813	0.090	-0.322	-0.424	1,518
Gender (no Reference)	0.082 (-0.61-0.774)	0.067	0.252	0.804	-0.102	0.065	1,892
Education status (reference: university)							
Primary school	0.152 (-0.544-0.848)	0.124	0.466	0.648	0.016	0.119	1,911
High school	0.182 (-0.502-0.866)	0.162	0.567	0.579	-0.043	0.145	2,192
Obesity	0.501 (-0.255-1,256)	0.384	1,413	0.178	0.159	0.343	1,983
Hypertension	0.808 (-0.413-2,029)	0.504	1,411	0.179	0.116	0.342	3,435
Diabetes mellitus	-1,320 (-2,978-0.339)	-0.688	-1,696	0.111	-0.050	-0.401	4,428

F=1,487, p=0.242, R^2=44.2%, corrected R^2=14.5%, β_0: Unstandardized beta coefficient, β_1: Standardized beta coefficient, r_1: Zero-order correlation, r_2: Partial correlation. Because the SDMT changes did not have a normal distribution, Ln conversion was applied. ACE-R: Addenbrooke's Cognitive Examination-Revised, SDMT: Symbol Digit Modality test, CI: Confidence interval.

memory, verbal fluency, language, and visuospatial ability. Patients with persistent loss of smell for more than 3 months had lower SDMT scores on the second examination after 6 months. These findings indicated that the duration or persistence of loss of smell may be related to cognitive function rather than whether or not loss of smell development in patients with COVID-19. Our results can be interpreted as loss of smell may last longer in patients whose cognitive functions are affected in the early post-COVID-19 period; especially attention and concentration disorders and regression in the speed of information processing in patients whose loss of smell continues longer may develop within the further period. Patients in whom olfactory dysfunction continued for longer than 6 months after COVID-19 reported headache, mental clouding, or both more frequently. This finding was interpreted as cognitive impairment, and headache may be related to more severe olfactory loss.[32] Patients complaining of both dysgeusia and hyposmia during acute illness showed a lower improvement in memory tests than those without.[33] On the other hand, it has been suggested that advanced age and mild subtle cognitive deficits may be factors related to long-term olfactory dysfunction after COVID-19.[34]

In our study, an increase that reflects the recovery of cognitive function was found in the ACE-R and SDMT scores repeated after 6 months in the group of patients who had COVID-19, whether or not accompanied by loss of smell. This result was also considered to indicate the effect of COVID-19 on cognitive function. The recovery of cognitive function based on the checkup examination in both groups with and without loss of smell indicated that loss of smell may not be a factor directly related to the development of cognitive dysfunction. However, it was found that there was no significant recovery after 6 months in cognitive domains including attention, concentration, and speed of information-processing in the group with loss of smell lasting more than 3 months as compared with the group with loss of smell lasting less than 3 months; it was considered that the duration of loss of smell may be an effective factor for the recovery of cognitive functions after 6 months. From another perspective, our results indicated that cognitive function may have been affected in patients with COVID-19, but this effect may be recoverable, especially in patients with short-term loss of smell. Factors such as repair or compensation mechanisms are likely to be intact in patients with COVID-19, or that genetic or other predisposing factors do not exist in these patients, as in the other neurodegenerative diseases, may clarify the fact that the course of the damage leading to COVID-19-related cognitive dysfunction was not progressive and could be recovered.

The results of studies investigating the relationship between COVID-19 and cognitive dysfunction vary. Although no difference was found in terms of cognitive test results 4 months after SARS-CoV-2 infection in patients with mild-moderate COVID-19 in one study,[35] impairment in at least one cognitive domain was reported after 3 months in 78% of the patients in another study.[36] In a systematic review and meta-analysis, cognitive impairment developed in approximately 1/5 of the patients within 12 weeks or longer following COVID-19.[9] In another systematic review, cognitive deficit was found at a rate of 25%.[5] In studies on COVID-19-related cognitive affection, findings reflecting dysfunction of various cognitive domains, especially processing speed, executive functioning, memory, and attention disorders, were found.[3-5,33,37-40] The results of studies on the course of COVID-19-related cognitive dysfunctions over time also include differences.[5] It was reported that cognitive functions improved over time in certain studies.[33,40] Ongoing, prolonged, or permanent cognitive deficits were also identified.[1,33,41,42]

In our study, although olfactory dysfunction continued for longer than 3 months, it was observed that it recovered in most patients, and olfactory dysfunction persisted 12 months after COVID-19 in only 2 patients. In a 47-year-old female patient, the ACE-R and SDMT scores at the initial examination were significantly lower. The test scores of the second patient, a 19-year-old female, were lower but not as significant as those of the first patient. An increase in the test scores was found in both patients in the second examination after 6 months, but the significant decrease in the test scores of the first patient continued. Different brain areas associated with cognitive functions overlap with the olfactory pathways. The multiregional involvement of olfactory stimuli, including the orbitofrontal cortex, amygdala, and hippocampus, explains the relationship between odor perception and memory formation.[43-45] Various processes such as inflammation, alterations in neurogenesis of peripheral and central structures of the olfactory system, and functional changes in brain structures may explain the link between loss of smell and cognitive impairment, especially in patients with COVID-19-related prolonged olfactory disturbances.[46,47] Poor recovery of cognitive function may also be a sign of more severe derangement in cognitive circuits.

Greater severity of acute illness, duration of symptoms, advanced age, female sex, and preexisting comorbidities are frequently identified risk factors for cognitive affection.[5,9,38,42] In our study, it was determined that any of the factors, including age, gender, educational status, obesity, hypertension, and DM, were not effective on the temporal change in cognitive test results, and the improvement in cognitive functions developed independently of these factors. It was considered that mechanisms related to COVID-19 may play a role in the recovery of cognitive function, as well as in the affectation of cognitive function.

As the clinical severity of COVID-19 worsens, the impact on cognitive function may become more pronounced, with hypoxic brain damage coming into play. Therefore, patients with milder COVID-19 were included in the study to more accurately evaluate the direct effect of COVID-19 on cognition. Patients older than 60 years were not included in our study, considering the possibility of subclinical or mild cognitive impairments and the fact that cognitive impairments can be triggered more easily for various reasons in these patients.

Study Limitations

The evaluation of olfactory dysfunction based on self-reported assessment of the sense of smell, not clinical or electrophysiological tests, was a study limitation. However, this evaluation also made it possible to determine the loss of smell that is directly related to COVID-19. It is possible to detect pre-existing disorders that patients are unaware of using scent tests.

CONCLUSION

Our results indicate that patients with COVID-19 may possibly experience temporary and greatly improved cognitive impairment independent of olfactory dysfunction. Although loss of smell was not found to be associated with cognitive function, the relationship between prolonged and persistent olfactory dysfunction and cognitive impairment is remarkable.

MAIN POINTS

- COVID-19 may affect cognitive functions.
- Cognitive impairment caused by COVID-19 is mostly reversible.
- Olfactory dysfunction is a common symptom in the COVID-19 pandemic.
- Cognitive impairment after COVID-19 may occur with or without olfactory dysfunction.
- The duration of olfactory dysfunction is associated with cognitive impairment.

ETHICS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and with the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (approval number: 116/16, date: 26.07.2021).

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

Authorship Contributions

Surgical and Medical Practices: C.D., F.A.E., A.C.Ü., Concept: C.D., F.A.E., B.G., A.C.Ü., H.G., Design: C.D., B.G., H.G., Data Collection and/or Processing: C.D., F.A.E., A.C.Ü., Analysis and/or Interpretation: C.D., B.G., H.G., Literature Search: C.D., A.C.Ü., H.G., Writing: C.D., B.G., H.G.

DISCLOSURES

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

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RESEARCH ARTICLE

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Effect of Smoking, Alcohol Consumption, and Obesity on Bone Metabolism: A Study on Post-Menopausal North-Cypriot Women

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Abstract

BACKGROUND/AIMS: Obesity and osteoporosis are prevalent and intricate health conditions involving multiple etiological factors. Although obesity is traditionally considered beneficial to bone health, the pathophysiological relationship between obesity and bone health is controversial. This study aimed to evaluate the effect of obesity on osteoporosis in postmenopausal North Cypriot women.

MATERIALS AND METHODS: A total of 241 postmenopausal North Cypriot women were included in the study. The height and weight of the patients were recorded, and the body mass index (BMI) was calculated for each patient. The T-scores and bone mineral density (BMD) of the femoral neck and total femur were recorded. Patients were questioned about their history of oral contraceptive and supportive medication (Ca, bisphosphonates, vitamin D), alcohol consumption, and smoking habits.

RESULTS: The patients' ages were approximately 36-84 years (mean: 61.5±9.11), and their BMI was 16.8 kg/m^2 and 47.4 kg/m^2 (28.55±5.26 kg/m^2). Mean T-scores at the femoral neck and total femur were -1.06±0.96 and -0.86±1.01, respectively. The mean BMDs at the femoral neck and total femur were 0.839±0.115 kg/m^2 and 0.880±0.122, respectively. There was a statistically significant correlation between age and T-score and BMD of the femoral neck and T-score and BMD of the total femur. There was a statistically significant correlation between BMI and the femoral neck T-score and BMD of the femoral neck. There was a statistically significant correlation between BMI and total femur T-score and BMD of the total femur. No statistically significant difference was detected in the mean T-scores and BMD values between the groups regarding the use of oral contraceptive or supportive medication and smoking or alcohol consumption.

CONCLUSION: Our results show that obesity has a positive effect on BMD in postmenopausal North Cypriot women. Further studies with larger patient groups are needed to better understand the impact of obesity on bone health.

Keywords: Obesity, osteoporosis, osteopenia, body mass index

INTRODUCTION

Osteoporosis is a systemic skeletal disease that causes deterioration in the microarchitecture of bone tissue, leading to increased bone fragility.[1] The prevalence of this disease is rising worldwide, with an aging population and prolonged life expectancy.[2,3] The major complication of osteoporosis is insufficiency fractures, which lead to morbidity, mortality, decreased quality of life, and a substantial economic burden on society.

Considering the factors affecting bone metabolism, osteoporosis is simply classified as primary (postmenopausal and age-related) or

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secondary.[4,5] Bone mineral density (BMD) was used to predict fracture risk.[6,7] Age, gender, smoking, alcohol consumption, steroid use, and diseases affecting bone metabolism increase the risk of osteoporotic fractures regardless of BMD.[7-11]

Obesity, which can be referred to as the age epidemic, is defined as the excessive accumulation of fat in the body and is considered a chronic metabolic disease related to both environmental and genetic factors.[2] Body mass index (BMI) is widely used to determine the degree of obesity.[6] Obesity and osteoporosis are potentially preventable and treatable conditions that are often referred to as "silent diseases" because they may not exhibit warning signs until complications arise. Various mechanical, biochemical, and hormonal mechanisms have been proposed to explain the relationship between adipose tissue and bone. In general, evidence suggests that obesity may have a protective effect against postmenopausal osteoporosis.[12-15] However, it is worth noting that there are also studies that report contradictory results.[16-18]

Smoking and alcohol consumption are well-known causes of osteoporosis. There are some direct and indirect pathophysiological mechanisms discussed in the literature to explain the effect of smoking on bone health (inhibitor effect on osteogenesis and angiogenesis, alteration in body weight, alteration in parathyroid hormone, oxidative stress, etc.).[19,20] High alcohol intake is related to increased fracture risk, but there seems to be a threshold effect, as alcohol consumption of 2 units or less per day does not cause an increase in osteoporotic fractures.[10]

In fact, a complex pathophysiological relationship between obesity, smoking, alcohol consumption, and bone that is still not fully understood.

North Cyprus has a unique geographical location with ethnic diversity. To our knowledge, no study has investigated the effects of obesity, smoking habits, and alcohol consumption on BMD in patients living in North Cyprus. In this article, we aimed to investigate the effects of these factors on postmenopausal osteoporosis in North Cypriot women.

MATERIALS AND METHODS

The study was conducted in accordance with the ethical standards of the Near East University Institutional Research Committee, and IRB approval (approval number: 2020/85-1182, date: 26.11.2020) was obtained. Patients provided informed consent regarding the publication of their data.

For this cross-sectional study, a questionnaire was administered to 509 North Cypriot women who were referred for Dual-energy X-ray absorptiometry examinations at the radiology department of our hospital between January 2021 and December 2021. Questionnaires were asked about their menstrual status, the presence of conditions that could contribute to osteoporosis, alcohol consumption and smoking habits, history of oral contraceptive use, and the use of supportive medications such as calcium, bisphosphonates, and vitamin D. Two hundred sixty-eight patients (58 premenopausal patients and 210 post-menopausal patients, those receive anti-osteoporosis treatment or suffering from diseases that may cause secondary osteoporosis) were excluded, and the remaining 241 postmenopausal treatment-naive patients were included in the study (Figure 1). For each patient, their height and weight were documented, and the BMI was computed (kg/m^2). Additionally, T-scores and BMD measurements of the femoral neck and total femur were recorded.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 28 (SPSS, Chicago, IL, USA). Statistical significance was set at $p<0.05$. "Shapiro-Wilk test" was used to determine whether the data had a normal distribution. Because the data showed a normal distribution $p>0.05$), "t-test for independent samples" was used in comparisons between the groups and "Pearson correlation analysis" was used to examine the relationships between variables.

RESULTS

The patients in the study had a wide age range, ranging from 36 to 84 years, with a mean age of 61.5 years [±9.11 standard deviation (SD)]. BMI varied from 16.8 kg/m^2 to 47.4 kg/m^2, with an average BMI of 28.55 kg/m^2 (±5.26 SD).

Among the participants, 63 patients (26%) reported a history of oral contraceptive use, and 56 patients (23.2%) reported being smokers (54 reported to be current smokers, and only 2 of them had a history of smoking). Among the 241 patients, 5 patients reported consuming alcohol more than twice a week (group 1), 9 of them less than twice a week (group 2), and 36 less than once a month (group 3). One hundred and ninety-one patients were non-drinkers (group 4). Because of the low number of patients in groups 1 and 2, with the recommendation of the statistician we worked with, patients were divided into two groups: non-drinkers (n=191, 79.3%, group 4) and drinkers (n=50, 20.7%, groups 1, 2 and 3). Vitamin D levels were recorded in only 105 of the 241 (43%) patients, and the values were approximately 4-110 ng/mL, in a wide range.

The clinical and demographic characteristics of the patients are summarized in Table 1, and the duration of menopause was demonstrated in Figure 1.

The T-scores at the femoral neck were between -2.9 and 3.2 (mean, -1.060.96±). The BMDs at the femoral neck were between 0.617 kg/m^2 and 1.33 kg/m^2 (mean, 0.8390.115±). T scores at the total femur were between -3.3 and 3.2 (mean, -0.861.01±) and BMD at the total femur were between 0.586 kg/m^2 -1.355 kg/m^2 (mean, 0.8800.122±).

A statistically significant negative correlation was observed between age and both the femoral neck T-score and the BMD of the femoral neck ($r=-0.2133$, $p<0.001$ and $r=-0.2568$, $p<0.001$, respectively), as shown in Figure 2. Additionally, there was a weak but statistically significant negative correlation between age and both the total femur T-score and the BMD of the total femur ($r=-0.1359$, $p=0.035$ and $r=-0.148$, $p=0.022$, respectively), as indicated in Figure 3.

There was a statistically significant positive correlation observed between BMI and both the femoral neck T-score ($r=0.2858$, $p<0.001$) and the BMD of the femoral neck ($r=0.2783$, $p<0.001$), as shown in Figure 4. Furthermore, a statistically significant positive correlation was found between BMI and both the total femur T-score ($r=0.4487$, $p<0.001$) and the BMD of the total femur ($r=0.4446$, $p<0.001$), as presented in Figure 5.

No statistically significant differences were observed in the mean T-scores and BMD of the femoral neck and total femur when considering

Table 1. Clinical and demographic characteristics of the patients		
Female, (n)		241
Age (years) (mean ± SD)		36-84 (61.59.11±)
BMI kg/m² (mean ± SD)		16.8-47.4 (28.555.26±)
Smoking cigarette n (%)		56 (23.7)
Consumption of alcohol, n (%)		50 (20.7)
BMD kg/m² (mean ± SD)	T-scores at the femoral neck	0.617-1.33 (0.8390.115±)
	T-scores at the total femur	0.586-1.355 (0.8800.122±)
Oral contraceptive use, n (%)		63 (26)
Supportive medication, n (%)		156(64.7)
SD: Standard deviation, BMD: Bone mineral density, BMI: Body mass index.		

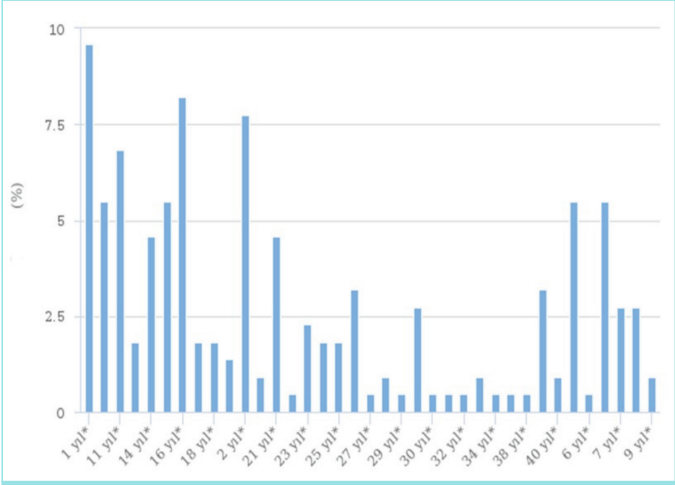

Figure 1. Duration of menopause of the patients.

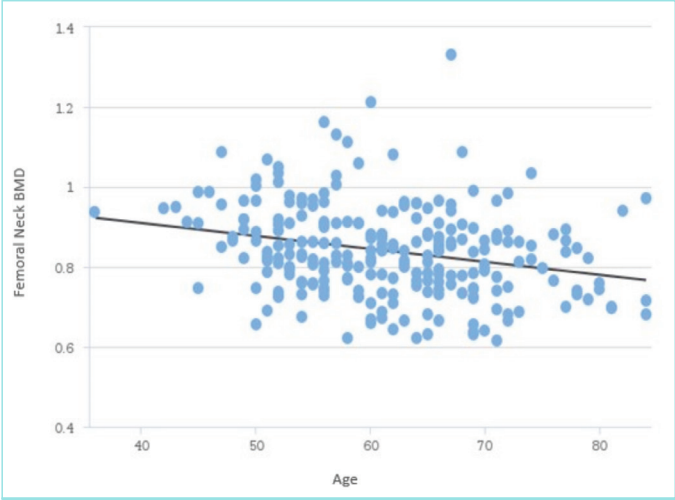

Figure 2. Correlation between age and BMD of femoral neck (kg/m²).

BMD: Bone mineral density.

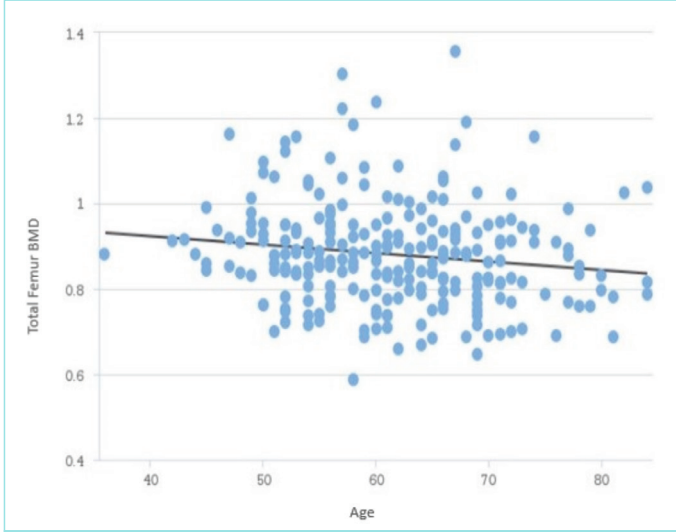

Figure 3. Correlation between age and BMD of total femur (kg/m²).

BMD: Bone mineral density.

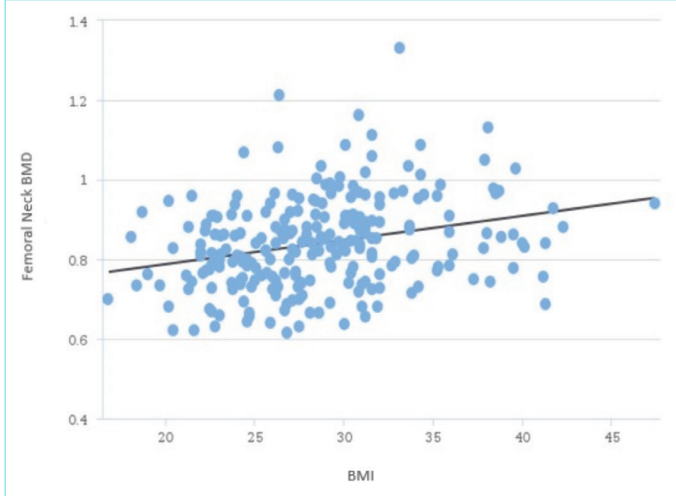

Figure 4. Correlation between BMI (kg/m²) and BMD of the femoral neck (kg/m²).

BMI: Body mass index, BMD: Bone mineral density.

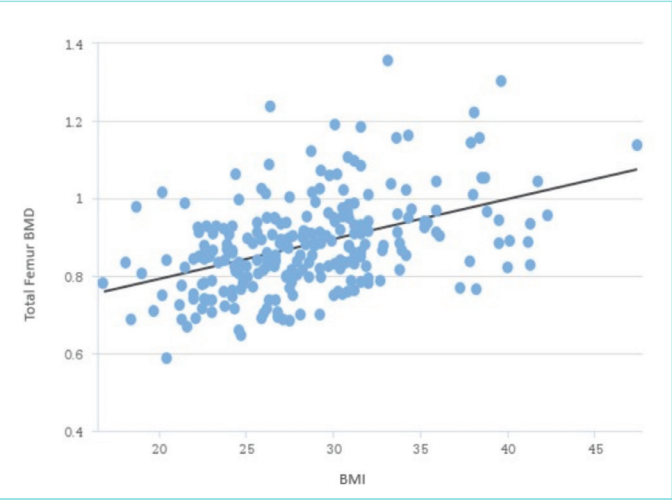

Figure 5. Correlation between BMI (kg/m²) and BMD of total femur (kg/m²).

BMI: Body mass index, BMD: Bone mineral density

the use of oral contraceptives (p=0.051, p=0.052, p=0.079, p=0.080). There were no statistically significant differences in the mean T-scores and BMD of the femoral neck and total femur with smoking (p=0.390, p=0.577, p=0.714, p=0.834) or alcohol consumption (p=0.903, p=0.681, p=0.529, p=0.609).

DISCUSSION

Based on our findings, several conclusions can be drawn regarding the etiology of osteoporosis: 1) Age and osteoporosis: We observed a correlation between older age and a higher prevalence of osteopenia and osteoporosis. This suggests that as women age, they are at an increased risk of developing these conditions. 2) Obesity and osteoporosis: Our study supports the widely accepted idea that obesity has a beneficial effect on osteoporosis. Postmenopausal osteoporosis was found to be less common in women with obesity. This suggests that a higher BMI may offer some protection against the development of osteoporosis in post-menopausal women. 3) Alcohol intake, smoking, and oral contraceptives: Our analysis did not find any significant effects of oral contraceptive use, alcohol intake, or smoking on the development of postmenopausal osteoporosis. This implies that these factors may not be significant contributors to the risk of developing osteoporosis in postmenopausal women, at least in the context of our study.

Consistent with the findings of our study, previous studies have demonstrated a positive effect of higher BMI on BMD in most cases.[2,14,15,21-23] Notably, Zhang and Pu[14] identified a positive relationship between obesity and BMD, while underscoring the importance of maintaining a moderate BMI level (approximately 24.3 kg/m²) in adults over the age of 50 to achieve an optimal balance between BMI and BMD. Additionally, Ma et al.[15] identified a BMI saturation value (approximately 26 kg/m²) for femoral and spinal BMD in all participants aged 50 years and older. Collectively, these findings suggest that a high BMI can have a positive impact on bone density, especially in older adults. However, there may be an upper limit or saturation point beyond which the benefits of a higher BMI on bone density plateau. These insights are valuable for understanding the complex relationship between body composition and bone health in aging populations.

The findings from the meta-analysis by Qiao et al.[2] are consistent with our study results, indicating that adults with obesity tend to exhibit higher BMD levels than individuals with healthy weight. Similarly, a study conducted by Mazocco and Chagas[21] reported that obese women had a lower prevalence of osteopenia and osteoporosis than those who were normal weight or overweight. This suggests the potential protective effect of obesity against bone-related conditions. Additionally, Saarelainen et al.'s[22] long-term study on postmenopausal women supports these observations. Their research indicated that obesity delayed the onset of osteopenia by approximately 5 and 9 years at the spine and femoral neck, respectively, in postmenopausal women. These findings emphasize the significant role of obesity in influencing the timeline of bone health changes, particularly in postmenopausal women.

Indeed, there is an ongoing debate and evolving research surrounding the relationship between increased fat mass (obesity), smoking, and alcohol consumption and the risk of osteoporotic fractures. Nicotine inhibits osteogenesis and angiogenesis. Smoking also has indirect effects on bone health through the loss of appetite, causing alteration of body weight, parathyroid hormone, and increased oxidative stress. Studies have also shown that smokers have a greater risk of hip fractures than non-smokers.[24] High alcohol intake was also shown to be associated with a significant increase in hip fracture risk, but no significant risk was reported at intakes of 2 units and less daily.[10] While some studies have suggested the potential protective effects of high body fat on bone health, recent findings have raised questions about these assumptions.[16-18,25,26] Song et al.[25] showed that BMI can have different effects on various parts of the skeletal system. For instance, a higher BMI was positively associated with lumbar and calcaneal BMD, but it had no significant effect on femoral neck and forearm BMD.[25] Compston et al.[16] indicated that obesity does not necessarily protect against fractures in postmenopausal women. In fact, it increases the risk of ankle and upper leg fractures.[16] Gnudi et al.[26] found that the relationship between BMI and fracture risk varied according to fracture site. For instance, increased BMI was associated with a higher risk of humerus fractures but lower risk of hip fractures. No significant relationship was observed between BMI and wrist or ankle fractures.[26] Although vertebral fractures are generally considered rare in individuals with obesity, some studies, like the one by Pirro et al.[27], have suggested an increased risk, particularly in postmenopausal women. In summary, the impact of obesity on bone health is multifaceted, and the relationship between obesity and fracture risk is not uniform across all bone sites. Obesity does appear to increase the risk of falls, especially in individuals older than 60 years, which can contribute to fractures. Additionally, the fracture pattern varies, with obese individuals experiencing more fractures at certain sites (e.g., ankle, leg, humerus) and fewer at others (e.g., wrist, hip, pelvis). These findings emphasize the need for personalized healthcare and risk assessment when considering the effects of obesity on bone health.[12,27-32]

The controversial findings in the relationship between obesity and osteoporosis can be attributed to a complex interplay of factors. These factors include the multifactorial interaction between bone and adipose tissue, which involves both metabolic and mechanical effects. Additionally, ethnic and cultural differences, social and economic conditions, and environmental factors may all contribute to

the varying associations between obesity and osteoporosis. The World Health Organization (WHO) recommends specific BMI thresholds for defining overweight and obesity, which can vary across populations. In Western populations, the WHO recommends using BMI ≥25 kg/m^2 for the definition of overweight and BMI ≥30 kg/m^2 for obesity.[33] However, for Asian populations, including Asians in North Cyprus, the WHO, in collaboration with the International Association for the Study of Obesity and the International Obesity Task Force, has proposed lower BMI cutoff values. These include 23.0-24.9 kg/m^2 for classifying individuals as overweight and ≥25.0 kg/m^2 for identifying obesity.[34] Variations in the BMI cutoff values used to define overweight and obesity across different ethnic groups can indeed have implications for discussions regarding the relationship between obesity and osteoporosis. It is important to recognize that these differences may impact how researchers and healthcare professionals assess and interpret the association between obesity and bone health in diverse populations. However, it is worth noting that as of now, specific studies addressing the appropriate cutoff values for overweight and obesity in the Middle East, including North Cyprus. The absence of region-specific data highlights the need for further research to better understand how these classifications apply to populations in this geographical region and to assess their impact more accurately on health outcomes like osteoporosis.

Study Limitations

This study has several limitations that should be considered when interpreting the findings. The most significant limitation of this study is the relatively small sample size, which may not be fully representative of the entire population of North Cyprus. As a result, the generalizability of the study's results to the broader population may be limited. Another important limitation of this study was its focus on the BMD values of the femur, with BMD values of the lumbar vertebrae not included in the analysis. Because BMD measurements at different skeletal sites can provide valuable insights into bone health, the omission of lumbar vertebral data represents a limitation. Additionally, the exclusion of men and premenopausal women, as well as its restriction to BMD values of the femur alone, may limit the breadth of the conclusions. The wide sample size is another limitation for the study to draw conclusions. Because of the low number of patients with records of vitamin D values (105 of 241 patients, 43%) comparing the levels of vitamin D, their effect on BMD would not represent the entire study group and was therefore not studied.

In summary, although this study offers valuable insights, it is essential to acknowledge these limitations and consider them when interpreting the results. Future research endeavors with larger and more diverse participant groups, as well as comprehensive BMD measurements, will contribute to a more thorough understanding of the mechanism of osteoporosis. Including a more diverse participant group in terms of sex, menopausal status, and vitamin D values and considering BMD values at both lumbar vertebrae and femur sites would provide a more comprehensive understanding of the relationship between different etiologic factors and osteoporosis.

CONCLUSION

This study is an important milestone as the first research of its kind conducted in postmenopausal North Cypriot women. The study findings revealed a notable trend: as age increased, the prevalence of osteoporosis also increased. In addition, the study observed that obese women had a lower prevalence of osteoporosis. These findings contribute to our understanding of the association between BMI and osteoporosis in this specific population and provide valuable insights into bone health in postmenopausal women in North Cyprus. These conclusions highlight the complex interplay between various factors, including age and BMI, in the development of postmenopausal osteoporosis. Further research and larger studies may provide deeper insights into these relationships.

MAIN POINTS

- Postmenopausal osteoporosis is less common in obese North Cypriot women than in normal-weighted ones.
- Region-specific studies with larger study groups are needed to understand the complex relationship between obesity and osteoporosis.
- Alcohol consumption, smoking, and supportive medication appear to have no effect on postmenopausal osteoporosis development.

ETHICS

Ethics Committee Approval: The study was conducted in accordance with the ethical standards of the Near East University Institutional Research Committee, and IRB approval (approval number: 2020/85-1182, date: 26.11.2020) was obtained.

Informed Consent: Patients provided informed consent regarding the publication of their data.

Authorship Contributions

Surgical and Medical Practices: Y.K., M.T., Concept: Y.K., M.T., Design: Y.K., M.T., Data Collection and/or Processing: Y.K., M.T., Analysis and/or Interpretation: Y.K., M.T., Literature Search: Y.K., M.T., Writing: Y.K., M.T.

DISCLOSURES

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RESEARCH ARTICLE

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Different Perspectives for Determining the Optimal Treatment Modality for Gastroesophageal Reflux Disease: Application of the Fuzzy Technique for Ordering Preference by Similarity to Ideal Solution Method

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Abstract

BACKGROUND/AIMS: Gastroesophageal reflux disease (GERD) has spread worldwide over time, impacting most populations in most nations. Therefore, determining the most effective treatment method for GERD is crucial because the most appropriate treatment option must be selected to reduce the effects of GERD and improve the quality of life of patients. This study aimed to introduce a different perspective for determining the optimal treatment modality for GERD.

MATERIALS AND METHODS: To determine the optimal treatment modality in the treatment of GERD, this study has applied the fuzzy technique for ordering preference by similarity to ideal solution (TOPSIS) method to evaluate antacids, histamine blockers, proton pump inhibitors (PPIs), and prokinetics, which are treatment options for GERD against 15 criteria: cost, availability, dose, frequency, allergy, path, safety, efficacy, age, other health condition, GERD stage, treatment duration, success rate, drug-drug interaction, and drug-food interaction.

RESULTS: The closeness coefficients (Ci) of each treatment alternative were used to determine their rankings. The treatment option with the highest closeness coefficient was considered the best. The ranking shows that PPIs are the best treatment for GERD because they had the highest Ci value of 0.642. The treatment option with the lowest Ci value was antacids, which had a Ci value of 0.33.

CONCLUSION: Implementing the Fuzzy TOPSIS method can guide decision-makers in more systematically evaluating complex decisions and choosing the most appropriate treatment modality. Consequently, it is thought that this study will help clinicians make more informed and scientifically based decisions regarding the treatment of GERD.

Keywords: Fuzzy TOPSIS, gastroesophageal reflux disease, proton pump inhibitors, antacids, treatment

INTRODUCTION

The backward movement of acid from the stomach to the esophagus, which is a tube that links the mouth to the stomach, causes a condition known as gastroesophageal reflux disease (GERD) or chronic acid reflux. The lower esophageal sphincter (LESP) is a valve at the end of the esophagus that, when it is healthy and operating well, should shut when food reaches the stomach. If it is not healthy or is not functioning properly, the valve may not close properly. Regurgitation of stomach acid may be a problem for certain people because the valve does not close adequately when it should. When this occurs, the acid backwash travels back up the esophagus, down the throat, and into the mouth, where it leaves a sour taste.[1]

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As of 2019, 783,95 million individuals all over the world were projected to have suffered from GERD. A total of 77.53% more instances were reported between 1990 and 2019, 74.79% more cases occurred, and 77.19% more years of life were lost as a result of impairment. The age-standardized global incidence rate (ASIR) and the global young mortality rate (ASYR) both increased from 0.05 to 0.06 during the study period. Both rates were at a previous level of 0.06. In 2019, Tropical Latin America dominated the rankings for all three age-standardized illness burden metrics, namely ASPR, ASIR, and ASYR. However, East Asia received the lowest score in the ASPR. In every annual category of GERD prevalence and incidence, as well as in every annual category of young-onset GERD prevalence and incidence, females continuously outnumbered males during the entire period of 1990-2019. There was a correlation between having a higher sociodemographic index and having lower GERD-related Acute Symptom Severity Ratings (ASPR, ASIR, and ASYR) in the year 2019.[2]

Histological alterations in the esophageal mucosa may contribute to the development of a variety of potentially diagnosable illnesses, including Barrett's esophagus, reflux esophagitis, and non-erosive reflux disease.[3]

Symptoms of GERD include asthma, a painful throat, persistent coughing, a constant need to clear one's throat, and unexplained chest discomfort.[2] The frequent and bothersome symptoms of GERD and the complications of this disease, such as inflammation of the esophagus, stricture of the esophagus, ulceration of the esophagus, perforation of the esophagus, metaplasia, and esophageal cancer, have a huge negative impact on the quality of life of patients who suffer from GERD in regards to their overall health.[4]

The very high frequency of GERD and the chronic nature of the condition imply that treatment is very expensive, which is a burden for patients, the people who care for them, and the healthcare system as a whole.[5] Clinical management of GERD affects the lives of many and uses up a great deal of healthcare and social services, thereby making them poorer as their resources go toward the treatment of the disease.[3]

Since GERD has far-reaching negative consequences on patients' quality of life, it is crucial to assess current treatments to create more effective options, which will avoid the waste of resources associated with experimenting with different treatment options. Selection of the optimal treatment modality among different treatment methods requires multi-criteria decision-making (MCDM) method. A thorough decision-making process is highly challenging, particularly when dealing with constantly changing information and circumstances. Making decisions while considering several criteria and using multiple decision-makers (DMs) is known as MCDM. The technique for ordering preference by similarity to ideal solution (TOPSIS) is one of the most popular techniques, which was proposed by Hwang and Yoon.[6] It has been widely embraced in several use cases because of its ease of use, flexibility, computing efficiency, and broad mathematical notion. Fuzzy TOPSIS, which is the conventional TOPSIS method's extension to Fuzzy logic, has also been effectively applied in several fields.[7-11]

This study aimed to propose a Fuzzy TOPSIS-based method for selecting the optimal treatment modality among different treatment options for GERD. In the existing literature, the optimal treatment method for GERD has not yet been considered an MCDM problem from this perspective. Thus, determining the optimal treatment modality for GERD will significantly contribute to the literature.

Alternatives to Gastroesophageal Reflux Disease Treatment

Several modalities are available for GERD treatment and these modalities include the following: medications such as antacids, histamine blockers, proton pump inhibitors (PPI), and prokinetic medicines.[12]

Antacids

Given that they have been on the market for consumers to buy for a sizeable length of time, antacids are among the pharmaceutical families that have the largest market share. The widespread use of antacids in the 19th century probably helped those who suffered from stomach troubles find some relief. Antacids are a kind of drug that is used to alleviate hyperacidity by mixing magnesium, calcium, or aluminum salts[13] that elevate the alkalinity of the stomach, neutralize acidity, limit the synthesis of pepsin, and induce the release of bicarbonate and prostaglandin[14] that help reduce the symptoms of GERD. Antacids perform their job by neutralizing acid produced in the stomach, which prevents acid from moving into the duodenum. Pylorospasm, pain, acid-chyme digestion, and corrosion are only a few of the many ailments that an antacid can help. Although the mechanism of action of all antacids includes the binding of hydrogen ions to the stomach, the effectiveness of an antacid may depend on the specific salts used in its manufacturing.

Histamine Blockers

The two main types of anti-ulcer drugs are H2 receptor blockers and H2 receptor antagonists (H2RAs). Both terms refer to the same group of medications.[15] H2RAs prevent the natural ligand histamine from binding to and activating the histamine H2 receptors present in the gastric parietal cells; thus, they are responsible for the reduction in acid production in the stomach. As a result, H2 blockers play the role of an adversary in a context involving competition. In response to food, the stomach enterochromaffin-like cells generate histamine, which binds to histamine H2 receptors in parietal cells and stimulates an increase in acid production. The activation of the enzyme adenylate cyclase results in an increase in the amount of cellular cAMP, which in turn drives the formation of further stomach acid. An enzyme known as protein kinase A (PKA) is stimulated by cAMP. PKA phosphorylates H+/K+ ATPase transporters, which helps them move to the plasma membrane where they can perform their work. There is a greater potential for enhanced acid secretion from parietal cells as a result of a higher concentration of H+/K+ ATPase transporters in the plasma membranes of these cells. Blocking histamine receptors is how H2RAs work to prevent histamine from stimulating acid generation by parietal cells. Therefore, the amount of acid produced in the stomach as a reaction to histamine is decreased.[16] It only takes 60 min for H2RAs to start functioning in the digestive system, and they continue doing so for 4-10 h, making them ideal for the ad hoc treatment of symptoms that only occur occasionally. The anti-acidity effects of H2RAs are reliable and consistent across the board.[17]

Proton Pump Inhibitors

PPIs, also known as proton-pump inhibitors, are a type of medication that is often prescribed to patients with acid-related conditions. In the production of PPIs, the benzimidazole molecule serves as the jumping-

off point.[18] PIs are beneficial because they reduce the amount of acid produced in the stomach. After being absorbed by the body in the top portion of the small intestine, these medications have an effect on parietal cells in the stomach. In parietal cells, PPIs inhibit the activity of the proton-pumping enzyme H+/K+ ATPase. The production of stomach acid is completed with the help of this enzyme, which is the final stage of the process. PPIs are intriguing substances because they are inactive prodrugs. The acidic secretory canaliculi of parietal cells need to cleave PPI to have an impact. They become active as a result of this operation. In the liver, cytochrome P450 enzymes are responsible for PPI breakdown. Although various P450 enzymes are required for the breakdown of different PPIs, CYP2C19 is by far the most important of these enzymes. PPIs, are among the most efficient medications for lowering the production rate of stomach acid.[19,20]

Prokinetic Agents

Pressure in the LESP, is raised by Prokinetics. They also accelerate the rate at which the stomach empties and promote esophageal peristalsis. Some examples are agonists of the GABA-B receptor, dopamine receptor, and agonists for the 5-hydroxytryptamine (5-HT) receptor. The stimulation of the release of acetylcholine from parasympathetic nerve roots is the mechanism by which 5-HT receptor agonists encourage bowel movement and emptying of the stomach.[21,22]

MATERIALS AND METHODS

This study was approved by the Near East University Scientific Research Ethics Committee (approval number: 2023/117-1779, date: 26.10.2023).

This research uses the Fuzzy TOPSIS, which is a well-known method for resolving MCDM issues. Through literature review and consultation with experienced doctors and pharmacists, the study identified 15 criteria that are essential for administering treatments to evaluate the 4 treatment alternatives for GERD, namely, acidic agents, histamine blockers, PPIs, and prokinetic agents. According to expert opinions, cost, availability, dose, frequency, allergy, path, safety, efficacy, age, other health conditions, GERD stage, treatment duration, success rate, drug-drug interaction, and drug-food interaction have been determined as criteria, as shown in Table 1. The treatment alternatives were evaluated against those 15 criteria by three experts: One gastroenterologist and two final-year PhD students in the pharmacy department. Each expert independently evaluates and ranks the criteria in their unique way because they are knowledgeable about the subject matter and consider the relative significance of each alternative and the criteria. For each criterion, the weights allocated by each expert were combined to create a single set. A typical approach in the Fuzzy TOPSIS method is to find the average of the weights assigned by experts.

TOPSIS Idea

The TOPSIS method simplifies the identification of solutions that match criteria by assuming that the utility of each criterion tends to increase or decrease monotonically. Possible suboptimal solutions are proposed, and their Euclidean distance from the best solution is calculated. We can rank alternatives by comparing their relative distances and see how they stack up against one another. Like the ELECTRE technique, In the first step of the TOPSIS approach, the dimensions of the criteria are transformed into non-dimensional criteria.[23] By decreasing the time required to reach both positive and negative optimal solutions, TOPSIS may help users choose the best course of action (NIS). This method ranks criteria and attains peak performance in MCDM. The Fuzzy TOPSIS assessment technique was used to evaluate all qualities by area.[24]

Fuzzy Theory

In mathematics, a fuzzy set can be used as a helpful tool for dealing with ambiguous or erroneous information. The classic set theory approach can be expanded by considering an element's partial membership in a set. In contrast to the binary nature of classical set theory, which holds that an item is either a part of a set or not, fuzzy set theory holds that the degree of membership in a set may vary from 0 to 1, with 0 being the least likely and 1 being the most likely. An element's membership level in a set can have values ranging from 0 (totally not a member) to 1 (totally a member). The membership function assigns a membership degree to an element based on the characteristics of the element.[25]

Table 1. Treatment alternatives and criteria for GERD treatment

Decision makers	Treatment alternatives	Symbol	Criteria
Decision-maker 1 Decision-maker 2 Decision-maker 3	Antacids Histamine blockers Proton pump inhibitors Prokinetic agents	C1	Cost
		C2	Availability
		C3	Dose
		C4	Frequency
		C5	Allergy
		C6	Path
		C7	Safety
		C8	Efficacy
		C9	Age
		C10	Other health conditions
		C11	GERD stage
		C12	Treatment duration
		C13	Success rate
		C14	Drug-drug interaction
		C15	Drug-food interaction

GERD: Gastroesophageal reflux disease.

Fuzzy sets are useful in many areas, such as artificial intelligence, control systems, pattern recognition, and decision-making. This method works effectively with complex and unpredictable systems where it is difficult to obtain reliable data and draw firm conclusions.[26]

Fuzzy TOPSIS

Popular MCDM approaches that use fuzzy set theory to cope with uncertainty and imprecision include the Fuzzy TOPSIS.[25] In 1981, Hwang and Yoon[6] devised a method for selecting the best choice from a group of possibilities. The method involves calculating the distance between each option and the ideal and anti-ideal solutions to determine which option is the best.[27] The characteristics of the most beneficial options are represented by the ideal solution, while the characteristics that are least desired are represented by the anti-ideal solution.[28]

The proposed method goes beyond the traditional TOPSIS approach for managing ambiguities and imprecise data by introducing Fuzzy logic into the decision-making process. Fuzzy logic is a type of artificial intelligence. When ranking alternative solutions, the traditional TOPSIS method considers both the distance from the negative ideal solution and the total number of possibilities. In terms of the positive ideal solution, each criterion is represented by its highest possible potential value. On the other hand, when identifying the negative ideal solution, each criterion is represented by its lowest possible potential value. The use of fuzzy sets in Fuzzy TOPSIS allows for the consideration of uncertainty and ambiguity in both the decision criteria and probable solutions.[6] By comparing how close a solution is to an ideal solution to how far away it is from an ideal negative solution, the classic TOPSIS method assigns a rating to each possible solution. Each criterion value is maximized in the positive ideal solution and minimized in the negative ideal solution. The perfect solution would maximize all of the criterion values. The use of fuzzy sets in Fuzzy TOPSIS allows for the consideration of uncertainty and ambiguity in both the decision criteria and probable solutions.[29] The following steps are applicable to the Fuzzy TOPSIS:

Step 1: Identify various alternatives and criteria: As the starting point for applying the Fuzzy TOPSIS techniques, you must identify the various alternatives and criteria to be used. In this study, 4 alternative treatments for GERD were identified. The treatment alternatives were evaluated against 15 criteria: cost, availability, dose, frequency, allergy, path, safety, efficacy, age, other health conditions, GERD stage, treatment duration, success rate, drug-drug interaction, and drug-food interaction.

Step 2: Establish/form the decision matrix: In the first step, a direct-relation fuzzy matrix is created. In this study, a pairwise comparison of the 3 DMs was conducted. The direct connection matrix is generated by taking the arithmetic mean of the 3 experts' opinions. Before turning into fuzzy integers, the weights were expressed using linguistic variables as part of the Fuzzy TOPSIS technique. After this, the weights are then converted. The preferences of those in charge of making decisions might be reflected in the weights, which could be expressed in the form of linguistic variables. Table 2 shows the Fuzzy scale used in this study.

Step 3: Normalize the decision matrix: Once the criteria and weights were established, the data for each treatment choice were transformed to fit a comparable scale. This goal was achieved using either a linear or non-linear transform. As demonstrated in the following connection, it is possible to construct a normalized choice matrix by making use of both positive and negative ideal solutions:

$$\tilde{r}_{ij} = \left(\frac{a_{ij}}{c_j^*}, \frac{b_{ij}}{c_j^*}, \frac{c_{ij}}{c_j^*}\right) \; ; \; c_j^* = max_i \, c_{ij} \; ; \textit{Positive ideal solution} \tag{1}$$

$$\tilde{r}_{ij} = \left(\frac{a_j^-}{c_{ij}}, \frac{a_j^-}{b_{ij}}, \frac{a_j^-}{a_{ij}}\right) \; ; \; a_j^- = min_i \, a_{ij} \; ; \textit{Negative ideal solution} \tag{2}$$

Step 4: Calculate weighted normalized decision matrix: The weighted normalized decision matrix can be obtained by multiplying the exact weight value for each parameter in the normalized fuzzy decision matrix. The given weights are the weighted normalized matrix. Here, are the steps used for its computation:

$$\tilde{v}_{ij} = \tilde{r}_{ij} . \tilde{w}_{ij} \tag{3}$$

where $\tilde{w}_{ij}$ represents the weight of criterion c_j.

Step 5: Compute the positive and negative ideal solutions (FPIS) and Negative Ideal Solution (FNIS): The FPIS and FNIS of the alternatives are respectively described as follows:

$$A^* = \{\tilde{v}_1^*, \tilde{v}_2^*, \ldots, \tilde{v}_n^*\} = \left\{\left(\max_j v_{ij} \,|i \in L\right), \left(\min_j v_{ij} \,|i \in K\right)\right\} \tag{4}$$

$$A^- = \{\tilde{v}_1^-, \tilde{v}_2^-, \ldots, \tilde{v}_n^-\} = \left\{\left(\min_j v_{ij} \,|i \in L\right), \left(\max_j v_{ij} \,|i \in K\right)\right\} \tag{5}$$

Where $\tilde{v}_i^*$ is the maximum value of i and $\tilde{v}_1^-$ is the minimum value of i for all alternatives. The positive and negative ideal solutions are represented by L and K, respectively.

Step 6: Calculate the separation measures: The separation between each alternative and FPIS, and the separation between each alternative and FNIS are respectively obtained as follows:

$$S_i^* = \sum_{j=1}^n d(\tilde{v}_{ij}, \tilde{v}_j^*) \qquad i=1,2,\ldots,m \tag{6}$$

$$S_i^- = \sum_{j=1}^n d(\tilde{v}_{ij}, \tilde{v}_j^-) \qquad i=1,2,\ldots,m \tag{7}$$

Here, d is the distance between two fuzzy numbers obtained as follows when two triangular fuzzy numbers (a_1, b_1, c_1) and (a_2, b_2, c_2):

$$d_v(\tilde{M}_1, \tilde{M}_2) = \sqrt{\frac{1}{3}[(a_1 - a_2)^2 + (b_1 - b_2)^2 + (c_1 - c_2)^2]} \tag{8}$$

where $d(\tilde{v}_{ij}, \tilde{v}_j^*)$ and $d(\tilde{v}_{ij}, \tilde{v}_j^-)$ represent crisp numbers.

Step 7: Compute the closeness coefficient (C_i) and rank the alternatives: The closeness coefficient (C_i) of each alternative is obtained by the following formula:

$$C_i = \frac{S_i^-}{S_i^+ + S_i^-} \tag{9}$$

Table 2. Fuzzy scale

Code	Linguistic terms	L	M	U
1	Very low	1	1	3
2	Low	1	3	5
3	Medium	3	5	7
4	High	5	7	9
5	Very high	7	9	9

Table 3. Decision matrix

	Cost	Availability	Dose	Frequency	Allergy	Path	Safety	Efficacy	Age	Other health conditions	GERD stage	Treatment duration	Success rate	Drug-drug interaction	Drug-food interaction
Antacids	(1,000, 1,000, 3,000)	(5,667, 7,667, 9,000)	(4,333, 6,333, 8,333)	(5,000, 7,000, 8,333)	(1,000, 1,667, 3,667)	(1,000, 1,667, 3,667)	(4,333, 6,333, 8,333)	(2,333, 4,333, 6,333)	(2,333, 3,667, 5,667)	(1,667, 3,667, 5,667)	(1,000, 1,000, 3,000)	(1,000, 1,667, 3,667)	(1,000, 2,333, 4,333)	(4,333, 6,333, 8,333)	(3,667, 5,667, 7,667)
Histamine blockers	(1,000, 3,000, 5,000)	(4,333, 6,333, 8,333)	(4,333, 6,333, 7,667)	(1,667, 3,667, 5,667)	(1,000, 2,333, 4,333)	(2,333, 4,333, 6,333)	(3,667, 5,667, 7,667)	(2,333, 4,333, 6,333)	(2,333, 4,333, 6,333)	(3,667, 5,667, 7,667)	(1,000, 2,333, 4,333)	(1,000, 1,000, 3,000)	(1,667, 3,667, 5,667)	(4,333, 6,333, 8,333)	(5,000, 7,000, 8,333)
Proton pump inhibitors	(2,333, 4,333, 6,333)	(5,667, 7,667, 9,000)	(1,667, 3,667, 5,667)	(1,000, 3,000, 5,000)	(1,000, 1,667, 3,667)	(1,000, 3,000, 5,000)	(6,333, 8,333, 9,000)	(4,333, 6,333, 8,333)	(1,667, 3,667, 5,667)	(3,667, 5,667, 7,667)	(4,333, 6,333, 8,333)	(1,667, 3,667, 5,667)	(6,333, 8,333, 9,000)	(5,667, 7,667, 9,000)	(5,667, 7,667, 9,000)
Prokinetic agents	(5,000, 7,000, 9,000)	(1,000, 3,000, 5,000)	(1,000, 1,667, 3,667)	(1,000, 1,667, 3,667)	(4,333, 6,333, 8,333)	(2,333, 4,333, 6,333)	(1,667, 3,667, 5,667)	(2,333, 4,333, 6,333)	(5,667, 7,667, 8,333)	(5,667, 7,667, 9,000)	(1,000, 3,000, 5,000)	(1,000, 3,000, 5,000)	(3,000, 5,000, 7,000)	(2,333, 4,333, 6,333)	(5,000, 7,000, 9,000)

GERD: Gastroesophageal reflux disease.

Table 4. Normalized decision matrix

	Cost	Availability	Dose	Frequency	Allergy	Path	Safety	Efficacy	Age	Other health conditions	GERD stage	Treatment duration	Success rate	Drug-drug interaction	Drug-food interaction
Antacids	(0.111, 0.111, 0.333)	(0.630, 0.852, 1,000)	(0.520, 0.760, 1,000)	(0.600, 0.840, 1,000)	(0.120, 0.200, 0.440)	(0.158, 0.263, 0.579)	(0.481, 0.704, 0.926)	(0.280, 0.520, 0.760)	(0.280, 0.440, 0.680)	(0.185, 0.407, 0.630)	(0.120, 0.120, 0.360)	(0.176, 0.294, 0.647)	(0.111, 0.259, 0.481)	(0.481, 0.704, 0.926)	(0.407, 0.630, 0.852)
Histamine blockers	(0.111, 0.333, 0.556)	(0.481, 0.704, 0.926)	(0.520, 0.760, 0.920)	(0.200, 0.440, 0.680)	(0.120, 0.280, 0.520)	(0.368, 0.684, 1,000)	(0.407, 0.630, 0.852)	(0.280, 0.520, 0.760)	(0.280, 0.520, 0.760)	(0.407, 0.630, 0.852)	(0.120, 0.280, 0.520)	(0.176, 0.176, 0.529)	(0.185, 0.407, 0.630)	(0.481, 0.704, 0.926)	(0.556, 0.778, 0.926)
Proton pump inhibitors	(0.259, 0.481, 0.704)	(0.630, 0.852, 1,000)	(0.200, 0.440, 0.680)	(0.120, 0.360, 0.600)	(0.120, 0.200, 0.440)	(0.158, 0.474, 0.790)	(0.704, 0.926, 1,000)	(0.520, 0.760, 1,000)	(0.200, 0.440, 0.680)	(0.407, 0.630, 0.852)	(0.520, 0.760, 1,000)	(0.294, 0.647, 1,000)	(0.704, 0.926, 1,000)	(0.630, 0.852, 1,000)	(0.630, 0.852, 1,000)
Prokinetic agents	(0.556, 0.778, 1,000)	(0.111, 0.333, 0.556)	(0.120, 0.200, 0.440)	(0.120, 0.200, 0.440)	(0.520, 0.760, 1,000)	(0.368, 0.684, 1,000)	(0.185, 0.407, 0.630)	(0.280, 0.520, 0.760)	(0.680, 0.920, 1,000)	(0.630, 0.852, 1,000)	(0.120, 0.360, 0.600)	(0.176, 0.529, 0.882)	(0.333, 0.556, 0.778)	(0.259, 0.481, 0.704)	(0.556, 0.778, 1,000)

GERD: Gastroesophageal reflux disease.

Table 5. Weighted normalized decision matrix

	Cost	Availability	Dose	Frequency	Allergy	Path	Safety	Efficacy	Age	Other health conditions	GERD stage	Treatment duration	Success rate	Drug-drug interaction	Drug- food interaction
Antacids	(0.007, 0.007, 0.022)	(0.042, 0.057, 0.067)	(0.035, 0.051, 0.067)	(0.040, 0.056, 0.067)	(0.008, 0.013, 0.029)	(0.011, 0.018, 0.039)	(0.032, 0.047, 0.062)	(0.019, 0.035, 0.051)	(0.019, 0.029, 0.046)	(0.012, 0.027, 0.042)	(0.008, 0.008, 0.024)	(0.012, 0.020, 0.043)	(0.007, 0.017, 0.032)	(0.032, 0.047, 0.062)	(0.027, 0.042, 0.057)
Histamine blockers	(0.007, 0.022, 0.037)	(0.032, 0.047, 0.062)	(0.035, 0.051, 0.062)	(0.013, 0.029, 0.046)	(0.008, 0.019, 0.035)	(0.025, 0.046, 0.067)	(0.027, 0.042, 0.057)	(0.019, 0.035, 0.051)	(0.019, 0.035, 0.051)	(0.027, 0.042, 0.057)	(0.008, 0.019, 0.035)	(0.012, 0.012, 0.035)	(0.012, 0.027, 0.042)	(0.032, 0.047, 0.062)	(0.037, 0.052, 0.062)
Proton pump inhibitors	(0.017, 0.032, 0.047)	(0.042, 0.057, 0.067)	(0.013, 0.029, 0.046)	(0.008, 0.024, 0.040)	(0.008, 0.013, 0.029)	(0.011, 0.032, 0.053)	(0.047, 0.062, 0.067)	(0.035, 0.051, 0.067)	(0.013, 0.029, 0.046)	(0.027, 0.042, 0.057)	(0.035, 0.051, 0.067)	(0.020, 0.043, 0.067)	(0.047, 0.062, 0.067)	(0.042, 0.057, 0.067)	(0.042, 0.057, 0.067)
Prokinetic agents	(0.037, 0.052, 0.067)	(0.007, 0.022, 0.037)	(0.008, 0.013, 0.029)	(0.008, 0.013, 0.029)	(0.035, 0.051, 0.067)	(0.025, 0.046, 0.067)	(0.012, 0.027, 0.042)	(0.019, 0.035, 0.051)	(0.046, 0.062, 0.067)	(0.042, 0.057, 0.067)	(0.008, 0.024, 0.040)	(0.012, 0.035, 0.059)	(0.022, 0.037, 0.052)	(0.017, 0.032, 0.047)	(0.037, 0.052, 0.067)

GERD: Gastroesophageal reflux disease.

The optimal choice was closest to the FPIS and most distant from the FNIS. The closeness coefficients for each treatment alternative were used to determine their rankings. The treatment option with the greatest closeness coefficient was considered the best.

RESULTS

By applying the Fuzzy TOPSIS method, the alternatives are evaluated in terms of various criteria, and the model results are shown step by step as follows:

Step 2: Form a decision matrix.

Fifteen criteria and 4 alternatives have been evaluated (ranked) using the Fuzzy TOPSIS method. The evaluation was conducted with three decision makers. The matrix below shows the arithmetic means of all of the 3 decision makers, as shown in Table 3.

Step 3: Form a normalized decision matrix.

Based on the positive and negative ideal solutions, the normalized decision matrix presented in Table 4 was calculated from equations 1 and 2.

Step 4: Weighted normalized decision matrix.

Based on the different weights of each criterion, the weighted normalized decision matrix presented in Table 5 was calculated using equation 3.

Step 5: Define the fuzzy positive ideal solution (FPIS, A*) and the fuzzy negative ideal solution ($FNIS, A^{-}$).

The FPIS and FNIS of the alternatives presented in Table 6 were computed from equations 4 and 5.

Step 6: Calculate the distance between each alternative and the FPIS and the distance between each alternative and the FNIS.

The distances between each alternative and the FPIS and the distances between each alternative and the FNIS were computed from equations 6, 7, and 8, as shown in Table 7.

Table 6. Positive and negative ideal solutions

	Positive ideal	Negative ideal
Cost	(0.037, 0.052, 0.067)	(0.007, 0.007, 0.022)
Availability	(0.042, 0.057, 0.067)	(0.007, 0.022, 0.037)
Dose	(0.035, 0.051, 0.067)	(0.008, 0.013, 0.029)
Frequency	(0.040, 0.056, 0.067)	(0.008, 0.013, 0.029)
Allergy	(0.035, 0.051, 0.067)	(0.008, 0.013, 0.029)
Path	(0.025, 0.046, 0.067)	(0.011, 0.018, 0.039)
Safety	(0.047, 0.062, 0.067)	(0.012, 0.027, 0.042)
Efficacy	(0.035, 0.051, 0.067)	(0.019, 0.035, 0.051)
Age	(0.046, 0.062, 0.067)	(0.013, 0.029, 0.046)
Other health conditions	(0.042, 0.057, 0.067)	(0.012, 0.027, 0.042)
GERD stage	(0.035, 0.051, 0.067)	(0.008, 0.008, 0.024)
Treatment duration	(0.020, 0.043, 0.067)	(0.012, 0.012, 0.035)
Success rate	(0.047, 0.062, 0.067)	(0.007, 0.017, 0.032)
Drug-drug interaction	(0.042, 0.057, 0.067)	(0.017, 0.032, 0.047)
Drug-food interaction	(0.042, 0.057, 0.067)	(0.027, 0.042, 0.057)

GERD: Gastroesophageal reflux disease.

Step 7: Compute the closeness coefficient (C_i) and rank alternatives.

The closeness coefficient and C_i of each alternative were obtained from equation 9. The optimal candidate is nearest to the FPIS and most distant from the FNIS. The closeness coefficients of each alternative and their ranking order are presented in Table 8. Based on the implemented method's results, it was observed that PPIs are the best treatment for GERD because they had the highest C_i value of 0.642, as presented in Figure 1. The treatment option with the lowest C_i value was antacids, which had a C_i value of 0.33.

DISCUSSION

Fuzzy TOPSIS, a MCDM approach, was used to assess four treatment alternatives for GERD. After the evaluation of the GERD treatment alternatives by three experts, the ranking showed that PPIs were the number one treatment alternative for GERD, next is prokinetic agents and the least treatment alternative was anticacids. In a study conducted by Gashi et al.[30], to determine whether or not PPIs helped patients with erosive reflux disease by reducing their symptoms and promoting endoscopic repair. This prospective study included 380 individuals with a history of primary symptoms of erosive reflux. The heartburn system score and regurgitation score were used to assess symptoms before and during PPI treatment throughout the three-month period. Approximately 95% of patients had heartburn, 90% had regurgitation, and 70% had epigastric discomfort before PPI treatment. Pyrosis and regurgitation were quantitatively measured in all patients. Patients treated with PPIs showed improvements ranging from 90% to 20% in regurgitation, 70% to 10% in epigastric discomfort, and 95% to 25% in pyrosis. Complete recovery from erosive oesophagitis was observed in 71.67% of patients, with minimal progression observed in 1.05%. Patients with erosive reflux disease treated with PPIs exhibited significant improvement in symptoms and mucosal healing three months after therapy initiation.

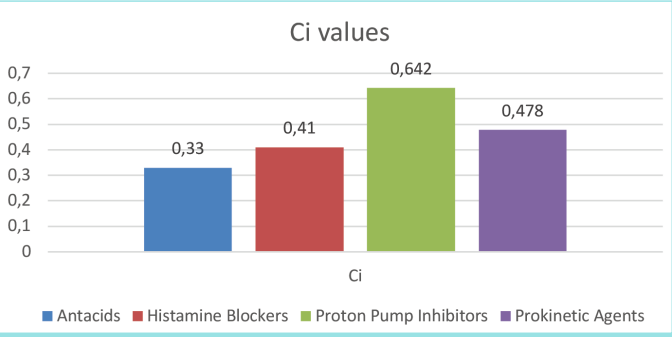

Figure 1. Graph of closeness coefficient values.

Table 7. Distance values of FPIS and FNIS

	Distance from positive ideal	Distance from the negative ideal
Antacids	0.303	0.15
Histamine blockers	0.27	0.188
Proton pump inhibitors	0.163	0.292
Prokinetic agents	0.237	0.217

FPIS: Fuzzy positive ideal solutions, FNIS: Fuzzy negative ideal solutions.

Table 8. Closeness coefficient values of the treatments

	C_i	Rank
Antacids	0.33	4
Histamine blockers	0.41	3
Proton pump inhibitors	0.642	1
Prokinetic agents	0.478	2

According to experts, the 15 criteria used in the study, cost, availability, dose, frequency, allergy, path, safety, efficacy, age, other health conditions, GERD stage, treatment duration, success rate, drug-drug interaction, and drug-food interaction, are very important factors when determining which treatment is suitable for people suffering from GERD. These factors should be considered because they influence the outcome of patient treatment. For example, cost ensures that treatment is accessible and sustainable, while availability ensures that treatment begins and continues on schedule. The correct dose and appropriate dosage increase drug effectiveness and patient compliance. Considering allergies and the path through which the medication is taken, patients do not encounter unfavorable responses and can conveniently consume the medication. Allergy and safety factors may also help prevent possible side effects and complications, while efficacy determines the success of the drug in relieving GERD symptoms. The age criterion is also an important criterion to ensure the suitability of the drug for individual patient profiles. On the other hand, considering other health conditions when choosing treatment for GERD is vital for managing drug interactions and side effects. Although the stage of the disease and duration of treatment also affect the effectiveness and success rate of the treatment plan, drug-drug, and drug-food interactions play an important role in maintaining the integrity of the treatment and the general health of the patient. In short, each criterion used in the study and evaluated by experts is very important.

Castell et al.[31], in their article entitled "Erosive Esophagitis: The Efficacy and Safety of Lansoprazole", a comparison of omeprazole 20 mg, omeprazole 10 mg, omeprazole 5 mg, and placebo was performed with a total of 188 patients with endoscopically confirmed erosive reflux esophagitis who were randomly assigned to receive either lansoprazole 30 mg (n=422), lansoprazole 15 mg (n=218), omeprazole 20 mg (n=431), or placebo (n=213) once daily for 8 weeks. Endoscopic assessments of healing were performed at 2, 4, 6, and 8 weeks. For lansoprazole 30 mg, the success rates at 2, 4, 6, and 8 weeks were 65.3%, 83.3%, 89.4%, and 90.0%, respectively. All active treatments were more effective than placebo, with lansoprazole 15 mg having a 56.3% success rate, omeprazole 20 mg having an 82.0% success rate, and placebo having a 23.9% success rate.

Study Limitations

As with all studies, this study also has limitations. This study was limited to the criteria used in the evaluation of treatment options for GERD. Additionally, the study was limited to experts who evaluated the criteria used in the study.

CONCLUSION

In this study, the Fuzzy TOPSIS method was implemented to select the optimal treatment modality among different treatment options for GERD. In the existing literature, determining the optimal treatment method for GERD has not yet been considered an MCDM problem. We used 15 criteria to evaluate the 4 treatment alternatives (antacids,

histamine blockers, PPIs, and prokinetic agents) of GERD using the Fuzzy TOPSIS technique. The evaluation was performed by one gastroenterologist and two final-year PhD students in the pharmacy department. According to the results, it has been observed that PPIs are the best treatment for GERD because they have the highest C_i value of 0.642, and the treatment alternative with the lowest C_i value of 0.33 is antacids.

Implementing the Fuzzy TOPSIS method would provide DMs with a useful tool to determine the optimal modality for GERD treatment. This approach would provide a more holistic decision-making process, taking into account multiple criteria when evaluating various treatment options. As a result, it is expected that this study will help clinicians make more informed and scientifically based decisions regarding the treatment of GERD. It is recommended to increase the number of criteria for the implemented Fuzzy TOPSIS method in future studies and to compare this method with other MCDM methods.

MAIN POINTS

- The Fuzzy TOPSIS method was implemented to determine the most appropriate treatment method among various treatment options for GERD.
- Determining the optimal treatment method for GERD, which is an MCDM problem, has never been examined before, and this work is the first to do so.
- Proton pump inhibitors are the best treatment for GERD because they have the highest Ci value of 0.642, and the treatment alternative with the lowest Ci value of 0.33 is antacids.
- This approach would provide clinicians with a more holistic decision-making process by considering multiple criteria when evaluating available treatment options for GERD and is believed to help clinicians make more informed and scientifically based decisions regarding the treatment of GERD.

ETHICS

Ethics Committee Approval: This study was approved by the Near East University Scientific Research Ethics Committee (approval number: 2023/117-1779, date: 26.10.2023).

Informed Consent: Patient consent is not required.

Authorship Contributions

Concept: A.F.T., İ.E., N.S., Design: A.F.T., İ.E., N.S., Data Collection and/or Processing: A.F.T., Analysis and/or Interpretation: A.F.T., İ.E., N.S., Literature Search: A.F.T., İ.E., N.S., Writing: A.F.T., İ.E., N.S.

DISCLOSURES

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

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RESEARCH ARTICLE

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Stroke in Patients with Active COVID-19 Infection: Case Series in a Single Center

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Abstract

BACKGROUND/AIMS: It became evident that severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) not only affects the upper and lower respiratory systems but also all organs expressing angiotensin-converting enzyme-2 receptors, including the central and peripheral nervous systems. In this retrospective study, we aimed to evaluate the characteristics of stroke patients with active SARS-CoV-2 infection.

MATERIALS AND METHODS: This retrospective observational study was conducted at a single center, the central state hospital of the North Cyprus, located in Nicosia. We retrospectively analyzed stroke patients who were also diagnosed with SARS-CoV-2 from January 2020 to April 2022. All patients were hospitalized, and a total of 33 patients with laboratory and radiological or clinical confirmation of SARS-CoV-2 infection were included in the study.

RESULTS: Among the 33 patients, 63.6% were men, and the mean age was 68.9 (SD ±16.4). 81.8% had an ischemic stroke, 6.1% had an ischemic stroke and hemorrhagic transformation, and 3.0% had both ischemic and hemorrhagic stroke and subdural hematoma. Transient ischemic symptoms were observed in 9.1% of patients. Of these patients, 30.3% had hypertension, 24.2% had diabetes, 12.1% had hyperlipidemia, 9.1% had coronary heart disease, and 21.2% had a previous stroke as a comorbidity.

CONCLUSION: In our study, patients had risk factors for stroke, and the severity of SARS-CoV-2 infection was correlated with the severity of clinical symptoms of stroke. In addition, lung involvement during infection.

Keywords: COVID 19, stroke, vaccination

INTRODUCTION

After the outbreak of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic in December 2019, it became evident that the virus not only affected the upper and lower respiratory systems but also affected all organs expressing angiotensin-converting enzyme-2 receptors, including the central and peripheral nervous systems.[1] Neurological complications, such as Guillain-Barré syndrome, encephalopathy, encephalitis, and stroke, are mostly encountered. As far as we know, respiratory viruses is a potential trigger of stroke,[2,3] yet it has been found that SARS-CoV-2 infection has a greater risk, especially for ischemic stroke.[4] Here, we report the stroke types, comorbidities, lung involvement, and vaccination status of 33 hospitalized patients with stroke diagnosed with SARS-CoV-2.

MATERIALS AND METHODS

This retrospective observational study was performed at a single center, the central state hospital of the North Cyprus, located in Nicosia. We retrospectively analyzed stroke patients who were also diagnosed

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with SARS-CoV-2 from January 2020 to April 2022. All patients were hospitalized. SARS-CoV-2 was confirmed as a positive result on high-throughput sequencing or real-time reverse transcription polymerase chain reaction analysis of throat and nose swap specimens. A total of 33 patients with laboratory and radiological or clinical confirmation of SARS-CoV-2 infection were included in the study. Radiological assessments including a computed tomography (CT) scan, of both chest and brain were performed on all patients, although cranial magnetic resonance imaging (MRI) was performed on patients without pacemakers, prosthetic materials, etc. Medical records, radiological reports of chest and brain CT and cranial MRI, data on age, sex, comorbidities [hypertension, diabetes mellitus, cardiac disease, hyperlipidemia, coronary heart disease (CHD), previous stroke etc.], National Institutes of Health Stroke Scale (NIHSS) Bamford scale, Modified Rankin Scale (mRS), admission to intensive care unit (ICU), oxygen treatment requirement, and vaccination status were collected. This study was approved by the Dr. Burhan Nalbantoğlu State Hopital Ethics Committee (approval number: YTK. 1.01 (Ek 11/2022), date: 25.04.2022). Verbal consent was obtained from all patients or from an accompanying relative.

Statistical Analysis

Categorical variables were presented as percentages, and continuous variables as mean ± standard deviation (SD) or median interquartile range. Comparisons of baseline variables were performed using χ^2 test for categorical variables. A value of $p<0.05$ was considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences software version 29.

RESULTS

A total of 33 hospitalized stroke patients with confirmed SARS-CoV-2 infection were included. Their mean age was 68.9 years (SD ±16.4) the youngest being 31 and the oldest being 93 at the time of stroke. Among the 33 patients, 63.6% (n=21) were men. Among all of the patients, 81.8% (n=27) had an ischemic stroke, 6.1% had an ischemic stroke and hemorrhagic transformation (n=2), and 3.0% had both ischemic and hemorrhagic stroke and subdural hematoma (n=1). Transient ischemic symptoms were observed in 9.1% (n=3) of the patients (Table 1). Of these patients, 30.3% had hypertension, 24.2 % had diabetes, 12.1% had hyperlipidemia, 9.1% had CHD, and 21.2% had a previous stroke as a comorbidity. Stroke severity of each patient is evaluated with NIHSS, the scores are further divided into three subgroups as follows; group 1, with an NIHSS of 0-5, group 2 score of 6-15, and group 3, a score of 16-24. Group 1 involved 63.6% (n=21) of the patients. Chest and brain CT scans were performed on all patients while the MRI was performed only on 78.8% (n=27) as the remaining were either not fit for an MRI scan or had other contraindications. Patients were further divided into subgroups according to their Bamford Scale scores: 24.2% (n=8) had a total anterior circulation stroke, 18.2% (n=6) had partial anterior circulation stroke, 21.2% (n=7) had posterior circulation syndrome, and 15.1% (n=5) had lacunar stroke. The remaining patients either had a transient ischemic attack or a combination of previously mentioned stroke types.

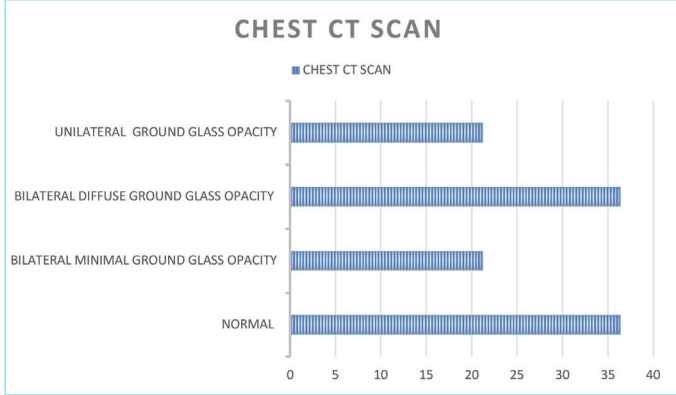
Of all patients, 63.6% (n=21) had thoracal involvement on CT scan. The patients were divided into 3 groups as shown in Graphic 1. 21.2% (n=7) had bilateral minimal ground-glass opacity, whereas 36.4% (n=12) had bilateral diffuse ground-glass opacity. The remaining 21.2% (n=7) only had unilateral involvement on chest CT scan.

As mentioned above, 63.6% of the patients had lung involvement, and 57.6% (n=19) were previously vaccinated. Among the vaccinated, only 36.8% (n=7) needed oxygen treatment and 26.3% (n=5) were admitted to the ICU. Among unvaccinated patients, 57.1% (n=8) required oxygen treatment and were all admitted to the ICU (Graphic 2). Among vaccinated patients, 94.7% (n=18) were discharged from the hospital, there was a 5.3% of exitus while discharge was 71.4% (n=10) and 28.6% of exitus among unvaccinated. A total of 5 patient were discharged as exitus and 4 of them were unvaccinated. These results were obtained using the chi-square test. Among patients with lung involvement, 80% (n=12) were discharged, whereas 88.9% (n=16) among patients who didn't have lung involvement. It has been found that patients with bilateral diffuse lung involvement were all admitted to the ICU; in addition, they had significantly higher mortality rates.

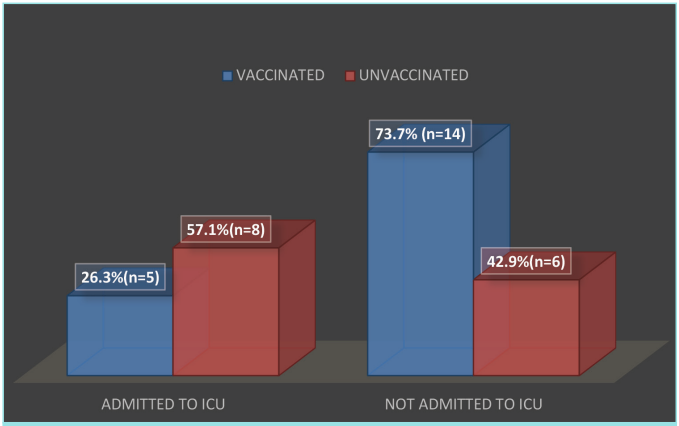
To evaluate disability after stroke, the mRS was used. Patients were divided into 2 subgroups according to their mRS. Group 1 consisted of patients with an mRS of 0-2 and group 2 with mRS 3-6. Only 7.7% (n=1) of patients in group 1 needed ICU, whereas 65% (n=13) in group 2.

Table 1. Demographic characteristics of stroke patients

		Vaccinated	Unvaccinated	Total
Number of patients		19	14	33
Gender	Female	5	7	12
	Male	14	7	21
Age	Mean	63.8 y	75.9 y	
	Median	61 y	76 y	
	Standard deviation	17.2	12.7	
	Minimum age	31 y	50 y	
	Maximum age	92 y	93 y	
Stroke	Ischemic and hemorrhagic transformation	0	2	2
	Ischemic and hemorrhagic transformation and subdural hematoma	1	0	1
	Ischemic	16	11	27
	Transient ischemic attack	2	1	3
	Sum of strokes	**19**	**14**	**33**



Graphic 1. The lung involvement among patients.
CT: Computed tomography



Graphic 2. Vaccination and ICU admission status.
CT: Computed tomography

DISCUSSION

There are reported complications during COVID infection and stroke is one of them.[5] Among several studies, the incidence of ischemic stroke in patients with SARS-CoV-2 was found to be 1.5%, which varied from as low as 0.1% to 6.9% among hospitalized patients.[6] In a recent meta-analysis, patients with severe SARS-CoV-2 infection had a 5-fold increased risk of stroke.[7] Li et al.[8] found in their study that advanced age, severe SARS-CoV-2 infection, a previous history of diabetes, hypertension, or cerebrovascular disease increase the risk of stroke. Another international retrospective study analyzed that patients with COVID-19 and acute ischemic stroke showed increased stroke severity and in addition 51% of patients with COVID-19 and acute ischemic stroke had severe disability at discharge (mRS score 4 vs. 2, $p<0.001$), with increased mortality compared with non-COVID controls.[9] In a recent systematic review including patients with cerebrovascular events in the context of SARS-CoV-2 infection, COVID-19 patients with ischemic stroke had a median NIHSS score of 15, presenting mostly with large vessel occlusion (79.6%), mainly due to either cryptogenic or cardioembolic strokes (44.7% and 21.9%, respectively).[7]

It has been found that there are different mechanisms responsible for stroke. Hypercoagulation, which causes thrombosis, can be responsible for stroke. Trombus formation is also explained by endothelial damage and abnormal blood stasis.[10] During severe infection, a cytokine storm is triggered by inflammation, which causes sepsis and coagulopathy. It has been shown that there are elevated levels of D-dimer and fibrinogen. Zhou et al.[11] and Tang et al.[12] demonstrated increased coagulation markers in their study.

In our study, patients also had risk factors for stroke, and in addition, it has been found that the severity of SARS-CoV-2 infection was correlated with the severity of the clinical symptoms of stroke. In particular, lung involvement during infection affects both mortality and stroke severity. We also found that vaccination status affected the severity of the disease and ICU hospitalization. In our study, all unvaccinated patients were admitted to the ICU, and mortality was higher in unvaccinated patients than in vaccinated patients. Another study found similar results to our study, indicating that patients with acute stroke who were vaccinated had lower NIHSS score at discharge and lower mRS after 3 months. Moreover, they also found that unvaccinated patients had an increased rate of hospitalization for SARS-CoV-2 and a higher mortality rate.[13]

Study Limitations

Although our study has limitations due to the restricted number of patients involved, the findings have been crucial in understanding the association between SARS-CoV-2 infection, vaccination status, and stroke severity.

CONCLUSION

Our study results indicate that SARS-CoV-2 infection particularly the severe form of the disease, has a negative impact on stroke severity.

MAIN POINTS

- Severe SARS-CoV-2 infection and lung involvement has worsened the severity of stroke and in addition the disability score at discharge.
- Although the pathogenesis is complex and risk factors play an important role we have found that co -existing SARS CoV-2 infection increased the duration of hospitalization, and as a result increased the mortality rate of stroke patients.
- According to our study we can also comment that vaccination against SARS CoV-2 has a protective effect particularly to the clinical symptoms of stroke and to admission to the ICU which influences the mortality rate.

ETHICS

Ethics Committee Approval: This study was approved by the Dr. Burhan Nalbantoğlu State Hopital Ethics Committee (approval number: YTK. 1.01 (Ek 11/2022), date: 25.04.2022).

Informed Consent: Verbal consent was obtained from all patients or from an accompanying relative.

Authorship Contributions

Surgical and Medical Practices: B.K., F.S., Concept: B.K., F.S., Design: B.K., F.S., Data Collection and/or Processing: B.K., F.S., S.E.M., Analysis and/or Interpretation: S.E.M., Literature Search: S.E.M., Writing: S.E.M.

DISCLOSURES

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RESEARCH ARTICLE

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Awareness, Attitudes, and Behaviors of Adults About Vaccination in the North Cyprus

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Abstract

BACKGROUND/AIMS: Epidemics of vaccine-preventable diseases (VPDs) are a growing concern worldwide; they have a significant and pervasive impact on individuals, as well as on public health and healthcare systems and the economy. People of all ages are affected by VPDs. Despite awareness and relatively good vaccination rates (VCR) in childhood, adult VCR are insufficient in our country, as in many countries.

MATERIALS AND METHODS: In this manner, we conducted a comprehensive population-level cohort study to evaluate the awareness, attitudes, and behaviors of a population aged over 18 years of age about adulthood vaccination. This is a cross-sectional, survey-based study that was conducted between July 2023 and September 2023 using a structured questionnaire and was carried out in Nicosia, the North Cyprus. A total of 960 surveys were analyzed, of which 67.92% were female and 32.08% were male.

RESULTS: It was determined that there was a statistically significant difference in the rates of adulthood vaccination according to the participants' age groups, gender, place of birth, professions, marital status, health status, and continued medication use ($p<0.05$). Adulthood VCRs of those aged ≤25, females, high-school graduates, and single were low, whereas those of Turkish citizens, healthcare workers, people with comorbidities, and who constantly use medication were high. Furthermore, it was statistically significant that knowledge about recommended adulthood vaccination and the protection provided by those vaccinations was high among those working in healthcare services ($p<0.05$).

CONCLUSION: The awareness level regarding adulthood vaccinations is insufficient. With vaccination, the incidence and mortality of VPDs in adults can be reduced and even reached the point of elimination, as observed for some childhood diseases. Reasons for non-vaccination should be addressed, and effective measures should be determined and taken to overcome these obstacles.

Keywords: Adult, vaccine, vaccination, awareness, North Cyprus

INTRODUCTION

A vaccine is a suspension of weakened viruses, bacteria, or their antigenic fragments that is given to the body primarily to prevent diseases by conferring active and passive immunity.[1]

Immunization with vaccines is one of the best health investments, saving millions of lives each year. It is the main defense against serious, preventable, and sometimes fatal, contagious diseases. It is safe and cost effective.[2-5]

People of all ages are affected by vaccine-preventable diseases (VPDs);[6] however, most vaccination policies target infants and children.[3] More than 100 million children worldwide are vaccinated each year; despite this awareness and relatively good vaccination rates in childhood, adult vaccination rates (VCR) are insufficient.[3-9]

Outbreaks of VPDs are a worldwide growing concern; they have a marked and widespread impact on public health as well as on individuals and thus on healthcare systems and the economy.[10,11] Globalization causes

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the quicker spread of infectious diseases because of the rapid mobility of people across borders.[5] Life expectancy increases logarithmically,[9] as morbidities increase with aging, and adults become more susceptible to infectious diseases; complications and mortality also increase with age too.[6,7,12] The immunity provided by childhood vaccination decreases (immunoscence). We should also take into account low vaccination coverage and the possibility of incomplete vaccination programs in childhood. There is a clear need for developing and implementing protective strategies[13] for aging. The coronavirus disease-2019 (COVID-19) pandemic has highlighted that preventive measures should be lifelong.[6]

The benefits of vaccination exceed those for those who are vaccinated to those who cannot (because of immune deficiencies, age or contraindications, etc.) by reducing the chance of physical contact between infected and vulnerable (herd immunity).[2,14] Furthermore, vaccination not only decreases transmission but also reduces the number of deaths, hospitalizations, incidence among risky groups of the population, functional losses, disabilities, antimicrobial resistance, socioeconomic issues, and the labor force.

Studies generally focus on adults aged over 65 years. Even if it is not enough, VCRs over 65 years have improved; however, younger adults who are at risk remain low. In our country, as in many others, most adults have not been vaccinated against adult VPDs.[6] It is important to understand the reasons for low uptake and barriers to effective vaccination, and awareness of the need for adult vaccination should be raised to make it a part of routine care.

In this manner, we conducted a comprehensive, population-level cohort study to evaluate the awareness, attitudes, and behaviors of the population aged over 18 years about adulthood vaccination. The secondary objective was to assess the impact of the COVID-19 pandemic on vaccination awareness and rates.

MATERIALS AND METHODS

This was a cross-sectional, survey-based study that was conducted between July 2023 and September 2023 using a structured questionnaire aiming to determine vaccination coverage, knowledge, and behaviors regarding adulthood vaccination. The referent population included healthcare professionals (doctors, dentists, nurses) and adults aged >18 years.

The questionnaire consisting of 27 questions was distributed both as an online questionnaire and a printed version; participants were carefully instructed to complete it only once. The self-report questionnaire was administered using Google Forms and disseminated using instant messaging apps (e.g., Whatsapp, Viber), social media (e.g., Facebook, Instagram), and institutional emails to doctors, nurses, and dentists currently working in the Turkish Republic of North Cyprus (TRNC). A printed version of the questionnaire was offered to patients admitted to Near East University Hospital as outpatients to the Department of Internal Medicine. The questionnaire was a self-administered questionnaire that captured information under the following sections: 1) demographic characteristics, 2) knowledge regarding adulthood vaccinations, routinely recommended vaccines in the guidelines before and after the COVID-19 pandemic, beliefs about vaccination, 3) vaccination status, and reasons for choosing to get vaccination or not.

Ethical approval for this study was obtained from the Scientific Research Ethics Committee of Near East University (approval number: YDU/2022/108-1663, date: 30.11.2022). Informed consent was obtained from all participants.

Statistical Analysis

The Statistical Package for the Social Sciences 26.0 software was used to statistically analyze the data obtained in this study. The distribution of participants according to their sociodemographic characteristics, general health and smoking status, information, awareness, and attitudes about adulthood vaccination were determined by frequency analysis. The chi-square test[2] was used for the univariate analysis of the effect of each factor on the vaccination status of the participants. Descriptive statistics were generated for each question in the survey. The confidence intervals with a p value of less than 0.05 were considered for inclusion in the multivariable logistic regression model.

RESULTS

A total of 960 surveys were analyzed in our study. 652 (67.92%) of the participants were female, and 308 (32.08%) were male. In the 960 surveys, the socio-demographic characteristics of the participants (Table 1), their distribution according to their health status and smoking status (Table 2), the distribution of some characteristics regarding information on adult vaccines are shown (Table 3), and Table 4 shows the participants included in the study. Pearson X^2 test results are given to compare the adult vaccination status according to the sociodemographic characteristics of the participants. It was determined that there was a statistically significant difference between the rates of vaccination in adulthood according to the participants' age groups, gender, place of birth, profession, marital status, health status, and continuous medication use ($p<0.05$). It was observed that the adult vaccination rates of those aged 25 years and under, women, high school graduates, and single individuals were low. Turkish citizens, healthcare workers, people with chronic diseases, and people who constantly use medication had high adult vaccination rates.

Table 1. Sociodemographic characteristics of the participants

	Number (n)	Percentage (%)
Gender		
Female	652	67.92
Male	308	32.08
Place of birth		
TRNC*	597	62.19
TR**	304	31.67
Others	59	6.15
Education		
Primary	43	4.48
High-school	144	15.00
University	773	80.52
Marital status		
Single	314	32.71
Married	604	62.92
Widow	42	4.38

In Figure 1, participants' awareness about adult vaccines and vaccine protection is compared according to their professions. According to our study, it was statistically significant that knowledge about recommended adulthood vaccination and the protection provided by those vaccinations was found to be higher for those who work in healthcare services ($p<0.05$).

DISCUSSION

In this study, we aimed to reveal the awareness, attitudes, and behaviors of adults living in TRNCs regarding adult vaccination. This is the first time such a study has been conducted in the general population living in the study area. As in other studies conducted for the same purpose

Table 1. Continued

	Number (n)	Percentage (%)
Having children		
Yes	569	59.27
No	391	40.73
Working status		
Yes	692	72.08
No	268	27.92
Profession		
Not working	202	21.04
Student	100	10.42
Dentist	16	1.67
Doctor	94	9.79
Nurse	97	10.10
Other healthcare workers	98	10.21
Other professions	353	36.77
Insurance status		
Yes	918	95.62
No	42	4.38

*TRNC: Turkish Republic of North Cyprus, **TR: Turkish Republic

Table 2. General health conditions and smoking status of participants

	Number (n)	Percentage (%)
Chronic systemic disease		
Yes	268	27.92
No	692	72.08
Regular medication		
Yes	339	35.31
No	621	64.69
Regular check-ups		
Yes	463	48.23
No	497	51.77
Any contraindications for vaccination		
Yes	20	2.08
No	845	88.02
Don't know	95	9.90
Smoking		
Yes	277	28.85
No	683	71.15

Table 3. Participants' characteristics regarding adulthood vaccinations

	Number (n)	Percentage (%)
Information about adulthood vaccination		
Have information	442	46.04
Do not have the necessary information	518	53.96
Time to get information about adulthood vaccination (n=442)		
Before pandemics	367	83.03
After pandemics	75	16.97
Source of information about adulthood vaccination (n=442)*		
Doctor	231	52.26
Social media	105	23.76
Professional knowledge	115	26.02
Friend	35	7.92
TV	17	3.85
Family	9	2.04
COVID-19 vaccination		
Yes	931	96.98
No	29	3.02
Vaccination status after 19 years (non-COVID)		
Yes	450	46.88
No	401	41.77
Not sure	109	11.35
Vaccines received after the age of 19 (except for COVID) (n=450)		
Tetanus	299	66.44
Flu (influenza)	193	42.89
Hepatitis B	173	38.44
Hepatitis A	42	9.33
Pneumonia (pneumococcus)	35	7.78
Human papilloma virus	23	5.11
Measles-mumps-rubella	5	1.11
Meningitis (meningococcus)	3	0.67
Shingles (varicella-zoster)	1	0.22
Considering oneself at risk in terms of vaccine-preventable diseases		
Yes	237	24.69
No	368	38.33
No idea	355	36.98
Reasons for not getting vaccinated		
Lack of knowledge	297	30.94
Do not consider themselves at risk	132	13.75
Fear of side effects	63	6.56
Do not believe in vaccine protection	15	1.56
Believing that harm outweighs benefits	27	2.81
Out of time	30	3.13
Information about possible side effects of vaccines		
Have information	210	21.88
Partially know	473	49.27
No information	277	28.85
Ideas about the protection provided by vaccination		
Protective	206	21.46
Partially protective	312	32.50
Not protective	13	1.35
No idea	429	44.69

*More than one answer can be given. TV: Television, COVID-19: Coronavirus disease-2019.

Table 4. Comparison of adult vaccination status according to participants' sociodemographic characteristics

	Adulthood vaccination							
	Yes		No		Don't remember		X^2	p
	n	%	n	%	n	%		
Age group								
25 years and younger	51	29.48	95	54.91	27	15.61	54,136	0.001*
26-35 years	91	41.18	88	39.82	42	19.00		
36-45 years	119	51.07	95	40.77	19	8.15		
46-55 years	114	55.07	79	38.16	14	6.76		
56 years and older	75	59.52	44	34.92	7	5.56		
Gender								
Female	290	44.48	293	44.94	69	10.58	8,437	0.015*
Male	160	51.95	108	35.06	40	12.99		
Place of birth								
TRNC	259	43.38	273	45.73	65	10.89	11,878	0.018*
TR	164	53.95	105	34.54	35	11.51		
Others	27	45.76	23	38.98	9	15.25		
Education Level								
Primary school	18	41.86	21	48.84	4	9.30	8,271	0.082
High-school	53	36.81	72	50.00	19	13.19		
University	379	49.03	308	39.84	86	11.13		
Profession								
Non-healthcare	285	39.09	351	48.15	93	12.76	73,874	0.001*
Healthcare	165	71.43	50	21.65	16	6.93		
Marital status								
Single	116	36.94	151	48.09	47	14.97	21,453	0.001*
Married	316	52.32	232	38.41	56	9.27		
Widowed	18	42.86	18	42.86	6	14.29		
Chronic disease								
Yes	145	54.10	94	35.07	29	10.82	8,230	0.016*
No	305	44.08	307	44.36	80	11.56		
Regular medication								
Yes	183	53.98	120	35.40	36	10.62	10,991	0.004*
No	267	43.00	281	45.25	73	11.76		

*P<0.05. TRNC: Turkish Republic of North Cyprus, TR: Turkish Republic.

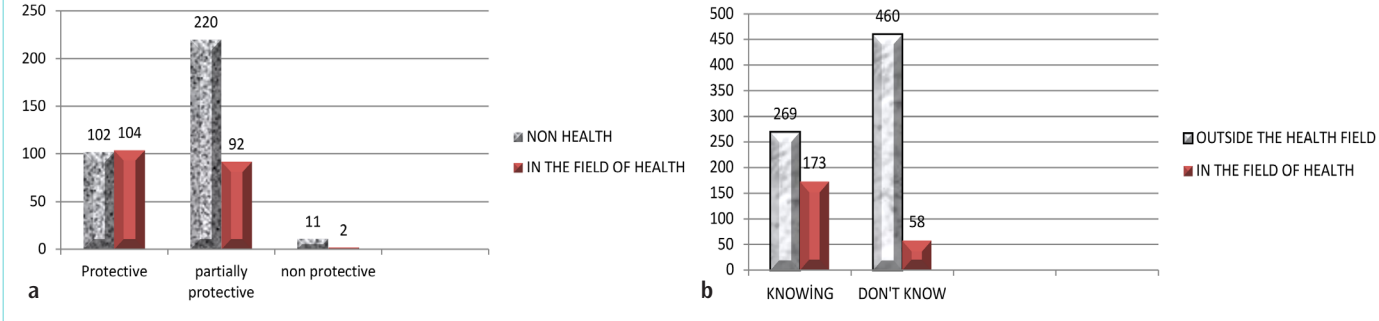

Figure 1. Comparison of participants' knowledge about adult vaccines and vaccine protection according to profession (a, b) p<0.05.

in various countries, adult VCRs were not found satisfactory. In a study published by Uthoff et al.[14] in 2023, annual influenza vaccination rates were far from the recommended rates, and the rates for pneumococcal, Herpes Zoster, and other available vaccines were even lower. In this study, we found that 96.98% of the participants received the COVID-19 vaccine, 46.88% received another vaccine other than COVID after age 19, 66.44% received tetanus, 42.89% received influenza, and 38.44% received hepatitis B vaccine. The pneumococcal vaccination rate was very low and ranked 5th (7.78%).

Only ¼ of the participants in our study considered themselves at risk for diseases requiring adult vaccination. A total of 21.46% of people had an opinion about the protection of adult vaccines. Adult VCR was found to be high in risk groups such as those working in the healthcare field, those with chronic diseases, and those who constantly use medication, as expected. However, although awareness of adult vaccination among healthcare workers was generally high, the vaccination rate was not at the desired level. Thus, in their study among healthcare professionals in 2019, Evren et al.[13] found that although the level of knowledge about influenza and pneumococcal vaccines was high, vaccination rates were low.

Vaccination is the most effective and safe preventive health service for preventing infectious diseases, and it is reported that VPD are becoming more common in adults, with an increase in both relative and real cases. The main reasons for this are explained by the decrease in immunity to vaccines over time, the lack of recommended booster vaccine doses in adults, and the existence of people who were incompletely vaccinated or never vaccinated during childhood. In addition, susceptibility to infectious diseases increases with the weakening of the immune system because of both aging and the increase in chronic diseases in adults.[15] However, interest in adult vaccinations and vaccination rates is quite low. E.g. none of the participants in Aşık et al.'s[16] study received all adult vaccinations. Only 59% have received any adult vaccination at some point in their life. In North Cyprus, according to our study, 46.8% of people have received an adult vaccine other than the COVID vaccine, where the application rates of childhood vaccines are very high both in Türkiye and in our country.[17] Likewise, while the rates of childhood vaccinations are very high in Western countries, those in adults are quite low for reasons such as knowledge gaps, fear of side effects, concerns about their effectiveness, and the perception of not being in the risk group.[18,19]

According to our study, the most common reasons for the low rates of adult vaccinations can be listed as the rates of those who had information about side effects and vaccine protection were low (21.8-21.4%), and only 24.6% of our participants considered themselves at risk for diseases that can be prevented by adult vaccination. Although the adult vaccination rates of people with a chronic disease who constantly take medications and healthcare workers were higher than those of others, they were generally low. In many countries, adult vaccination is inadequately administered, similar to our results. It has been reported that even in developed countries, the VCRs for adults are low. However, immunization services must be continued in adulthood because adults are highly exposed to VPD in their working and social environments. In a study conducted on adults and elderly people aged over 18 years in Türkiye, it was found that 65% of the participants were susceptible to diphtheria, 569 were susceptible to tetanus, and 90% were susceptible to whooping cough. It was reported that 78% of the study participants needed a tetanus vaccine, 90% a whooping cough vaccine, and 96% a diphtheria vaccine.[20] In our study, less than half of the participants had received another vaccine other than COVID-19 after the age of 19 years, and we found that 66.44% of them had had tetanus.

As is is known, flu can lead to common and serious diseases and even serious complications such as secondary bacterial pneumonia. Additionally, flu vaccination plays an indirect role in preventing invasive pneumococcal infection, which tends to occur during flu season.[21] However, among healthcare professionals, the rate of flu vaccination is not at the desired level. The flu vaccination rate among all participants was 42.8%.[13]

According to the CDC survey, 20% of people aged 65 years and older had received a flu vaccine and never received a pneumococcal vaccine. Some European countries have reported approximately 50% coverage for pneumococcal vaccination in high-risk populations. Most countries do not even report these rates. Some studies have shown that the most important obstacle to vaccination is that most high-risk patients are not even aware of it. This study also showed that advice from healthcare professionals is the most important factor for being vaccinated.[22]

Therefore, healthcare providers play a critical role in informing patients about vaccination.[23] Several studies have shown that the provision of vaccines by healthcare professionals is an independent predictor of pneumococcal and influenza vaccine uptake in the elderly.[24] These data demonstrate that the education of healthcare professionals indirectly refers to the education of society. The vaccination rate of healthcare workers in the United States is over 75%, but in many European countries it is below 30%.[25]

Vaccination has been an important issue among both the public and healthcare professionals since March 2020, when the COVID-19 outbreak was declared a pandemic by the World Health Organization.[26] TRNC is a defection-dependent republic with a population of 350,000, located in the Eastern Mediterranean. After the first case of COVID-19 was identified in March 2020, a combination of precautions taken on time by the country's council of ministers depending on science board decisions helped TRNC successfully control the first wave of the pandemic, and the country became COVID-19-free for about 2.5 months.[29] During the period when we planned our study, our participants' awareness, knowledge, and attitudes about the disease were quite good, thanks to the early and reliable information provided by both social media and healthcare professionals about COVID-19 infection. In our study, it was determined that 96.98% of the participants were vaccinated against COVID-19, whereas the percentage of participants who knew about adulthood vaccinations was 83.03% before the pandemic. Similar rates of COVID-19 have been reported in studies from other countries. The general level of knowledge about both the symptoms of the disease and ways to prevent it is quite high, and awareness and vaccination rates were found to be even higher, especially among hospital employees.[7, 27, 28]

Most of those who received adult vaccinations were men between the ages of 36-45. Adult vaccination rates were found to be high for those who were T.R. nationals, had higher education levels, were constantly taking medications, and were working in healthcare services.

Study Limitations

There are some limitations to our study: firstly, most of the participants were reached through an online survey; most of them were living and working in the city center. We did not have the opportunity to reach

people with different educational and social statuses in rural areas. Therefore, it may not be appropriate to generalize the results to the entire population. Second, only awareness and attitudes about adult vaccination were investigated. Application and methods to prevent diseases were not examined. Third, since the period in which our study was conducted was during the COVID-19 epidemic, all attention was focused on the epidemic; other adulthood vaccines or preventable diseases were more in the background. The study results may have differed if it was conducted before pandemic.

CONCLUSION

Adulthood immunization is a current and important issue all over the world. We tried to show that adulthood vaccination awareness among the adults living in TRNC is not enough, similar to many countries, even in healthcare facilities, and is not taken into account as needed. In our study, we demonstrated that education is crucial for awareness and continuation. In order to be protected from preventable diseases, it is necessary to develop immunization programs with an understanding of lifelong immunization, activate public resources to finance this service, and provide regular active training to raise awareness among healthcare professionals and the public. Moreover, the issue of vaccine hesitancy and even vaccine rejection, which is increasing all over the world, should be handled carefully, and protecting public health should be a high-level goal. With vaccination, the incidence and mortality of preventable diseases in adults can be reduced, and these diseases can be brought to the point of elimination, as in some childhood diseases. Reasons for non-vaccination should be addressed, and effective measures should be determined and taken to overcome these identified obstacles.

MAIN POINTS

- Increase of awareness attract attention to the importance of vaccination among adults.
- Vaccination may provide a decrease in the incidence and mortality of VPDs in adults as in some childhood diseases.
- Addresing the reasons for non-vaccination help to overcome the obstacles thus leading to an increase in the vaccination rates.

ETHICS

Ethics Committee Approval: Ethical approval for this study was obtained from the Scientific Research Ethics Committee of Near East University (approval number: YDU/2022/108-1663, date: 30.11.2022).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: D.G.S., G.B., M.T., N.D.Ö., Concept: D.G.S., G.B., M.T., N.D.Ö., Design: D.G.S., G.B., M.T., N.D.Ö., Data Collection and/or Processing: D.G.S., G.B., M.T., N.D.Ö., Analysis and/or Interpretation: D.G.S., G.B., M.T., N.D.Ö., Literature Search: D.G.S., G.B., M.T., N.D.Ö., Writing: D.G.S., G.B., M.T., N.D.Ö.

DISCLOSURES

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RESEARCH ARTICLE

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Effects of Preoperative Information Methods on Anxiety in Patients Scheduled for Impacted Third Molar Surgery

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Abstract

BACKGROUND/AIMS: Extraction of impacted I3M teeth is the most common surgical procedure and causes the greatest anxiety in patients. The aim of this study was to measure the effect of verbal, live action, and animated video information on a patient's anxiety level before impacted I3M tooth extraction. The null hypothesis of this study was that there was a decrease in the anxiety levels of patients who were informed of the procedure by watching an animated video.

MATERIALS AND METHODS: The study had prospective cross-sectional design. The study was conducted at the department of oral and maxillofacial surgery. A total of 90 patients who met the inclusion criteria were divided into three groups. Patient anxiety was measured at three different timepoints: pre-information (T0), post-information (T1), and post-operation (T2) using the Modified Dental Anxiety Scale (MDAS), Amsterdam Preoperative Anxiety and Information Scale (APAIS-A), APAIS-B, APAIS-C, State-Trait Anxiety Inventory-1 (STAI-1), STAI-2, and the Hospital Anxiety and Depression Scale (HADS) tests. In addition, the age and gender of the participants were recorded.

RESULTS: When the T0, T1, and T2 timepoint values were examined between the groups, significant differences were observed in the MDAS, APAIS-A, APAIS-B, APAIS-C, and HADS-D values. For T1, MDAS, APAIS-B, and APAIS-C values, the anxiety levels of the group watching an animated video were significantly lower than those of the group watching a live action video.

CONCLUSION: Although it was determined in the study that the three different types of information led to a decrease in the general anxiety level of patients, the superiority of the animated video in reducing the pre-operation anxiety level should be taken into consideration.

Keywords: Impacted third surgery, anxiety, animated video

INTRODUCTION

Dental anxiety (DA) occurs during dental treatments and is defined as tension, stress, anxiety, or anger and frustration experienced by the patient.[1,2] The factors that cause DA include local anesthesia, pain, fear of rotating instruments, and sounds that the patient hears when on the dentist's chair. Impacted mandibular third molar (I3M) surgery, which is one of the most common surgical procedures in dentistry, has been reported to be the most worrying procedure in patients[3]. I3M extraction is associated with pain, swelling, and trismus, apart from the general complications associated with dental treatment. The patient's anticipation of these problems can cause a high level of anxiety before undergoing I3M extraction.[4,5] In addition, DA can also be caused as a result of previous dental experiences.[6] In particular, acute anxiety can cause various physiological (nausea, vomiting, diarrhea, urinary frequency, etc) and behavioral disorders. Extraction of the I3Ms in patients with DA can be difficult not only for patients but also for surgeons. It has been observed that the duration of the operation is significantly longer, the rate of facial swelling is higher, and the pain is higher in patients with DA.[1,7-9]

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Dentists might use a visual analog scale or other specific scales, such as the State-Trait Anxiety Inventory (STAI), the Modified Dental Anxiety Scale (MDAS), or the Intermittent Anxiety Response Scale, to identify anxious patients.[10,11] Conversely, informative videos are widely used to explain surgical procedures. Although the effect of preoperative information techniques on anxiety related to impacted I3M surgery has been investigated in some studies, there is no consensus on the most effective method for reducing DA.[12-15]

In the literature, there are no studies that investigated the effect of informing patients with an animated video of the extraction procedure before I3M tooth extraction and their anxiety level. The aim of this study was to measure the effect of verbal, live-action videos, and animated video information about the procedure on patient anxiety level before impacted I3M tooth extraction. The null hypothesis of this study was that there is no differences between the anxiety levels of patients who were informed about different procedures.

MATERIALS AND METHODS

Study Design and Ethical Considerations

The Declaration of Helsinki was adopted for this study, and the Ankara University Faculty of Dentistry Local Ethics Committee approved this retrospective study (approval number: 36290600/20, date: 08.03.2018). This study included 90 patients who underwent third molar extraction under local anesthesia between September and November 2018 at the Ankara University Faculty of Dentistry, Department of Oral, Dental, and Maxillofacial Surgery. Patients were informed about the study and procedure, and a written informed consent form was provided by the preoperative evaluation clinic. If the patient had additional questions, they were also included in the study.

Power analysis using G*Power was conducted for a study involving repeated measurements (with a repetition of 3) in animated, verbal, and video-based groups (with a total of 3 groups), where data were collected. The foundational analysis in this study relies on repeated measures analysis of variance, with an effect size of 0.30, an α value of 0.05, and a power value (1-β) of 0.80 considered in the power analysis. The total sample size was 75. Therefore, it is recommended to recruit a minimum of 25 participants from each group.

The Spielberger State Anxiety Inventory-State version (STAI-S), Hospital Anxiety (HADS-A) and Depression Scale (HADS-D), MDAS, and Amsterdam Preoperative Anxiety and Information Scale (APAIS) are widely used to assess patient DA and were used in this study. Patient anxiety was measured at three different timepoints: pre-information (T0), post-information (T1), and post-operation (T2) using the MDAS, APAIS-A, APAIS-B, APAIS-C, STAI-1, STAI-2, and HADS tests. In addition, the age and gender of the participants were recorded.

The inclusion criteria were as follows: adults aged 18-40 years, with American Society of Anesthesiologists physical condition scores of I and II, absence of any systemic disease, and those who do not regularly use medications.

The exclusion criteria were an inability to read and understand Turkish, significant impairment in vision or hearing, an existing psychiatric disorder, age under 18 years, previous surgical dental treatment, and watching an informative video on this subject.

Each patient was examined by the same physician who performed the surgical intervention. Patients were divided into three groups:

Group 1: Patients who were verbally informed about I3M extraction before surgery.

Group 2: Patients who were shown a live action video of impacted I3M extraction before surgery.

Group 3: Patients who were shown an animated video about impacted I3M extraction before surgery.

Prior to the surgical intervention, participants in each group received live video, verbal, and animated information separately from the same experienced physician in the operating room. The total duration of these sessions was 10 minutes. Patients were randomly assigned to groups 1, 2, and 3 using an online random allocation software (www.randomization.com). Information was provided to the patients upon completion of the questionnaires. All patients in the waiting room received the MDAS, APAIS-A, APAIS-B, APAIS-C, STAI-1, STAI-2, and HADS questionnaires 60 minutes before surgery. The demographic data section (age and gender) of the form was completed by the patients. After the patients were informed of the different information techniques, the same questionnaires were completed by the patients again.

Surgery was performed by the same physician using the standard technique, and the patient was under local anesthesia without premedication or sedation. In all cases, an envelope was incised, and the mucoperiosteal flap was removed. Impaction of the teeth is related to class II positions B of the Pell & Gregory classification, and the duration of the operation is 15 minutes. A bone incision was made at 40,000 rpm, irrigation was performed using surgical markets and drills, and the impacted tooth was extracted. After controlling the bleeding, the flap was closed with a 3.0 black silk suture. The live and animated videos portrayed every moment of the surgical procedure, from suturing opening to suturing closure, accompanied by sounds specific to the operation. Patients refilled the MDAS, APAIS-A, APAIS-B, APAIS-C, STAI-1, STAI-2, HADS-A, and HADS-D questionnaires in the waiting room 20 minutes after surgery. Questionnaires were filled out by the patients in the same room and at the same table as before surgery. Patients were postoperatively prescribed 1000 mg of amoxicillin and clavulanic acid and 25 mg of dexketoprofen. They were also instructed to use mouthwash with 0.2% chlorhexidine after 1 day and for 1 week. An ice pack was applied to the operation area for at least 60 minutes after the operation. After 1 week, the patients were called for control.

Modified Dental Anxiety Scale

The MDAS was developed by Humphris et al.[16] by incorporating an injection-related question into Corah's Dental Anxiety Scale. This scale employs a five-point Likert-type scale with five options, yielding total scores ranging from 5 to 25.[17,18]

Amsterdam Preoperative Anxiety and Information Scale

In 1996, Moerman et al.[19] developed the APAIS, which is used to assess preoperative anxiety. This test categorizes anxiety into three sources: anxiety about anesthesia (APAIS-A), anxiety about lack of information (APAIS-B), and anxiety about surgery (APAIS-C). The APAIS consists of six statements related to these sources to evaluate anxiety. To standardize the questionnaire, each statement was assigned a numerical value

based on a five-point Likert scale indicating severity, ranging from 1 to 5 (1=none, 2=mild, 3=moderate, 4=severe, and 5=extreme severity). Anesthesia anxiety was determined by summing the scores of questions 1 and 2, surgical anxiety by questions 4 and 5, and overall anxiety by all six questions. Questions 3 and 6 assessed the desire for information regarding anesthesia and surgery, respectively. Scores on the APAIS range from 6 (lowest) to 30 (highest).[19]

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a four-point Likert-type scale developed by Zigmond and Snaith[20] to assess the risk of anxiety and depression in patients, as well as to measure the severity and changes in these conditions. The HADS comprises a total of 14 questions, where odd-numbered questions evaluate anxiety and even-numbered questions evaluate depression. The scale is divided into two subscales: anxiety (HAD-A) and depression (HAD-D). Based on a study conducted in Turkey, the cut-off score for the anxiety subscale was 10/11, while that for the depression subscale was 7/8. Therefore, patients who scored above these thresholds were identified as at risk. Scores on both subscales ranged from 0 (lowest) to 21 (highest). HADS is often preferred because it focuses on psychological symptoms rather than physical symptoms associated with anxiety and depression.[20]

Speilberger State Anxiety Inventory

The STAI-S is extensively employed in anxiety research, although it is not specifically designed for DA. This inventory consists of two scales, each comprising 20 items that assess state and trait anxiety levels. STAI-trait (STAI-1) measures a patient's underlying or enduring anxiety level, while STAI-state (STAI-2) gages their current anxiety level. Each of the 20 items was rated on a four-point scale. Scores on the STAI range from 20 to 80, with interpretations typically categorized as follows: scores of 20 to 37 indicate no or low anxiety, scores of 38 to 44 indicate moderate anxiety, and scores of 45 to 80 indicate high anxiety levels.[22,23]

Statistical Analysis

The data collected in this study were analyzed using SPSS 25.0 software. Descriptive statistics, including mean, standard deviation, minimum, median, and maximum, were employed to summarize the data. Additionally, the Shapiro-Wilk test was used to assess the normality of the data distribution. The assumption of homogeneity of variance was tested using the Levene's test. For comparisons involving more than two dependent groups with normally distributed data, repeated measures analysis of variance (ANOVA) was conducted. For data that did not exhibit normal distribution, Friedman's analysis was performed instead. Bonferroni's analysis was performed following any statistically significant differences between measurements. The significance level was set at $p<0.05$ and $p<0.01$. While gathering data, the researchers conducted one-on-one interviews. We only recorded the scores without collecting sub-questions; therefore, we could not assess reliability. However, in the studies where we obtained the scales, the Cronbach's alpha coefficient was high. Effect sizes (Eta-squared, η^2) indicating the proportion of variance in dependent variables explained by each independent variable (survey method) are reported in Tables 1-5. Eta-squared values were interpreted using Cohen's guidelines, where values of 0.02, 0.13, and 0.26 or above correspond to small, medium, and large effect sizes, respectively. These effect sizes were calculated to assess the impact of each survey method on anxiety measures to ensure transparency and reliability of the study findings.

RESULTS

Out of the 127 patients initially assessed, 37 did not meet the inclusion criteria, leaving 90 who met the criteria and consented to participate. Among them, 22 had a prior surgical dental treatment history, and 11 declined to complete the postoperative questionnaires. Consequently, the study included 90 patients (20 females and 10 males, aged 18 to 40 years). The patient recruitment process is depicted in the Consolidated Standards of Reporting Trials flowchart (Figure 1).

There were no statistically significant differences between groups in terms of mean age ($p=0.621$; Table 1), and the distribution of males and females was similar across groups ($p=0.105$; Table 2).

Evaluation of anxiety levels at T0, T1, and T2 timepoints for patients receiving verbal information (group 1) revealed that T2 APAIS-B values were significantly lower than T0 APAIS-B values. Additionally, T2 STAI-I values were significantly lower than T1 STAI-I values ($p<0.05$; Table 3).

For patients who were informed through live action video (group 2), evaluation of anxiety levels at the T0, T1, and T2 time points revealed that the T2 MDAS values were lower than the T0 and T1 MDAS values. Moreover, T2 APAIS-B values were significantly lower than T1 APAIS-B values (Table 4).

Analysis of anxiety levels at T0, T1, and T2 for patients informed through animated videos (group 3) revealed that T2 APAIS-A values were lower than T0 APAIS-A values (Table 5).

Comparing T0, T1, and T2 anxiety levels across all groups (Table 6) revealed differences in MDAS, APAIS-A, APAIS-B, APAIS-C, and HADS-D scores. Specifically, T1 MDAS values were significantly lower in patients

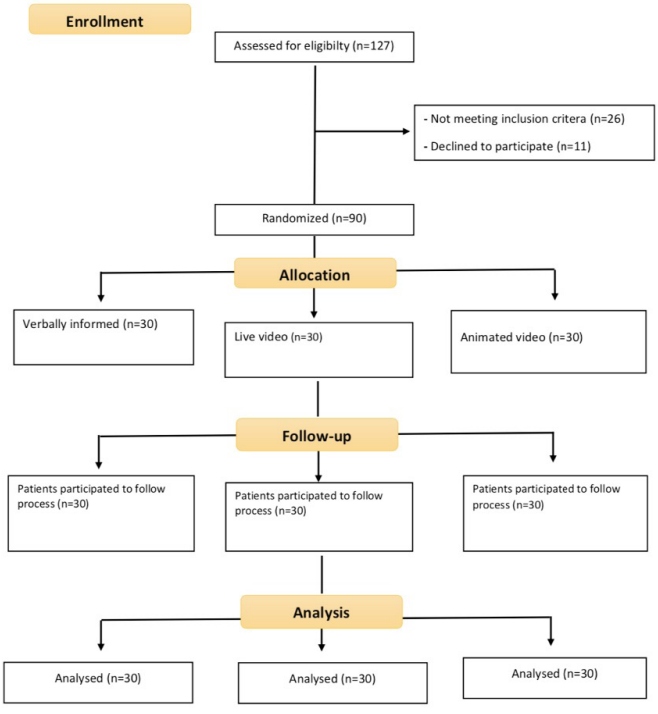

Figure 1. The patient recruitment process is explained in the consolidated standards of reporting trials flowchart.

who were informed through animated videos than in those who were informed through live action videos. Additionally, APAIS-A values at T1 were significantly lower in patients informed through animated and live action videos than in those informed verbally. T1 APAIS-B and APAIS-C values were significantly lower in the animated video group than in the live action video group. Lastly, T1 HADS-D values were significantly lower in the animated video group than in the verbal information group.

Table 1. Distribution of age by group

Age							ANOVA test	p	Effect size
	n	Min.	Median	Max.	Mean	SD	F		
Group 1	30	18	24	33	24.17	3.82	2.31	0.105	0.050
Group 3	30	18	23	31	23.43	3.48			
Group 2	30	18	25	32	25.43	3.64			

*p<0.05. Min.: Minimum, Max.: Maximum, SD: Standard deviation.

Table 2. Gender distribution by group

n		Group 1		Group 2		Group 3		Chi-square test	p	Effect size
		%	n	%	n	%				
Gender	Male	10	33.3	7	23.3	10	33.3	X^2=0.952	0.621	0.008
	Female	20	66.7	23	76.7	20	66.7			

*p<0.05.

Table 3. Comparative analyses of surveys conducted after patients were verbally informed about the surgical procedure

		n	Min.	Median	Max.	Mean	SD	Test	p	Effect size	Bonferroni	p
MDAS	T0	30	5	14	22	13.4	4.14	F=1.858	0.180	0.060		
	T1	30	5	14	22	13.3	4.37					
	T2	30	5	14	21	12.53	4.06					
APAIS-A	T0	30	3	5	9	5.23	1.96	X^2=0.844	0.656	0.014		
	T1	30	2	5	8	5.2	1.92					
	T2	30	2	5	10	4.97	1.99					
APAIS-B	T0	30	3	5	10	5.9	2.14	X^2=12.36	0.002*	0.206	T2<T0	0.002*
	T1	30	2	5	10	5.73	2.36				T2<T1	0.015*
	T2	30	2	5	10	5.27	2.24					
APAIS-C	T0	30	2	4	9	4.8	1.83	X^2=0.553	0.758	0.009		
	T1	30	2	4	10	4.87	2.11					
	T2	30	2	4	10	4.73	2.03					
STAI-2	T0	30	32	45.5	51	45.03	4.56	X^2=2.48	0.289	0.041		
	T1	30	39	45	66	45.67	4.46					
	T2	30	39	45	62	45.53	4.13					
STAI-1	T0	30	27	41	50	39.6	6.35	X^2=8.985	0.011*	0.150	T2<T1	0.002*
	T1	30	20	42	50	40.07	7.30					
	T2	30	20	41	46	38.43	6.80					
HADS-A	T0	30	3	7	17	7.43	3.52	F=1.119	0.333	0.037		
	T1	30	0	7	18	7.77	4.25					
	T2	30	0	7	12	6.67	3.25					
HADS-D	T0	30	3	6	12	7.23	2.96	F=0.589	0.500	0.020		
	T1	30	0	7	13	6.93	3.69					
	T2	30	0	7	20	6.7	4.29					

F: Analysis of variance, X^2: Friedman test, *p<0.05, Min.: Minimum, Max.: Maximum, SD: Standard deviation, MDAS: Modified Dental Anxiety Scale, APAIS: Amsterdam Preoperative Anxiety and Information Scale, STAI: State-Trait Anxiety Inventory, HADS: Hospital Anxiety and Depression Scale.

Table 4. Comparative analyses of surveys conducted after patients were informed about the surgical procedure using live action video

		n	Min.	Median	Max.	Mean	SD	Test	p	Effect size	Bonferroni	p
MDAS	T0	30	6	12.5	22	12.97	3.68	F=14,261	0.001*	0.330	T2<T0 T2<T1	0* 0*
	T1	30	6	15	24	14.73	4.26					
	T2	30	6	12	19	11.87	2.99					
APAIS-A	T0	30	2	3	8	3.87	1.61	X^2=2,000	0.368	0.033		
	T1	30	2	4	10	3.97	1.87					
	T2	30	2	4	7	3.7	1.32					
APAIS-B	T0	30	2	6	10	5.77	1.92	F=12,719	0.000*	0.305	T2<T0 T2<T1	0.011* 0*
	T1	30	2	6	10	6.6	2.04					
	T2	30	2	5	10	4.93	1.86					
APAIS-C	T0	30	2	5	8	5.27	1.48	F=2,933	0.086	0.092		
	T1	30	2	6	10	5.7	1.8					
	T2	30	2	5	8	5.1	1.52					
STAI-2	T0	30	3	47	56	47.1	4.25	F=3,066	0.057	0.096		
	T1	30	40	46	56	46.03	3.66					
	T2	30	40	46	56	46.03	3.85					
STAI-1	T0	30	29	40	53	39.83	4.52	X^2=3,352	0.187	0.056		
	T1	30	32	40	55	40.8	4.81					
	T2	30	32	39	51	39.9	3.06					
HADS-A	T0	30	2	7.5	16	7.6	3.29	X^2=1,581	0.454	0.026		
	T1	30	2	8	13	8.17	3.22					
	T2	30	1	8	13	7.7	2.76					
HADS-D	T0	30	1	5.5	10	5.47	2.56	X^2=5,531	0.063	0.092		
	T1	30	1	6	13	5.8	2.73					
	T2	30	1	5	12	5.23	2.62					

F: Analysis of variance, X^2: Friedman test, *p<0.05, Min.: Minimum, Max.: Maximum, SD: Standard deviation, MDAS: Modified Dental Anxiety Scale, APAIS: Amsterdam Preoperative Anxiety and Information Scale, STAI: State-Trait Anxiety Inventory, HADS: Hospital Anxiety and Depression Scale.

DISCUSSION

Anxiety experienced before impacted I3Ms is a common clinical problem that leads to many consequences, such as prolonged processing time, increased postoperative pain, slowed recovery, and even postponed treatment.[2] Managing patients' preoperative anxiety remains a major challenge in maxillofacial surgery, regardless of newly developed surgical and pharmacological techniques.[24] Various scales have been developed to assess all aspects of DA. It has been reported that filling out these scales before treatment does not have a negative effect on the fear and anxiety level of the patients.[16]

To ensure the reliability of clinical trial data, one or more scales were used to evaluate DA. Schuurs and Hoogstraten[25] compared six different scales and found that the scales were not sufficient to evaluate their findings. Patient anxiety before surgery may be caused by the hospital environment, anesthesia, surgical procedure, postoperative pain anxiety, or previous dentist experiences. Multiple scales are needed to measure DA in all aspects. In this study, four different scales were used to better analyze the source of DA and the obtained results. The MDAS, APAIS, STAI, and HADS scales were preferred for this study because they were understandable, easy to use, and suitable for statistical studies.

In many studies, it has been observed that informing patients of different techniques can reduce their anxiety levels.[12] However, other studies have shown that the level of anxiety increases depending on the surgical technique.[26] Other studies have measured the anxiety levels of patients after receiving verbal information.[14,27] In this study, there was no significant decrease in patient anxiety level according to the pre-information (T0) and post-information (T1) scales for those who received verbal information. Only after the operation did a significant decrease in the APAIS-B and STA-I scale scores. This significant decrease may be due to patients' satisfaction with the information given and their trust in the doctor. In the literature, many studies have measured patient anxiety caused by watching informative videos about the surgical procedure.[2,12,14,22,23,27,28] Although there are studies reporting that watching informative videos before surgery reduces anxiety in patients,[12] others have reported that watching videos does increases[2,14] the level of anxiety. Kazancioglu et al.[2] reported that in their study of 300 patients who applied to the clinic for I3M tooth extraction, the level of anxiety increased in patients who were shown videos before the operation. In this study, patients who were informed by watching videos had significantly lower postoperative (T2) MDAS and APAIS-B scale scores. There was no significant difference between the T0 and T1 time points. The contradictory results of the studies might have

Table 5. Comparison of surveys conducted after patients were informed about the surgical procedure using animated video

		n	Min.	Median	Max.	Mean	SD	Test	p	Effect size	Bonferroni	p
MDAS	T0	30	5	12	21	11.9	3.95	X^2=1,326	0.515	0.022		
	T1	30	6	11.5	20	11.57	3.71					
	T2	30	5	11	18	10.67	3.91					
APAIS-A	T0	30	2	3	9	3.73	1.68	X^2=8,291	0.016*	0.138	T2<T0	0.05*
	T1	30	2	3	8	3.4	1.75					
	T2	30	2	2	6	2.93	1.36					
APAIS-B	T0	30	2	5	10	4.53	2.03	X^2=1,373	0.503	0.023		
	T1	30	2	5	8	4.77	1.65					
	T2	30	2	4	10	4.13	2.11					
APAIS-C	T0	30	2	4.5	9	4.47	1.96	X^2=2,469	0.291	0.041		
	T1	30	2	4	10	4.63	1.99					
	T2	30	2	4	10	4	2.24					
STAI-2	T0	30	32	44.5	57	44.93	5.63	X^2=1,564	0.458	0.062		
	T1	30	36	45.5	80	46.83	7.92					
	T2	30	31	43.5	55	44.33	5.39					
STAI-1	T0	30	28	38	51	38.37	5.88	X^2=3,784	0.151	0.063		
	T1	30	32	38	80	39.8	8.85					
	T2	30	31	42	75	41.77	8.74					
HADS-A	T0	30	0	7	19	6.87	3.76	X^2=1,312	0.519	0.022		
	T1	30	2	7	15	6.5	2.69					
	T2	30	0	6	13	6.03	3.3					
HADS-D	T0	30	0	4.5	10	4.8	2.38	F=1,249	0.290	0.041		
	T1	30	0	5	9	4.53	2.53					
	T2	30	0	4.5	15	5.23	3.77					

F: Analysis of variance, X^2: Friedman test, *p<0.05, Min.: Minimum, Max.: Maximum, SD: Standard deviation, MDAS: Modified Dental Anxiety Scale, APAIS: Amsterdam Preoperative Anxiety and Information Scale, STAI: State-Trait Anxiety Inventory, HADS: Hospital Anxiety and Depression Scale.

varied depending on the viewing content and cultural structure of the population. Although the images and sounds are explanatory and comforting for some patients, they can also be disturbing for others. Conversely, patients might have already watched online videos about the surgical procedure, some of which could have presented misleading content.[29]

In this study, the low anxiety levels observed in the postoperative tests (T2) could be attributed to the fact that the operation was completed. Although verbal and video information was found not to affect preoperative anxiety levels, reduced postoperative anxiety levels suggest that it may be useful for reducing DA in future dental procedures.

To date, there are only few published reports supporting the use of 2D cartoon animations to inform patients about different surgical aspects. Tou et al.[30] showed animated videos to patients before bowel surgery and reported a decrease in anxiety levels. The null hypothesis of this study was that animated videos led to a greater decrease in anxiety levels than verbal and live action video content. Low anxiety levels were found in the postoperative tests (T2), which is an expected result due to the fact that the operation had been completed. An important finding of this study concerns the differences between the values in the post-information (T1) tests. Accordingly, the T1 MDAS, APAIS-A, APAIS-B, and APAIS-C values of patients who watched the animated video were significantly lower than the T1 values of the other groups. In addition, the T1 HADS-D values of patients who were shown live action and animated videos were lower than those who were verbally informed. This study showed that animated videos were more successful in reducing preoperative anxiety than other methods. In the animated video, blood and tools did not look as invasive as they did in the live action video, which allowed the patient to see images that the patient could not imagine from the verbal information. The moment when patients and surgeons have the most problems is when the operation takes place; thus, the method of informing the patient with an animated video should be carefully evaluated. Finally, the development of animated videos can influence and improve the dialog between patients and physicians.

Sancak and Akal[15] evaluated the effect of different preoperative verbal and written information on DA using different scales and observed that written information reduced postoperative anxiety scores. In this study, the fact that the written information was not evaluated can be considered a limitation of the study.[15]

Animated videos can be a useful technique to reduce DA. This study can be expanded to reduce the level of DA before different surgical techniques and to help determine the variability of animated videos

Table 6. Comparison of the types of surveys conducted in the groups

		Group	n	Min.	Median	Max.	Mean	SD	Test	p	Effect size	Bonferroni	p
MDAS	T0	1	30	5	14	22	13.4	4.14	F=1,158	0.319	0.026		
		2	30	6	12.5	22	12.97	3.68					
		3	30	5	12	21	11.9	3.95					
	T1	1	30	5	14	22	13.3	4.37	F=4,436	0.015*	0.093	G3<G2	0.011
		2	30	6	15	24	14.73	4.26					
		3	30	6	11.5	20	11.57	3.71					
	T2	1	30	5	14	21	12.53	4.06	X^2=3,532	0.171	0.018		
		2	30	6	12	19	11.87	2.99					
		3	30	5	11	18	10.67	3.91					
APAIS-A	T0	1	30	3	5	9	5.23	1.96	X^2=11,489	0.003*	0.109	G3<G1 G2<G1	0.023*
		2	30	2	3	8	3.87	1.61					
		3	30	2	3	9	3.73	1.68					
	T1	1	30	2	5	8	5.2	1.92	X^2=15,155	0*	0.151	G3<G1 G2<G1	0.010*
		2	30	2	4	10	3.97	1.87					
		3	30	2	3	8	3.4	1.75					
	T2	1	30	2	5	10	4.97	1.99	X^2=20,336	0*	0.210	G3<G1 G2<G1	0.000*
		2	30	2	4	7	3.7	1.32					
		3	30	2	2	6	2.93	1.36					
APAIS-B	T0	1	30	3	5	10	5.9	2.14	X^2=7,674	0.022*	0.065	G3<G2	
		2	30	2	6	10	5.77	1.92					
		3	30	2	5	10	4.53	2.03					
	T1	1	30	2	5	10	5.73	2.36	F=6,057	0.003*	0.122	G3<G2	0.002*
		2	30	2	6	10	6.6	2.04					
		3	30	2	5	8	4.77	1.65					
	T2	1	30	2	5	10	5.27	2.24	X^2=5.43	0.066	0.039		
		2	30	2	5	10	4.93	1.86					
		3	30	2	4	10	4.13	2.11					
APAIS-C	T0	1	30	2	4	9	4.8	1.83	X^2=4,882	0.087	0.033		
		2	30	2	5	8	5.27	1.48					
		3	30	2	4.5	9	4.47	1.96					
	T1	1	30	2	4	10	4.87	2.11	X^2=6,527	0.038*	0.052	G3<G2	0.015*
		2	30	2	6	10	5.7	1.8					
		3	30	2	4	10	4.63	1.99					
	T2	1	30	2	4	10	4.73	2.03	X^2=8,298	0.016*	0.072	G3<G2	0.010*
		2	30	2	5	8	5.1	1.52					
		3	30	2	4	10	4	2.24					
STAI-2	T0	1	30	32	45.5	51	45.03	4.56	X^2=3,182	0.204	0.013		
		2	30	39	47	56	47.1	4.25					
		3	30	32	44.5	57	44.93	5.63					
	T1	1	30	39	45	66	45.67	4.46	X^2=0.546	0.761	0.002		
		2	30	40	46	56	46.03	3.66					
		3	30	36	45.5	80	46.83	7.92					

F: Analysis of variance, X^2: Friedman test, *p<0.05, Min.: Minimum, Max.: Maximum, SD: Standard deviation, MDAS: Modified Dental Anxiety Scale, APAIS: Amsterdam Preoperative Anxiety and Information Scale, STAI: State-Trait Anxiety Inventory, HADS: Hospital Anxiety and Depression Scale.

for age- and sex-specific anxiety. With the development of technology and the increase in screen use from an early age, the effect of animated videos on DA in children requires further study.

Study Limitations

In this study, the patient population was limited to individuals aged 18-40 years, as those with any previous dental surgery experience were excluded from the study. As previously reported, earlier dental experiences can affect the anxiety level of patients.[31] Although dental surgery might not be performed, patients can experience a fear of anesthesia and rotary instruments during other dental procedures. This fear might have caused differences in the answers to the scales, especially about anesthesia, which is a limitation of the study.

CONCLUSION

Although it was determined in the study that three different types of information led to a decrease in the general anxiety level of patients, the superiority of animated videos in reducing anxiety levels before an operation should be taken into consideration. Testing this method with different operations and techniques could help reduce DA in patients.

MAIN POINTS

- Animated videos can be a useful technique to reduce dental anxiety (DA).
- The development of animated videos can influence and improve the dialogue between patients and doctors.
- With the development of technology and the increase in screen use from an early age, the effect of animated videos on DA in children requires further study.

ETHICS

Ethics Committee Approval: the Ankara University Faculty of Dentistry Local Ethics Committee approved this retrospective study (approval number: 36290600/20, date: 08.03.2018).

Informed Consent: Patients were informed about the study and procedure, and a written informed consent form was provided by the preoperative evaluation clinic.

Authorship Contributions

Surgical and Medical Practices: M.E.Y., M.Ö., E.P.B., Concept: M.E.Y., M.Ö., E.P.B., Design: M.E.Y., M.Ö., E.P.B., Data Collection and/or Processing: M.E.Y., M.Ö., E.P.B., Analysis and/or Interpretation: M.E.Y., M.Ö., E.P.B., Literature Search: M.E.Y., M.Ö., E.P.B., Writing: M.E.Y., M.Ö., E.P.B.

DISCLOSURES

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

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RESEARCH ARTICLE

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Efficacy and Safety of Sacral Neuromodulation in Patients with Lower Urinary Tract Dysfunction: A Five-Year Experience in North Cyprus

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Abstract

BACKGROUND/AIMS: Sacral neuromodulation (SNM) therapy is a well-tolerated treatment modality for voiding dysfunctions. The aim of this study was to evaluate the efficacy and safety of SNM in patients with voiding dysfunction in the Turkish Republic of Northern Cyprus (TRNC) and to share our current experience.

MATERIALS AND METHODS: This retrospective study included a cohort of 39 patients who received SNM treatment between April 2018 and December 2023. Patients diagnosed with urinary retention and bladder overactivity were included in the study. History of the disease and etiologies, urinalysis, residual voiding volume, voiding diaries, global response assessment scale, and complications in response to treatment were analyzed.

RESULTS: The study included 39 participants (27 females and 12 males, with a mean age of 60.2±10.9 years. Overall, the treatment success rate was 65.7%. The average duration for implanting leads was 40.8±7.9 minutes. There were no reported cases of infection. However, electrode migration occurred in 2.8% of cases, and device-related pain occurred in 10.3%. The post-void residual volume in patients with urinary retention decreased from >200 mL to <100 mL following treatment. The typical number of urinary incontinence episodes among patients with OAB was 5±2 per day, which significantly decreased to 2.6±1.27 per day following treatment.

CONCLUSION: SNM is a reliable and safe treatment method for patients who are suitable for this treatment. In TRNC, the necessary infrastructure and technical support are available to treat and monitor patients and manage potential complications. However, to achieve higher success rates and more robustly analyzed treatment outcomes, multicenter randomized trials and studies with larger sample sizes are required.

Keywords: Lower urinary tract symptoms, overactive bladder syndrome, sacral neuromodulation, urinary retention, voiding dysfunction

INTRODUCTION

Sacral neuromodulation (SNM) is an innovative treatment for lower urinary and bowel dysfunction that differs from conventional therapies.[1,2] This minimally invasive treatment involves electrical stimulation of the sacral nerves to restore pelvic organ function. This treatment modality has been successfully applied in the Turkish Republic of Northern Cyprus (TRNC) in the last 5 years, and a patient cohort has been established.

The development of SNM can be traced back to the early 1980s. Tanagho and Schmidt's[3] groundbreaking contributions laid the foundation for this field, showcasing the therapeutic potential of electrical stimulation of sacral nerve roots in treating urinary incontinence. The same stimuli affect neural pathways that govern fundamental processes, including urinary and fecal retention, and have demonstrated efficacy in treating dysfunctional conditions. Nevertheless, the precise mechanism of action underlying SNM remains uncertain despite conjecture and speculation.

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In contrast, rather than directly stimulating the detrusor or urethral sphincter for motor purposes, it is posited to influence spinal cord reflexes and cerebral involvement by modulating afferent signaling. The widely accepted theory suggests that SNM blocks or disrupts afferent input to the sacral spinal cord, thereby inhibiting detrusor overactivity and ultimately relieving urinary frequency and urgency symptoms. Since then, technological advances and clinical research have focused on expanding the efficacy and applications of this method.

Experience in the North Cyprus

SNM therapy has been sanctioned by the Food and Drug Administration (FDA) since 1997, and over two hundred thousand patients have been implanted with it.[4] SNM is a treatment modality that has been used for more than 375,000 patients worldwide. Healthcare advancements in TRNC are commensurate to those in the Republic of Türkiye. Reimbursement approval for SNM was granted to Türkiye's healthcare system in 2007. During the years 2007-2013, there was a transitional period for reimbursement, but the path was subsequently cleared for this treatment approach.[5] In 2016, a local distributor and a medical company providing technical support began operations in the field of SNM in the TRNC, resulting in the establishment of appropriate conditions. Consequently, the first SNM for bladder overactivity was performed in 2018. Subsequently, it was applied in tens of cases of TRNC in the field of urology due to overactive bladder (OAB) and urinary retention, and in the field of general surgery, it was used once in the treatment of fecal incontinence.

Our research focused on patients receiving minimally invasive SNM for urologic problems in TRNC. The aim of our study was to evaluate the efficacy and reliability of SNM in patients with voiding dysfunction and to investigate their concordance with the literature.

MATERIALS AND METHODS

Study Design

This retrospective study included a cohort of 39 patients who received SNM therapy between April 2018 and December 2023 in North Cyprus. The patients were diagnosed with urinary retention and OAB. The study collected a range of information, including a detailed history of the disease, urinalysis, post-voiding residual urine, voiding diary, specific evaluations (such as the OAB symptom score, number of urinary incontinence, number of pads, number of catheterizations, and residual urine amount measured by the catheter), global response assessment scale, and etiologies of all patients.

*Urodynamics study results were not included in the dataset.

*Urodynamic evaluation may help identify and direct therapeutic interventions for patients with OAB and urinary retention. Nevertheless, it is not typically advised before SNM. In our series, urodynamic assessments were not conducted in all patients; thus, their outcomes were not considered in the study.

Eligibility Criteria

Patients without sex discrimination or an age limit were included in the study. The presence of neurogenic disorders or diabetes mellitus did not hinder patient participation. Only patients aged 18 years were excluded. During patient selection, patients with mental and psychological disorders who might have follow-up problems were not offered SNM treatment. For male patients, the exclusion criteria included concurrent or known benign prostatic hyperplasia, as well as active or inactive urinary tract calculi in both sexes. Furthermore, the presence of either functional or anatomical urethral stricture, which represents intravesical obstruction in both males and females, was considered sufficient for the exclusion of participants from the study.

Ethical Considerations

Patients were informed of the surgical procedure and provided consent forms prior to treatment initiation. This study adhered to the ethical guidelines established by the Declaration of Helsinki and was approved by the Ethics Committee of Dr. Burhan Nalbantoglu State Hospital (approval number: 20/24).

Statistical Analysis

Descriptive statistics were used to analyze the characteristic features. Categorical data were expressed as numbers (n) and percentages, whereas quantitative data were presented as mean ± standard deviation. Categorical variables were compared using the chi-square test between groups if the groups were independent. For all statistical analyses, a p-value 0.05 was considered statistically significant. Data analysis was performed using SPSS Windows, version 28.0.

Treatment and Follow-up Protocols

All patients received SNM treatment in two phases, with an Interstim™ II. Before 2021, the tined lead electrode was not MRI-compatible. In the first stage, the treatment effect was evaluated using an external pulse-generating device. The initial test phase was performed using prophylactic antibiotics under sedation and in the prone position. The position and covering of the patient are such that the anus and bilateral feet are clearly visible and observable. For entry, the appropriate entry point is marked bilaterally under 90-degree fluoroscopic guidance. After the most important stage for navigation is achieved, local anesthesia is provided using prilocaine for the marked points (A path is followed in accordance with the H technique described by Matzel).[6] Fluoroscopy (C-Arm) was performed at an angle of 180°, and the access needle was inserted into sacral 3 foramen under sagittal imaging at an angle of 60°. Subsequently, the muscles around the anus were observed to contract simultaneously during plantar flexion or flexion of the thumb on the same side, following external electrical stimulation. In the event of an undesirable response or omission of input, the input point is altered, and the optimal response is pursued. We strived to provide responses below 2 mA in magnitude. After ensuring the location of the needle, the guidewire was sent. Subsequently, the tract was dilated and a 4-pole electrode was inserted. The initial phase, known as the test period, extends over a duration-2-3 weeks. In cases in which patients exhibited a benefit of 50% or more during this phase, the permanent implantation phase commenced. The following implantable pulse generator (IPG) implantation, patients were regularly monitored through clinical evaluations. The occurrence of wound infection, pain at the wound site, reflected pain, electrode migration, and shifts in the benefit rate have all been documented. Therefore, adjustments or complexities that may arise in subsequent appointments could necessitate therapeutic interventions, program alterations, or IPG removal.

RESULTS

The study included 27 female and 12 male patients. The average age was 60.2±10.9 years, with the youngest patient being 33 years old and the oldest being 86 years old. The mean body mass index (BMI) of the participants was 26.96±3.1. Seven patients received treatment for urinary retention and 32 for an OAB. In 31 patients, the underlying etiology was idiopathic, whereas in eight patients, it was neurological (three patients with multiple sclerosis, four patients with spinal cord trauma, and one multiple spinal disc hernia operation). The distribution of leads was 26 on the right side and 13 on the left. The average time for lead placement was 40.8±7.9 minutes, and the first stage assessment was conducted 16.7±3.2 days after placement. Table 1 summarizes the patient characteristics according to indication.

Three patients underwent tined-lead electrode removal due to unsuccessful treatment outcomes. Of the patients who underwent lead electrode removal in the first stage, two had neurologic etiology, and one had idiopathic etiology. In 2 patients with neurogenic etiology, urinary retention was indicated, whereas the other patient received SNM treatment for OAB. The remaining 36 patients were treated with permanent IPG. While monitoring these patients, several complications arose, including battery failure in one patient (2.8%) and restless leg syndrome in another patient, at a rate of 2.8%. Furthermore, four patients experienced pain and discomfort at the time of IPG implantation. The IPG of the patient with battery failure was replaced with local anesthesia. The revised program for patients with restless legs syndrome resolved these complications. Two patients who experienced pain at the IPG site underwent IPG removal. Before treatment initiation, seven individuals diagnosed with OAB exhibited a recurrent history of urinary tract infections. Five of the patients no longer experienced recurrent tract infections after treatment. The remaining two patients are currently receiving antibiotic suppression therapy. The mean number of urinary incontinence episodes in patients with OAB was 5±2 per day, which decreased to 2.6±1.27 per day following treatment. This decrease was statistically significant. According to our data, among patients with urinary retention, two individuals had a post-void residual volume of >200 mL, while two others had a 150-200 mL volume. All patients showed significant improvement after treatment, with a post-void residual volume of 100 mL. No patient required clean intermittent catheterization before or after surgery. One patient who rarely experienced stress incontinence was cured.

The overall success rate was 65.7% for all patients who underwent SNM and were followed up. Of the patients who were followed up and treated with IPG, 30 had OAB and 4 had urinary retention at baseline. The treatment success rates were 65.8% and 65.25% for patients with OAB and urinary retention, respectively. There were no statistically significant differences in the success rates between the diagnoses of OAB and urinary retention. A significant difference ($p<0.05$) was observed in the comparison of the global response assessment before and after treatment between the OAB and urinary retention groups. In the evaluation of the 39 patients included in the study, age (0.07) and indication (0.37) had a significant effect on treatment outcomes, as determined by the linear regression test. Our model indicates that the indications for surgery and age play significant roles in predicting postoperative outcomes, whereas sex, BMI, and etiology did not show a significant effect in our patient cohort.

One patient required battery replacement throughout the monitoring period because of battery depletion at 42 months. One female patient (the youngest among them) turned off her IPG due to pregnancy. The following delivery, she reported no OAB symptoms and continued to be monitored while in the off position.

DISCUSSION

SNM therapy has been approved by the FDA for the treatment of refractory OAB syndrome and urinary retention.[7,8] Additionally, it has been used for off-label purposes, such as chronic pelvic pain and sexual dysfunction.[8,9] SNM therapy is not a conventional treatment method, and as a result, it is both intriguing and controversial for physicians and patients alike. Despite potential complications, SNM therapy is generally well tolerated and has promising success rates compared with medical and surgical treatments. In line with international guidelines, SNM therapy has been used as a third-line treatment for resistant dysfunctional voiding in the TRNC since 2018. Our patient series showed that OAB accounted for 82.1% of the cases and urinary retention accounted for 17.9%. The patient selection tended to follow a ratio of approximately 4:1 for OAB and urinary retention.

The fact that the durability of SNM treatment was extended to 60 months indicates that it is advantageous in terms of cost-effectiveness.[2] In our research, the inability to conduct a 60-month follow-up period

Table 1. Patient characteristics according to indications

Overactive bladder syndrome		**Urinary retention**	
Variable	**Value**	**Variable**	**Value**
Total number of patients			
Sex, n (%)			
- Male	8 (25%)	- Male	4 (57.1%)
- Female	24 (75%)	- Female	3 (42.8%)
Age (years)	59.4	Age (years)	60
BMI (kg/m^2)	26.8	BMI (kg/m2)	27.7
Etiology, n (%)			
- Idiopathic	27 (84.3%)	- Idiopathic	5 (71.4%)
- Neurogenic	5 (15.6%)	- Neurogenic	2 (28.5%)
Follow-up (months)	29 (6-51)	Follow-up (months)	24 (4-35)

BMI: Body mass index.

precluded us from conducting this assessment. Nonetheless, battery replacement was required in one patient (2.9%) during the follow-up period, which lasted for 42 months. Pretreatment anxiety often includes the need for repeated surgical interventions. The integration of long-lasting batteries and wireless charging technologies into these devices will increase their cost-effectiveness and reduce patient anxiety.

In the treatment of OAB, the improvement in symptoms from SNM reported in case series and randomized trials ranges from 64% to 88%.[10] In our study, the improvement in OAB was 65.8%, which is consistent with the findings reported in the literature. However, although recovery rates of 45-50% have been reported for urinary retention,[11] a higher rate of 65.25% was found in our study. The rationale for this conclusion can be defended by the careful selection of indications to identify subgroups. Nevertheless, in our view, the reason lies in the fact that our series consisted of only four patients, leading to a random outcome. It is worth mentioning that most patients who did not show improvement experienced urinary retention.

Infection at the site of IPG is noted in the literature, with a rate ranging between 8-11%.[12,13] The overall complication rate was 17.9%. Pain at the IPG site was 12.8%, whereas infection at the IPG site was not observed. This may be explained by the perioperative use of prophylactic antibiotics and their maintenance during the postoperative period. Technically, no different methods are used during IPG site preparation and IPG implantation.

Tined lead electrode dislocation or migration varies between 12% and 16% in the literature. In this study, tined lead electrode migration requiring revision was observed in only one patient (2.9%). Following a successful revision, the patient who developed complications was still receiving SNM treatment and benefited from this treatment (Figures 1,2). We believe that the disparity with the existing research can be primarily attributed to the small sample size of patients and the use of only tined lead electrodes.

The necessity for revisions during SNM treatment for patients, particularly in extensive series, occurs because of several factors. However, despite its effectiveness, safety, and well-tolerated nature, the need for revisions remains high.[14,15] In our series, revision rates were somewhat lower. The assessment suggests that the rigidity of patient selection and the comparatively shallow depth of patient selection diminish the necessity for revision. Consequently, as the number of our patients increases and our indications broaden, the number of individuals who may require revision may also increase. Hence, the divergence of our findings from the literature, particularly concerning complications, can be attributed to our restricted sample and the criteria employed in patient selection.

Study Limitations

This study has some limitations that should be considered. First, the retrospective study design may have influenced the results. Second, the small sample size and lack of homogeneity among the participants were factors that could affect the outcomes. Moreover, the absence of long-term follow-up and insufficient in-depth patient selection are additional limitations of the present study. The need for larger multicenter studies to further investigate the results and compare them with those of other studies is also highlighted.

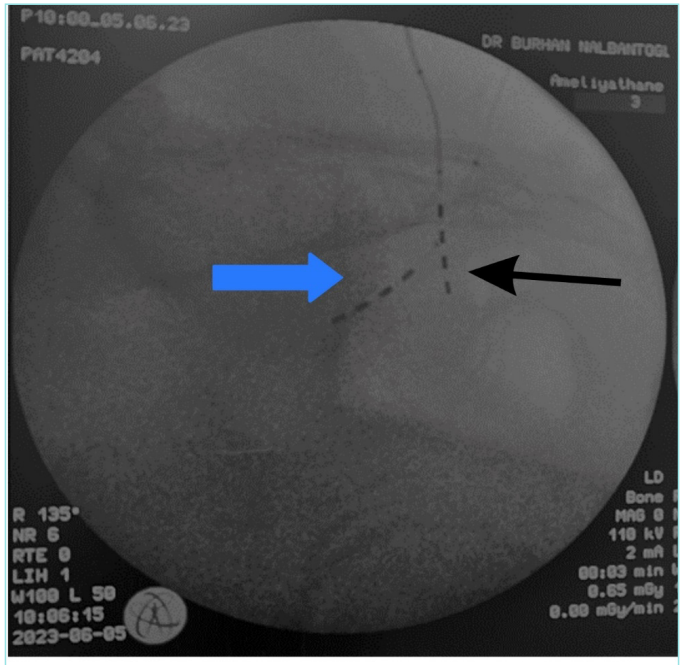

Figure 1. Migration of tined lead electrode. Note: The migration of the tined lead electrode (indicated by the blue arrow) can be visually monitored along with the fluoroscopic image of the newly implanted lead electrode (identified by the black arrow).

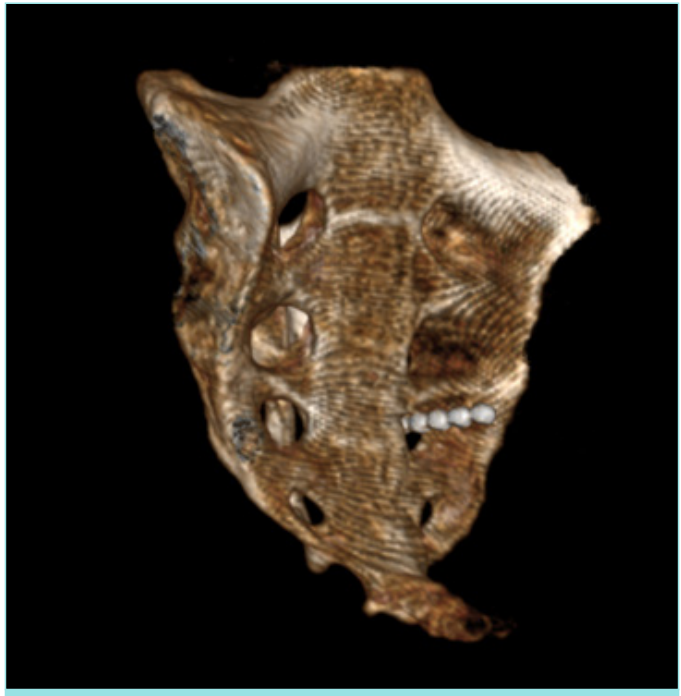

Figure 2. 3D computed tomography images of SNM. Note: 3D computed tomography image showing the appearance following successful lead electrode revision (white).

SNM: Sacral neuromodulation

CONCLUSION

Based on our findings, we conclude that SNM is safe and effective for suitable patients. The necessary infrastructure and technical support required to treat, monitor, and manage potential complications in patients are currently available, and TRNC's success rate for urinary retention is close to the success rate in OAB syndrome, according to our patient series. Undoubtedly, multicenter studies that incorporate control groups and larger sample sizes are necessary to achieve higher success rates and more robust analyses of treatment outcomes.

MAIN POINTS

- Efficacy and safety: Sacral neuromodulation (SNM) has been evaluated as an effective and safe treatment modality for patients with voiding dysfunction in the North Cyprus. The results demonstrate high success rates for managing both urinary retention and overactive bladder, with an overall effectiveness rate of 65.7%.
- Implementation and follow-up: SNM therapy consists of a two-step process: Initially, the effectiveness of the treatment is assessed with the help of an external pulse generator, followed by permanent implantation in patients who show a positive response. Regular follow-up appointments and proper technique programing primarily influence treatment success and the management of complications.
- Infrastructure and technical support: The necessary infrastructure and technical support for SNM are well established in the North Cyprus, facilitating the application of this treatment.
- Recommendations and future research: This study not only represents the first instance of collecting data from patients with voiding dysfunction in the North Cyprus, but it also contributes to the development of future research and patient groups. Furthermore, broadening the scope of the study's indications and conducting joint multicenter research could increase the number of patients who could benefit from these efforts.

ETHICS

Ethics Committee Approval: This study adhered to the ethical guidelines established by the Declaration of Helsinki and was approved by the Ethics Committee of Dr. Burhan Nalbantoglu State Hospital (approval number: 20/24).

Informed Consent: Patients were informed of the surgical procedure and provided consent forms prior to treatment initiation.

DISCLOSURES

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

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